COMPARISON OF TWO DIFFERENT CONCENTRATIONS OF MITOMYCIN-C IN THE SURGICAL TREATMENT OF PRIMARY OPEN ANGLE GLAUCOMA

Primer açık açılı glokomun cerrahi tedavisinde mitomisin-C' nin iki değişik konsantrasyonunun karşılaştırılması

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Abstract

Purpose: *We compared the effectiveness of trabeculectomy with mitomycin-C (MMC) in primary open angle glaucoma in two groups with two different doses.*

Patients and methods: *The first group consisted of 17 eyes of 17 patients that received MMC at a concentration of 0.5 mg/ml for 3 min to the episclera and 2 min under the scleral flap. The second group consisted of 13 eyes of 13 patients that received MMC at a concentration of 0.25 mg/ml for 3 min to the episcleral bed before the flap was dissected.*

Results: *Average follow-up was 20.7 months. Median values for preoperative intraocular pressure was 40 mmHg (range: 30-60) in the first group and 44 mmHg (range: 21-57) in the second group (p=0.93; Mann-Whitney U test). Median postoperative IOP was 4 mmHg (range: 1.1-20) in the first group and 9 mmHg (range: 5-12) in the second group (p= 0.02; Mann-Whitney U test). Median percentage IOP drop was 89.6 % (range: 58.3-98 %) in the first group and 80 % (range: 59.0-91.2%) in the second group (p= 0.03; Mann-Whitney U test). The number of hypotonous eyes was smaller in the second group and this was statistically significant (p=0.02; chi square test).*

Conclusion: *Reducing the dose and duration of application of mitomycin-C resulted in a lower incidence of hypotonous eyes and adjusting the dose of this antimetabolite to lower levels is necessary for the success and safety of the filtration surgery.*

Key Words: *Glaucoma, Mitomycin-C, Surgery, Trabeculectomy*

Özet

Amaç: *Bu çalışmada primer açık açılı glokom tanısı almış iki hasta grubunda trabekülektomi sırasında iki farklı dozda uygulanan mitomisin-C (MMC) nin etkilerinin karşılaştırılması amaçlanmıştır.*

Hastalar ve yöntem: *Birinci grupta bulunan 17 hastanın 17 gözüne, 0.5 mg/ml konsantrasyonda MMC, 3 dakika süreyle episkleraya ve 2 dak. süreyle skleral flep altına uygulandı. İkinci gruptaki 13 hastanın 13 gözüne ise 0.25 mg/ml konsantrasyonda MMC, 3 dakika süreyle episkleraya uygulandı.*

Bulgular: *Ortalama takip süresi, 20.7 aydı. Preoperatif göz içi basıncı (GİB) değerleri (ortanca) birinci grupta 40 mmHg (30- 60), ikinci grupta ise 44 mmHg (21-57) idi (p=0.93; Mann-Whitney U testi). Postoperatif GİB (ortanca), birinci grupta 4 mmHg (1.1-20) ve ikinci grupta 9 mmHg (5-12) idi (p= 0.02; Mann-Whitney U testi). GİB düşüş yüzdesi (ortanca), birinci grupta 89.6 % (58.3-98 %) ve ikinci grupta 80 % (59.0-91.2%) idi (p= 0.03; Mann-Whitney U testi). İkinci grupta hipoton gözlerin sayısı, birinci gruptan anlamlı derecede daha azdı (p=0.02; ki kare testi).*

Sonuç: *Mitomisin-C' nin doz ve uygulama süresinin azaltılması, hipoton göz oluşma insidansını azaltmıştır. Filtrasyon cerrahisinde MMC' nin dozunun düşürülmesi, operasyonun başarısı ve güvenliği açısından gereklidir.*

Anahtar Kelimeler: *Cerrahi, Glokom ,Mitomisin-C, Trabekülektomi*

Mitomycin-C (MMC), an antibiotic with antineoplastic activity basically inhibits formation of scatris in the operative field and has been shown to be very potent to inhibit fibroblast proliferation in tissue cultures (1, 2). Since there are some doubts as to the correct dosage and the safety of MMC, this study was designed to compare the effects of two different application patterns of MMC. The first concentration has previously been applied in our clinic (3). Since we have encountered with various side effects, hypotony in particular, we designed a protocol where MMC would be used in lesser concentrations.Application of MMC was also limited solely to the episcleral space, instead of the

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additional subflap site which had been previously applied. We evaluated and compared the result of 5 min (3 min episcleral and 2 min subflap site) application of 0.50mg/ml MMC with that of 3 min , 0.25mg/ml episcleral application.

PATIENTS AND METHODS

Records of all patients who had had trabeculectomy with MMC (5 min 0.50mg/ml application and 3 min 0.25mg/ml application) between January 1991 and February 1995 were reviewed. Only the patients who regularly attended to their follow-up visits during this period were included in the study. Other eligibility criteria for the study were as follows:

Patients with advanced primary open angle glaucoma with a preoperative intraocular pressure (IOP) > 20 mmHg despite maximal medical therapy (which consisted of topical beta blockers twice daily, carbonic anhydrase inhibitors 2 to 4 times 250 mg daily and pilocarpine eye drops 5 times a day or topical dipivefrine twice daily when necessary), patients with prominent disc cupping, defective visual fields and glaucomatous tonographic findings. Eyes with previous intraocular, laser or conjunctival surgery, or those which had had combined surgery with cataract extraction were not included in the study. Characteristics of the patients in both groups are summarized in Table 1. All trabeculectomies were performed similar to the classical method of Cairns (4); this included a limbus based conjunctival flap, a 1/3 thickness scleral flap (4x4 mm), and excision of a trabecular block (1x3 mm) followed by a peripheral iridectomy.

In the first group, after the preperation of the conjunctival flap, cellulose sponge (K-sponge, Katena products, N.J., USA) soaked with MMC (Mitomycin C, Kyowa Hakko Kogyo Co., Ltd. Japan) was applied at a concentration of 0.5 mg/ml for 3 min to the episclera and 2 min under the scleral flap. The second group received the same antimetabolite at a concentration of 0.25 mg/ml for 3 min to the episcleral bed before the flap was dissected.

In both groups, Tenon's capsule and the conjunctiva was draped over the sponge. Meticulous effort was spent not to injure the conjunctiva throughout the surgery. At the end of the application, the operative field which appeared pale was irrigated with 20 cc of balanced salt solution. The operation was completed in the usual way and the scleral flaps were closed with interrupted 5 to 7 monofilament 10/0 nylon (Alcon) sutures. Tenon's capsule was closed separately with interrupted 8/0 polyglactine (Vicryl; Ethicon) and conjunctiva with running 8/0 silk (Alcon) sutures. After surgery, a 1:1 mixture of subconjunctival gentamycin and dexamethasone phosphate was injected. Dexamethasone phosphate and 2% cyclopentolate eye drops were instilled postoperatively. All patients were controlled at the day of surgery and daily during the first week before discharge. After discharge, patients were seen at the outpatients department weekly during the first month and monthly thereafter. Visual acuity, characteristics of the conjunctival bleb, corneal findings, IOP, the depth of the anterior chamber, complications, problems and patients who received additional medical treatment were recorded. Average of last three IOP readings in the last three months was recorded for each patient and used for the statistical analysis (Tables 1&2). Surgical success was defined as an IOP 20 mmHg without medication. Hypotony was defined as an IOP 5mmHg on 3 consecutive readings which persisted for 6 weeks postoperatively. In cases of hypotony, presence of choroidal detachment, hypotony associated maculopathy or disc swelling was searched with direct and indirect ophthalmoscopy . In cases with lens opacities B-scan ultrasonography (Sonomed B-3000, Sonomed Inc.) was used for the interpretation of posterior segment. Statistical analysis was made by Mann-Whitney *U*, chi square and Fisher exact tests; p values less than 0.05 were considered as statistically significant. Data are presented as median values for age, preoperative and postoperative IOP as well as percentage IOP drop with their range. Informed consent for the use of MMC was obtained prior to surgery from the

patients. The study protocol and the consent forms were approved by the Erciyes University Scientific and Ethics Committees.

Results

Eligibility criteria was fulfilled with 30 eyes of 30 patients. The first group consisted of 17 patients and the second group, 13 patients. Average follow-up was 20.7 months. Median age of the patients was 65 years (range: 43-81) in the first group and 65 years (range: 54-75) in the second group (p= 0.95). Patients in the first group received MMC at a concentration of 0.5 mg/ml for 3 min to the episclera and 2 min under the scleral flap whereas those in the second group received MMC at a concentration of 0.25 mg/ml for 3 min to the episcleral bed before the flap was dissected.

Median preoperative IOP was 40 mmHg (range: 30-60mm Hg) in the first group and 44 mmHg (range: 21-57) in the second group (p= 0.93). Median postoperative IOP was 4.0 mmHg (range: 1.1-20 mmHg) in the first group versus 9.0 mmHg (range: 5 -12 mmHg) in the second group (p=0.02; Mann-Whitney *U* test). Median percentage IOP drop was 89.6 % (range: 58.3-98 %) in the first group as opposed to 80 % (range: 59-91.2%) in the second group (p=0.03).

Visual acuities were either stable or increased in 9 eyes in both groups (p=0.37; chi square test). Diminished visual acuities were detected in 8 eyes in the first group versus 4 eyes in the second group (p=0.37; chi square test).

Postoperative problems are summarized in Table 3. Hypotony and choroidal detachments were seen in 11 eyes in the first group and 3 eyes in the second group (p=0.02, chi square test).

In the first group, thinning and ulceration of the conjunctival bleb occurred in one patient (patient:13); this conjunctival defect re-epithelized after firm patching of the eye. No ulceration was seen in the eyes in the second group (p=0.57; Fisher exact test). Wound leakage was detected in 1 eye in the first group (patient 17). There was no wound leakage in the second group (p=0.57; Fisher exact test). Corneal epitheliopathy was not present in any of the groups . Lens opacities of varying degree were detected in 8 eyes (patients : 4, 7, 8, 9, 11, 12,13,14) in the first group versus 7 eyes (patients 1, 2, 4, 8, 9, 11, 12) in the second group (p=0.71; chi square test); three of these patients in the second group (patients 2, 4, 9) underwent subsequent cataract extraction. Cystic blebs were seen in 1 eye in the first group (patient 7) versus 4 eyes (patients 2, 6, 10, 12) in the second group (p=0.09; Fisher exact test).

Two patients in the first group (patients 8, 16) had elevated IOP and required additional medication to lower the IOP below 20 mmHg; no IOP elevation was detected in the second group (p=0.60; Fisher exact test).

Table I. Characteristics of the patients

Group I (Mitomycin C, 0.50 mg/ml concentration; 3+2 min)

No	Age	Sex	Eye	Preop IOP (mmHg)	Postop IOP (mmHg)	IOP drop %	Preop VA	Postop VA	Vision change	Bleb structure	Postop problems
1	63	M	L	60	13.6	77.3	nlp	nlp	0	diffuse	
2	66	M	R	37	5	86.5	10/10	10/10	0	prominent	hypotony
3	64	M	L	40	3.2	92	3/10	4/10	↑	prominent	hypotony
4	48	F	L	52	3.3	93.7	10 cm fc	p+p+	↓	prominent	hypotony
5	48	F	L	48	5	89.6	p+p+	1 m fc	↑	prominent	hypotony
6	70	F	R	40	3.6	91	2/10	3/10	↑	prominent	hypotony
7	76	M	R	52	4	92.3	10 cm hm	p+p+	↓	cystic	hypotony, ch. det.
8	64	F	L	48	20	58.3	4/10	3/10	↓	prominent	IOP
9	74	M	R	35	3.5	90	50 cm fc	30 cmfc	↓	diffuse	hypotony, ch. det.
10	71	F	R	55	1.1	98	1/10	2/10	↑	prominent	hypotony, ch. det.
11	65	M	R	38	10.3	73	5/10	2/10	↓	prominent	
12	43	F	R	38	3	92.1	3/10	30cmfc	↓	diffuse	hypotony, ch. det.
13	44	F	R	40	7.3	81.8	10/10	7/10	↓	prominent	hypotony, ch. det., disc swelling, bleb ulcer
14	50	F	R	34	10.3	69.7	8/10	7/10	↓	prominent	
15	81	M	R	30	4	86.7	3/10	3/10	0	prominent	
16	71	M	L	30	7.3	75.7	6/10	8/10	↑	prominent	IOP
17	77	F	L	30	2.7	91	p+p+	p+p+	0	diffuse	hypotony , ch. det., WL

Table I. Characteristics of the patients (continued)

Group II (Mitomycin C , 0.25mg/ml concentration; 3 min)

No	Age	Sex	Eye	Preop IOP (mmHg)	Postop IOP (mmHg)	IOP drop %	Preop VA	Postop VA	Vision change	Bleb structure	Postop problems
1	68	M	R	57	5	91.2	60cmfc	20cm hm	↓	prominent	
2	68	M	L	54	9.3	82.8	10cmfc	0.6*	↑	cystic	hypoton, ch. det.
3	65	M	R	32	12	62.5	2mps	0.4	↑	prominent	ch. det.
4	65	F	L	21	8.6	59	p+p+	0.8*	↑	prominent	
5	64	M	R	35	7	80	0.5	0.7	↑	diffuse	
6	69	M	L	48	7.6	84.2	p+ temp	p+ temp	0	cystic	
7	54	F	R	44	12	72.7	0.5	0.5	0	diffuse	
8	75	M	R	21	5	76.2	0.7	75cm fc	↓	prominent	
9	54	M	R	33	9.3	71.8	0.3	0.8*	↑	prominent	
10	70	M	L	56	9	83.9	0.2	0.4	↑	cystic	ch. det.
11	61	F	R	52	9	82.7	0.2	1mhm	↓	difuse	
12	65	M	R	45	11.3	74.9	0.3	p+p+	↓	cystic	
13	68	F	L	38	7	81.6	0.7	0.8	↑	diffuse	

VA: visual acuity; fc: finger counting; hm: hand motions; p+p+:perception and projection of light present; temp: temporal; nlp: no light perception; WL: wound leakage; ch.det.: choroidal detachment;
**received subsequent cataract extraction*

Table II. Intraocular pressure changes

	Preop IOP (median value with range)	Postop IOP (median value with range)	IOP drop (%) (median value with range)
1st Group (MMC , 0.50mg/ml; 3+2 min)	40 mmHg (30-60)	4 mmHg (1.1-20)	89.6 (58.3-98)
2nd Group (MMC ,0.25mg/ml; 3 min)	44mmHg (21-57)	9 mmHg (5-12)	80 (59-91.2)
p*	0.93	0.02	0.03

**Mann Whitney U test, MMC: Mitomycin-C*

Table III. Postoperative problems

	1st Group (MMC , 0.50mg/ml; 3+2 min)	2nd Group (MMC , 0.25mg/ml; 3 min)	p
Pressure rise (Postop TO>20mmHg)	2	0	0.60**
Hypotony choroidal detachment	11	3	0.02*
Disc swelling	1	0	0.57**
Lens opacities	8	7	0.71*
Cystic bleb	1	4	0.09**
Wound leakage	1	0	0.57**
Bleb ulceration	1	0	0.57**

**Chi squre test, **Fisher exact test, MMC: Mitomycin-C*

DISCUSSION

Although it is well documented that MMC effectively inhibits fibroblast proliferation, a well-known long term complication is hypotony or hypotony maculopathy (5, 6). MMC may also have a direct toxic effect on the ciliary epithelium (7).

To determine if MMC caused any damage to the ciliary body, Heaps and colleagues conducted a study with electron microscope revealing that ciliary body epithelial cells beneath the injection site were thinned at dosages of 0.1mg and higher; lower doses did not yield such results (8).

Hara and colleagues also reported pathologic changes of the ciliary epithelium, including intracellular vacuoles and swelling of mitochondria at eyes treated with 0.4mg/ml MMC. No such findings were reported at lower doses (9).

Turaçlı and his colleagues reported that MMC seemed to affect the proteoglycan cross-links between collagen fibrils at the electron microscopic level (10). Nuyts also reported pathologic changes at electron microscopic level (11). In another study, ciliary nerves exhibited destructive properties after the application of MMC (12). Topical MMC in rabbits yielded pathologic changes in the ciliary epithelium (13).

Several measures and treatment modalities have been tried for hypotonia. Corneal safety valve incision was reported to have decreased the incidence of hypotony(14). Surgical revision is a well known method with good results (15). While several authors had had favorable results with autologous blood injection under the scleral flap (16, 17), some others reported corneal blood staining (18, 19) and even severe visual loss after the injection (20). The scleral shield may be advantageous for reducing the incidence of hypotony maculopathy (21). Oversized bandage soft contact lens can also be a useful tool in the management (22). Hypotony maculopathy may be associated with scleral folds and such a case have been treated with pars plana vitrectomy (23).

Hypotony, on the other hand, is not always associated with maculopathy leading to visual loss. Our patients with postoperative hypotony in both groups did not have hypotony maculopathy and the hypotony usually resolved without medication within 6 to 8 weeks . A similar patient was reported by Kee and Kaufman; they reported a patient with hypotony without maculopathy, ongoing for over 23 months (24).

Cystic blebs are of concern since they carry the risk of rupture and bleb related endophthalmitis.

Mizoguchi et al. reported that the incidence of cystic blebs was 79 % in a series of 215 trabeculectomies with MMC (25) . Kim reported that there was a damage to the conjunctival epithelium in MMC filtering surgery (26). Decreased vascularity of filtering blebs may partially be due to a toxic effect of the agent on the endothelial cells of the conjunctival vessels (27).

Yamamato et al. evaluated cystic blebs ultrasonographically based on their reflectivity and concluded that eyes with good IOP control had low reflectivity (28) . In our study, cystic bleb was present in 1 eye in the first group and 4 eyes in the second group . Although the second group seemed to have higher number of cytic blebs, the difference did not reach statistical significance (p=0.09; chi square test). These patients were carefully monitored and received topical broad spectrum antibiotics; no serious infection occurred.

Incidence of endophthalmitis in the MMC trabeculectomies is usually higher than 5-fluorouracil trabeculectomies and the mostly isolated organisms were Streptococcal species (29). Greenfield reported that the incidence was 2.1% in a series of 773 trabeculectomies with MMC (30). Higginbotham reported this incidence as 2.6% (31). In inferior limbus trabeculectomies the risk was reported to increase to 11.9% (32). Other notable complication with the use of MMC is scleritis which has been reported to occur after MMC trabeculectomy (33). We observed wound leakage in one patient in the higher dose group; the patient was carefully followed with topical antibiotics; no infection occurred and the epithelization followed firm patching of the eye.

We used MMC trabeculectomy as a primary procedure and there is a debate with regard to this issue. Our patients, mostly non-compliant with the therapy had severe visual field losses and elevated IOPs as high as 70 mm Hg despite prescribed regiments; we considered them as high-risk patients and applied MMC as a primary procedure. Zacharia (34), Kitazawa (35) and Nuijts (36) also utilized MMC as the primary procedure and obtained favorable results .

Some of our patients had no light perception preoperatively ; although performing surgery on blind eyes is a controversial issue , examples may exist (37). Our patients were comfortable after the surgery, the outcome was favorable in terms of IOP reduction.

Our conjunctival flaps were limbus based; Berestka reported that no significant difference existed between limbus and fornix-based conjunctival flaps (38).

The appropriate dosage and duration of application of MMC is still controversial. While concentrations of 0.5 mg/ml have been used in earlier studies (39, 40, 41), others preferred 0.4 mg/ml (34, 42, 43), 0.2mg/ml (44, 45, 46) or even lower concentrations (35). Zacharia stated that there was a statistically significant association of hypotony with longer application time (34). The actual relation of MMC dosage to the formation of hypotony is as yet not known however, there is an increasing tendency towards reducing the dose of the MMC in many studies. Short time local application has also been suggested as an alternative to intraoperative application (47). In the first group, we used MMC at a concentration of 0.5 mg/ml for 3 min to the episclera and 2 min under the scleral flap . However, hypotony with or without choroidal detachment had been detected in 11 eyes. In the second group, the lesser dosage and application time yielded only 4 detached choroidals and the difference was statistically significant (p=0.02; Fisher exact test). Choroidal detachments generally settled with medical treatment within 6 to 8 weeks. In the first group, transient disc swelling accompanied hypotony in one patient . We have not encountered with disc swelling after reducing the dose in the second group .

Detectable amounts of MMC has been found in the aqueous humour within minutes of external application (48). Mietz et al. on the other hand

reported that the concentration of MMC in the sclera and the vitreous humour might be higher than that in the aqueous humour (49). The exact amount of MMC in the anterior chamber is yet to be revealed.

In the first group, visual acuity was decreased in 8 eyes whereas in the second group, it was decreased in 4 eyes (p=0.37; chi square test). Development of cataract was detected in all of the eyes with reduced vision.

Two eyes in the first group required additional postoperative medications to drop the IOP below 20 mmHg; no patients in the second group required such medication and the difference was not statistically significant (p=0.60; Fisher exact test).

We are aware of the fact that our study is a retrospective one and the results should be interpreted accordingly. In our study, lowering the concentration of MMC from 0.5mg/ml to 0.25mg/ml and the application time from 5 min to 3 min established favourable postoperative IOPs around 9mmHg with good functioning blebs. The incidence of hypotonous eyes was significantly lower than 5 min application. We conclude that adjusting the dose of this antimetabolite to lower levels is necessary for the success and safety of filtration surgery and application of the MMC at this dose and period may be considered as an acceptable method in the glaucoma filtering surgery.

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