

# The Effects of Reducing the Exposure Time of Mitomycin C in Glaucoma Surgery

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Topical application of mitomycin C has significantly increased the success rate of trabeculectomy. However the optimum exposure time of mitomycin C to the filtration site is not known. The purpose of this study was to determine whether adequate post-operative control of IOP and a lower incidence of post operative complications can be achieved by using mitomycin-C for a shorter period of time during trabeculectomy, performed in high risk glaucoma patients. **Methods:** Twenty eyes of patients of glaucoma, who were considered to be at high risk for failure because of their young age, previous ocular surgery like cataract extraction and trabeculectomy, inflammatory glaucoma, high myopia and prolonged anti-glaucoma medication, underwent trabeculectomy with topical application of 0.2mg/ml concentration of mitomycin C for three minutes. They were case matched with a group of same number of eyes of high risk glaucoma patients who received same concentration of drug for 5 minutes. **Results:** Twelve months after surgery, the mean pre-operative IOP decreased from 29.9mmHg to a post-operative level of 16.05mmHg in 3 minutes group, with a success rate of 85%, and from 29.35mmHg to 16.55mmHg in 5 minutes group, with the same success rate of 85%. The incidence of complications was higher in 5 minutes group, when total number of complications was compared. (p value < 0.05) Ocular hypotony developed in 3 (15%) eyes in 5 minutes group, and none in 3 minutes group. No patient developed hypotony related maculopathy in either group. Other complications like hyphema, post-operative uveitis, and conjunctival wound leakage were managed conservatively. **Conclusion:** The present study supports the conclusion of previous studies that mitomycin C is highly effective drug when used in association with trabeculectomy, and when used in concentration of 0.2mg/ml for three minutes is as effective in controlling post-operative IOP as is five minutes exposure time of the same concentration. Further, emphasizing that the shorter exposure of the drug is associated with lesser incidence of vision threatening complications.

**Key words:** Glaucoma surgery, exposure of time, mitomycin C

Trabeculectomy has been a filtering procedure of choice for control of IOP in most cases of glaucoma.<sup>1,2</sup> It is quick, technically easy to perform, has few complications and has high success rate<sup>3-9</sup>. However it has been observed that filtration failures are not infrequent, especially in eyes with risk factors for drainage failure<sup>10-14</sup> e. g congenital and developmental glaucoma, pseudophakic glaucoma, inflammatory glaucoma, trabeculectomy failure, black race, and high myopia etc (High risk glaucoma patients).

The most common cause of failure of glaucoma surgery is fibrosis of conjunctival bleb.<sup>15</sup> So the understanding of wound healing process, and pharmacological factors modulating this process are most notable advances in this field. In addition to other drugs, mitomycin-C has been extensively evaluated in a search of most suitable method of application<sup>16-18</sup>, its concentration, exposure time and mode of topical application<sup>19-23</sup>.

## Purpose:

The optimum exposure time of mitomycin-C to filtration site is still not known. A wide range of exposure time has been reported<sup>19-21</sup>. The purpose of this study was to determine whether adequate post-operative control of IOP and a lower incidence of post operative complications can be achieved by using mitomycin-C for a shorter period of time during trabeculectomy, performed in high risk glaucoma patients.

## Patients and methods:

After taking a detailed ophthalmic history including significant medical history and performing a complete ophthalmologic examination, forty eyes of 25 high risk glaucoma patients were included. Adequate control of diabetes and hypertension and treatment of ischemic heart disease prior to surgery were confirmed. A written consent was taken, explaining about the anesthesia, surgical procedure, and topical application of mitomycin-C intra-operatively.

Trabeculectomy was performed with fornix-based conjunctival flap, and with per-operative application of mitomycin-C under the conjunctivo-Tenon membrane on the surface of the sclera before the formation of a scleral flap which was 4x4mm in size. The procedure was completed by excision of 1.5mm x 1.5mm trabecular tissue, peripheral iridectomy, and then suturing the scleral and conjunctivo-Tenon flaps. The lamellar scleral flap was sutured with five 10/0 interrupted sutures, and Tenon and conjunctiva with three and two interrupted 10/0 sutures, respectively.

Postoperative medications included dexamethasone eye drops 4 times a day, chloramphenicol eye drops 4 times a day and atropine eye drops twice a day. These were continued for four to five weeks except for atropine eye drops, which were usually discontinued after two weeks, depending upon the anterior chamber reaction during the postoperative period. No suture lysis of the

scleral flap. with Argon Laser or surgically, was performed, although conjunctival sutures were removed in almost all cases when required.

**Results:**

Forty eyes of 25 patients of high risk glaucoma were studied. Fifteen patients were operated upon both eyes. In all patients, 0.2mg/ml concentration of mitomycin-C was used. Average age of patients was 42.13 years with a range of 6 months to 72 years. The patients were divided into following two groups:

Group I: Those who were treated with MMC for three minutes. (Table 1)

Group II: Those who were treated with MMC for five minutes. (Table 2)

Follow up time, for all patients, was 12 months.

For the purpose of comparison, the surgery was considered a "success" when post-operative IOP was equal to or less than 21mmHg without anti-glaucoma medication. Comparison between the two groups was performed using Fisher's exact test and chi-square analysis 2x2 table. A finding was considered significance at P value<0.05.

Mean pre-operative IOP for all eyes was 29.63 mmHg (range = 11 to 45 mmHg) and mean post-operative

IOP was 16.3mmHg (range= 07mmHg to 36mmHg) as measured on last follow up visit, the average reduction in IOP being 13.33mmHg. Over all success rate (Table 3) was 85 %. The mean pre-operative IOP in the two groups was similar (29.9mmHg in 3 minutes group and 29.35mmHg in 5 minutes group. The mean pre-operative IOP decreased from 29.9mmHg to a post-operative level of 16.05mmHg in 3 minutes group, with a success rate of 85%, and from 29.35mmHg to 16.55mmHg in 5 minutes group, with the same success rate of 85%. No statistically significant difference was found in the post-operative control of IOP between two groups. (p value> 0.05)

**Complications and their incidence (Table 3)**

The incidence of complications was higher in 5 minutes group, when total number of complications was compared. ( p value< 0.05) Ocular hypotony developed in 3 (15%) eyes in group II (5 minutes group), and none in group I (3 minutes group). One of these patients required surgical intervention for wound leakage. Neither patient had a significant visual loss. No patient developed hypotony related maculopathy in either group. Other complications like hyphema, post-operative uveitis, and conjunctival wound leakage were managed conservatively.

Table 1: Group I – Mitomycin C application for 3 minutes

Eyes	Age	Sex	Eye	Visual Acuity		IOP		Risk factor	Glaucoma Diagnosis.
				Pre-op	Post-op	Pre-op	Post-op		
1	54	M	L.E	6/6	6/9	14	12	Prolonged med. treatment	POAG
2	48	M	R.E	6/12	6/12	23	07	"	"
3	42	M	R.E	6/36	6/36	45	16	Relatively young	"
4	51	M	L.E	6/12 P	6/12P	11	12	Prolonged Med. treatment	"
5	45	F	L.E	6/9	6/9	38	20	Relatively young	"
6	01	M	L.E	Not recordable		39	36	Young age	Buphthalmos
7	03	F	L.E	"		38	12	"	"
8	6mon	M	RE	"		28	12	"	"
9	01	M	R.E	"		41	24	"	"
10	47	F	R.E	6/24	5/60	20	11	Aphakia	Aphakic Glauc.
11	60	F	L.E	6/60	6/24	40	12	Psuedophakia	Psuedophakic Glaucoma
12	25	M	R.E	HM	6/24	30	29	Corneal repair Vit. Hemorrhage	Traumatic Glaucoma
13	72	F	L.E	6/18	6/18	30	12	Psuedophakia	Psuedophakic Glaucoma
14	45	F	L.E	6/12	6/12	27	12	PI	PNAG
15	25	M	R.E	6/18	6/18	25	14	High Myopia Young age.	Juvenile Glaucoma
16	52	F	R.E	6/12	6/12	31	14	Prolonged Med. Treat.	POAG
17	62	M	R.E	6/18	6/18	30	15	Previous glaucoma-coma surgery	POAG
18	45	M	R.E	6/12	6/9	29	16	Relatively Young, PI	Chronic NAG
19	62	F	R.E	6/12	6/9	32	22	Psuedophakia	Psuedo-phakic Glaucoma
20	59	M	R.E	6/6	6/9	27	13	Prolonged Med. Treat.	POAG

Table 2: Group I - Mitomycin C application for 5 minutes

Eyes	Age	Sex	Eye	Visual Acuity		IOP		Risk factor	Glaucoma diagnosis.
				Pre-op	Post-op	Pre-op	Post-op		
1	54	M	R.E	6/9	6/9	14	14	Prolonged Med. Treat.	POAG
2	48	M	L.E	6/9	6/9	22	08	"	"
3	42	M	L.E	6/12	6/12	42	14	Relatively young	"
4	51	M	R.E	6/12 P	6/12 P	13	10	Prolonged Med. Treat.	"
5	45	F	R.E	6/9	6/9	40	21	"	"
6	01	M	R.E		"	38	26	Young age	Buphthalmos
7	03	F	R.E		"	35	11	"	"
8	8months	M	R.E		"	32	20	"	"
9	01	M	L.E		"	38	23	"	"
10	58	F	R.E	FC	FC	29	36	Aphakia, Repeat trab.	Aphakic Glaucoma.
11	16	F	L.E	6/24	6/24	35	18	Psuedophakia Young age.	Traumatic Glaucoma
12	65	F	L.E	PL	PL	26	08	"	Psuedo-phakic Glaucoma
13	25	M	R.E	6/24	6/18	29	19	"	"
14	30	M	L.E	6/6	6/6	20	09	Trab.	Juvenile Glaucoma
15	25	M	L.E	HM	HM	26	19	High Myopia Young age.	"
16	52	F	L.E	6/6P	6/6P	26	12	Prolonged Med. treatment.	POAG
17	62	M	L.E	6/24	6/24	32	14	Previous glaucoma surgery	POAG
18	45	M	L.E	6/60	6/60	28	14	Relatively Young, Trab	"
19	62	F	L.E	6/18	6/18	34	22	Psuedophakia	Psuedo-phakic Glaucoma
20	59	M	L.E	6/6	6/9	28	13	Prolonged Med. Treat.	"

Table 3: Complications of trabeculectomy with MMC during present study

Name of complication	5 minutes exposure		3 minutes exposure		Total No. of eyes
	No. of eyes	(%)	No. of eyes	(%)	
Conjunctival wound gap	2/20	(10%)	Nil		2/40 (5%)
Wound leakage with shallow AC	2/20	(10%)	Nil		2/40 (5%)
Surgery required	1/20	(5%)			1/40 (2.5%)
Choroidal detachment	1/20	(5%)	Nil		1/40 (2.5%)
Cataract formation	2/20	(10%)	1/20 (5%)		3/40 (7.5%)
Post-op Uveitis	1/20	(5%)	Nil		1/40 (2.5%)
HypHEMA	2/20	(10%)	1/20 (5%)		3/40 (7.5%)
Hypotony maculopathy	Nil		Nil		Nil
Vitreous loss *	Nil		Nil		Nil

\*All cases of Aphakic glaucoma and psuedophakic glaucoma, in which vitreous was found in AC, planned anterior vitrectomy was performed along with filtration.

Table 4: Comparison of reported series of filtering surgery with mitomycin c.

	Shield MB And others (1993)	Gordana Sunaric Megavand (1995)	S-Beaty And others (1998)	Misaki Ishioka And others (2000)	Robert Casson And others (2001)	D P S , O Brart And others. (2004)
MMC Concentr:	0.4mg/ml	0.2mg/ml	0.2mg/ml	0.04%	0.02%	0.2mg to 0.4mg/ml
Exposure time	3 - 5 min	2 - 5 min	5 min	3 min	2 min	2 min
Hypotony maculopathy (%age)	10 % (6/59)	2 % (1/50)	1.4% (1/72)	Nil	5% (1/21)	Nil
Success rate	72%	72%	72%	68.4%	81%	91%

**Discussion:**

The first report of glaucoma surgery with adjuvant mitomycin-C was by Chen.<sup>21</sup> Mitomycin C is an anti-cancer anti-biotic drug isolated from Streptomyces caespitosus. The mechanism by which mitomycin-C influence ocular tissues in filtration surgery, is not fully

understood. Tissue culture studies of rabbit's subconjunctival fibroblasts by Yamamoto<sup>22</sup> and Khaw<sup>23</sup> and human subconjunctival fibroblasts by Jampel<sup>24</sup> suggest that mitomycin C has its affects primarily on cell proliferation. This effect is not only concentration dependent, but also exposure time dependent in rabbits<sup>25</sup>

Studying the effects of mitomycin C on human Tenon's capsule fibroblasts, Jampel<sup>26</sup> only examined the effects on proliferation of cells and not on fibroblast migration, collagen production or local vasculature. Reduced vascularity of filtration bleb, in trabeculectomy with mitomycin topical application of mitomycin C, may enhance the other actions of the drug because it has been observed that mitomycin C is selectively toxic to hypoxic cells<sup>27</sup>.

So this ability of mitomycin to prevent proliferation of fibroblasts of sub-conjunctival tissue and those of Tenon's capsule after single application at filtration site, has significantly improved the success rate of glaucoma filtering surgery. Many studies have since confirmed the enhanced IOP lowering effect of trabeculectomy, augmented by mitomycin C<sup>16-21,26-32</sup>. However, the optimal concentration of mitomycin C and the duration of its exposure to the tissues, are still not known. Purpose of this study was to determine whether adequate post-operative control of IOP and a lower incidence of post operative complications can be achieved by using mitomycin-C for a shorter period of time during trabeculectomy, performed in high risk glaucoma patients.

The results of present study, regarding success rate for post-operative control of IOP and incidence of post-operative hypotony related maculopathy, are similar to the results of recently reported studies (Table 4). Shields MB et al<sup>19</sup> titrated the duration of exposure of eyes to mitomycin C according to the risk factors for failure of filtration from excessive fibrosis. Patients with relatively no risk were treated for 2 minutes, while an additional minute was added for each risk factor, e.g. young age, black race, repeat surgery etc, up to a maximum of 5 minutes. The reported success rate was 72%. The incidence of hypotony maculopathy was 10% (6/59) and it was mostly observed in patients treated with 0.4mg/ml concentration of mitomycin C for 5 minutes. Megavand<sup>28</sup> concluded that 2 minutes exposure time of 2mg/ml concentration of mitomycin C is as effective as 5 minutes exposure, while the complication rate remains the same. A success rate ( i.e. IOP < 21mmHg without anti-glaucoma medication.) of 72% was reported both in 2 minutes group and 5 minutes group, while prolonged hypotony developed in 8% (2/25 eyes) of patients in 2 minutes group and in 12% (3/25 eyes) of those of 5 minutes group. S.Beaty<sup>29</sup> and Misaki Ishioka<sup>30</sup> reported 72% and 68.4% success rates respectively, while incidence of hypotony maculopathy was only 1.4% and zero percent respectively. S. Beaty used 2mg/ml of mitomycin C for 5 minutes, while Misaki Ishioka used it for 3 minutes.

Robert Casser<sup>31</sup> reported 81% success rate and 5% incidence of hypotony maculopathy (1/21 eyes), using 0.02% mitomycin C for only 2 minutes. Similarly DPS' O Brart<sup>32</sup>, using 0.2mg/ml to 0.4mg/ml concentration of mitomycin C for 2 minutes, reported a relatively higher success rate (91%), without any case of hypotony related

maculopathy. These studies not only indicate that success rate of surgery remains the same by reducing exposure time of mitomycin C, but also the incidence of vision threatening complications of trabeculectomy with topical mitomycin C is reduced.

#### Conclusion:

The present study supports the conclusion of previous studies that mitomycin C is highly effective drug when used in association with trabeculectomy, and when used in concentration of 0.2mg/ml for three minutes is as effective in controlling post-operative IOP as is five minutes exposure time of the same concentration. Further, emphasizing that the shorter exposure of the drug is associated with lesser incidence of vision threatening complications of trabeculectomy with topical application of mitomycin C.

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