·Clinical Research·

Trabeculectomy with large area mitomycin-C application as a first-line treatment in advanced glaucoma: retrospective review

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Abstract

• AIM: To evaluate the outcomes of trabeculectomy with large area mitomycin-C (MMC) application as a first line treatment in advanced glaucoma.

• METHODS: The records of 55 patients with severe visual field defects undergoing trabeculectomy were retrospectively reviewed. The patients were classified as first-line therapy to either early trabeculectomy (initial trabeculectomy-Group 1) or long term medical therapy followed by trabeculectomy (primary trabeculectomy-Group 2). Trabeculectomy was performed with large-area MMC application. Intraocular pressure (IOP) values, visual acuities, mean deviations, morphology and function of the blebs, necessity for anti-glaucomatous medications and surgical complications were reported.

• RESULTS: There were 20 eyes of 18 patients in Group 1 and 37 eyes of 37 patients in Group 2. The mean preoperative IOPs in Groups 1 and 2 were 40.2±10.0mmHg (27-68mmHg) and 29.0±4.4mmHg (21-41mmHg), respectively (P=0.001). Average preoperative mean deviations (MD) in Groups 1 and 2 were 17.4±2.8dB (13.3-23dB) and 17.9±2.4dB (13.7-23.2dB), respectively (P=0.441). Postoperative IOPs significantly decreased and were comparable in both Groups. The mean number of medications was significantly higher in Group 2 (P=0.005). No cystic bleb formation was observed in Group 1, whereas 4 patients from Group 2 (10.8%) developed cystic bleb (P=0.040). No visually devastating complication has occurred in both Groups.

• CONCLUSION: Initial trabeculectomy with large area MMC application might be applied in patients with advanced glaucoma with low complication rates. Long-term topically applied anti-glaucomatous medications seem to increase the risk of cystic bleb formation.

• **KEYWORDS:** trabeculectomy; advanced glaucoma; large area mitomycin-C application
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INTRODUCTION

Trabeculectomy has been a gold standard for the treatment of glaucoma for years since its introduction to ophthalmology literature [1]. Its success rate has been ranged between 55% and 98% in the current literature [1-3]. Conventionally, it is a treatment of choice in patients with high intraocular pressure (IOP) despite maximally tolerated medical therapy. Patients presented with advanced glaucomatous damage with high IOP and severe visual field loss at the time of diagnosis carry significant risk for further progression and blindness. On the other hand, loss of central vision called "wipe-out" phenomenon might be encountered more frequently in patients with advanced glaucomatous damage even after the uncomplicated filtrating surgery[4,5].

These patients usually have to use various topical anti-glaucomatous agents for years before undergoing surgery. During this interval, disease may sometimes progress despite all measures. However, long-term topical anti-glaucomatous drug use was also been shown to induce subclinical conjunctival inflammation that was further linked to the failure of subsequent filtration surgery[6,7].

Several studies have shown superiority of initial trabeculectomy than conventional management to control the disease progression in newly diagnosed open angle glaucoma (OAG), irrespective of disease severity that also weakens the integrity of the study results[8-11].

Extend of IOP fluctuations before surgery and advanced

visual field loss at the time of diagnosis were reported to be associated with more visual field progression over long-term follow up in Collaborative Initial Glaucoma Treatment Study (CIGTS) [12]. The patients who have more dense baseline visual field scotomas (-10dB) showed better visual field control over time if treated with initial trabeculectomy other than medications. Many glaucoma specialists have a marked tendency to perform filtration surgery as a first line therapy in advanced disease but sufficient clinical evidence to justify this conviction does not exist[9,10].

Trabeculectomy with large area mitomycin-C (MMC) application have been a surgical treatment of choice in our clinical practice with diffuse blebs and low complication rates despite increased application area of MMC [13]. In the present study, we investigated the outcome of initial trabeculectomy with large area MMC application and to compare its results with trabeculectomy with large area MMC application after long term medical therapy in advanced glaucoma.

SUBJECTS AND METHODS

Subjects Records of 57 eyes of 55 primary open angle glaucoma (POAG) or pseudoexfoliative glaucoma (PXG) patients with advanced glaucoma that underwent trabeculectomy were included into study. Institutional ethics committee approval for the retrospective chart review was obtained. Patients were informed about the use of their medical records. Patients were divided into two groups. Complete ophthalmological examination had been performed in all study subjects including best corrected visual acuity with Snellen charts, IOP measurements with Goldman applanation tonometry, fundoscopy and cup-to-disc ratio assessments, gonioscopy and visual field analysis with Humphrey automated perimeter. Patients with a history of neovascular glaucoma, uveitic glaucoma, ocular surgery and other ocular conditions predisposing to optic neuropathy were excluded from the study. Diagnosis of advanced glaucoma was based on increased IOP (>21mmHg), glaucomatous cupping of optic disc (severe loss of neuroretinal rim at least three quadrants of the optic disc) and advanced glaucomatous visual field defects [with a mean deviation (MD) value of ≥12dB]. Advanced visual field defect was defined as sensitivity of ≤5dB either in >85% of test points, excluding the central four test points, or in >75% of test points including three of the central test points with threshold automated perimetry SITA standart 30-2 program of Humphrey Field Analyser (Carl Zeiss Meditec, Dublin, CA, USA).

Patients who had underwent trabeculectomy as soon as possible without long term antiglaucomatous therapy comprised Group 1 (initial trabeculectomy). On the other hand, patients who had been conventionally treated with maximal tolerated medical therapy at least 2 year comprised Group 2 (primary trabeculectomy). Only short term (5-7d) topical anti-glaucomatous treatment had been given in Group 1, just to avoid peroperative surgical complications related to sudden decrease in IOP. All of the surgeries had been performed by the same surgeon (Onolm).

Some of the patients who were included into our previously published paper and met the current inclusion criteria were also included in this study[13].

Methods Trabeculectomy with large-area MMC application in all cases was performed as previously described by Onol *et al* [13] A limbus-based conjunctival incision was performed 8-9mm posterior to the limbus and sclera was exposed after the blunt dissection of Tenon's capsule and conjunctiva (approximately between 11 and 1 o'clock). Conjunctiva was also undermined nasally and temporally via blunt dissection with Weskott scissors parallel to the limbus to create additional filtration areas (approximately between 9 and 3 o'clock). Before scleral flaps were dissected, 4mm ×4mm piece of sponge soaked with MMC was placed under the Tenon's capsule both temporally and nasally in addition to scleral flap area. MMC was applied for 2min with the dose of 0.2mg/mL. Then MMC application area was irrigated with balanced salt solution and a scleral flap of 5mm×5mm was dissected. When the entire corneoscleral limbus was exposed, trabeculectomy was performed with the excision of approximately 1mm ×3mm trabecular block followed by a peripheral iridectomy. Scleral flap was repositioned with three 10/0 monofilament nylon sutures and adjusted in such a manner that anterior chamber kept its depth allowing slow leakage from the edge of the scleral flap. The Tenon's capsule was closed with three interrupted and the conjunctiva was then closed with running 8/0 vicryl suture, respectively. Topical dexamethasone and antibiotic drops were given in all cases four times a day for 3 weeks. Dexamethasone was tapered during this time.

Preoperative informations including age, sex, IOP, cup-to-disc ratios and number of anti-glaucoma medications were recorded. Postoperative data including IOP, bleb morphology and function, the number of anti-glaucoma medications and complications related to surgery were retrospectively evaluated. Hypotonia was described as IOP measured ≤6mmHg. Target pressure was accepted as ≤14mmHg because of the advanced disease. IOP of ≤14mmHg without medication was accepted as complete surgical success whereas IOP of ≤14mmHg with any medication was defined as qualified surgical success. IOP of

Table 1 Pre- and post-operative MD values and IOP measurements in groups 1 and 2

Groups	Preoperative	The 6th months	The 1st year	The 2nd year	*P*
MD					
Group 1	17.4±2.8 (13.3-23)	17.5±2.9 (13.5-23)	17.7±2.9 (13.7-23.5)	18.6±2.7 (13.7-23.8)	[1](0.881, 0.704, 0.624)
Group 2	17.9±2.4 (13.7-23.2)	18.4-2.5 (14.0-23.6)	18.8±2.5 (14.3-23.6)	19.0-2.5 (14.5-23.8)	[1](0.425, 0.143, 0.057)
[2]*P*	0.441	0.238	0.157	0.106	
IOP					
Group 1	40.2±10.0 (27-68)	11.7±1.1 (10-14)	11.4±1.2 (10-14)	12.3±2.1 (10-17)	[3](0.001, 0.001, 0.001)
Group 2	29.0±4.4 (21-41)	11.5-2.0 (6.0-18.0)	11.6-2.3 (7.0-17.0)	11.2±2.5 (6.0-18.0)	[3](0.001, 0.001, 0.001)
[2]*P*	0.001	0.697	0.722	0.114	

MD: Mean deviation; IOP: Intraocular pressure; [1]Comparison between pre- and post-operative MD values either in groups 1 and 2; [2]Comparison between groups 1 and 2; [3] Comparison between pre- and post-operative IOP values either in groups 1 and 2.

>14mmHg with maximum medical treatment necessitating reoperation was defined as surgical failure.

Statistical Analysis IOP measurements, surgical successes and complications were compared by using Mann-Whitney *U*, independent samples *t*-test and Chi-square tests and correlations between number of preoperative medications and postoperative IOP and cystic bleb formation were evaluated with Spearman correlation test. SPSS version 11.0 system for personal computer was used and *P*-value of less than 0.05 was considered to be statistically significant.

RESULTS

There were 20 eyes of 18 patients in Group 1 and 37 eyes of 37 patients in Group 2. Mean ages of patients were 65.4±10.3 years (45-80 years) and 62.1±9.3 years (48-76 years) in Groups 1 and 2, respectively (P=0.312). Postoperative follow-up times were 24.9±1.3 months (24-27 months) and 25±1.1 months (24-28 months) (P=0.233). Thirteen patients (72.2 %) had PXG in Group 1 whereas 17 patients (45.9 %) in Group 2. Average preoperative MDs in Groups 1 and 2 were 17.4±2.8dB (13.3-23dB) and 17.9±2.4dB (13.7-23.2dB), respectively (P=0.441). The mean c/d ratios were also similar in both groups, determined as 0.84±0.06 (0.7-1.0) and 0.82±0.07 (0.7-1.0), respectively (P=0.785). The mean preoperative IOPs in Groups 1 and 2 were 40.2±10.0mmHg (27-68mmHg) and 29.0±4.4mmHg (21-41mmHg), respectively (P=0.001).

Postoperative IOPs were found to be decreased significantly but were found to be comparable in both Groups at 6th month, 1st and 2nd year. Postoperative MD values at 6th month, 1st and 2nd year in both groups were comparable and but it was tended to be more progressive in Group 2 (Table 1).

In Group 2, anti-glaucoma medications were carbonic anhydrase inhibitors, prostaglandins beta-blockers and alpha-adrenergic agonists. The mean duration of treatment was 6.0±1.5 years (2-8 years) in Group 2. In Group 1, mean number of topical anti-glaucoma medications was 0.05±0.2 (0-1) at 2nd year postoperatively in Group 1 (P=0.330). The mean number of topical anti-glaucoma medications in Group 2 was 3.3±0.7 (2-4) preoperatively whereas it was 0.4±0.7 (0-3) at 2nd year after the filtrating surgery (P=0.001). Postoperative number of anti-glaucoma medications was significantly different in both groups (P=0.005). The correlation between preoperative number of anti-glaucoma medications and postoperative IOP values was not statistically significant (r=0.133, P=0.575).

At the end of the second year, complete success was achieved in 18 eyes (90%) *vs* 25 eyes (67.6%) in Groups 1 and 2, respectively. Qualified success was achieved in 19 eye (95%) and 34 eyes (91.9%), respectively (P=0.653; P=0.950; Chi-square test.

In Group 1, pre and postoperative visual acuities ranged between hand movements and 20/20 which was equivalent to 0.35±0.54 (0.0-1.8)logMAR and 0.38±0.53 (0.0-1.8)logMAR (P=0.248). In Group 2, pre and postoperative mean visual acuities were 0.52±0.46 (0.0-1.8) and 0.57±0.46 (0.0-1.8) (P=0.526). In Group 1, 1 patient and in Group 2, 2 patients had decreased vision due to cataract and had been operated. Visual acuities increased after the operation. Wipe out phenomenon wasn't been encountered in any of the patients during follow up period.

There was no peroperative complication. Hypotonia was seen in 1 eye in Group 2 (2.7%) whereas none in Group 1 (P=0.950). Cystic bleb was observed in 4 eyes (10.8%) in Group 2, whereas none in Group 1 (P=0.040). No statistically significant correlation between number of preoperative anti-glaucoma medications and cystic bleb formation was found (P=0.688, r=0.096). Nonfunctional cystic blebs were treated by subsequent needling procedure successfully.

DISCUSSION

The aim of the trabeculectomy surgery is to decrease IOP, prevent further visual field loss and increase patient's quality of life. Even the target IOPs are achieved with medical therapy, visual field loss may occur because of IOP fluctuations which also further cause visual field loss. On the other hand, one can think that medical therapy seems safe

since surgical complications such as "wipe-out" phenomenon is are more frequently encountered in patients with advanced glaucoma [4,5]. Thus, in patients with advanced glaucoma with guarded prognosis, decision of going on with surgery or medical therapy is controversial. However, trabeculectomy as a first-line treatment seems to be advantageous because it leads to less visual field loss especially in advanced cases (-10dB) and to decreased drug-related side effects leading to bleb failure[6-12].

Some of glaucoma clinicians have a preconception that long-term anti-glaucoma medication prior to surgery may reduce the success rate of trabeculectomy. Failure of filtering surgery is attributed to excessive wound healing reaction during the early postoperative period which results in intense subconjunctival fibrosis[14]. Broadway *et al*[6] investigated the effect of topical anti-glaucoma medication on the cell population of conjunctiva in 124 patients undergoing filtration surgery by light microscopy. The patients were subdivided into four groups depending on medications used before surgery. They found that increased subclinical inflammation was associated with multiple drug therapy use for more than 3 years. All topical medications contained preservative, and the authors thought that subclinical conjunctival inflammation may correlate might have correlated with the duration of exposure to preservatives. Baudouin *et al* [15] confirmed anti-glaucomatous drug's effect on conjunctiva, and showed that the greater part of toxic or inflammatory effect was attributable to preservatives included. These factors should be taken into account especially in advanced cases in which diffuse and functional blebs are strongly needed to control IOP.

Broadway *et al* [7] also reported gradually lower success rate of trabeculectomy in multi-drug treated eyes. Lavin *et al* [8] achieved higher surgical success rate with initial trabeculectomy than trabeculectomy after multiple drug therapy for at least one year. On the other hand, these studies were thought to have low reliability because of methodological weakness due to heterogenous study groups and available topical medications in these times.

In our study, we aimed to investigate the results of trabeculectomy with large area MMC application in advanced glaucoma as a first-line treatment. We found that IOP significantly reduced in both groups but the need for an additional anti-glaucoma medication was found to be significantly higher in Group 2 and success rates were higher in Group 1. Although we did not perform histological analysis, we thought that further chemical inhibition provided by large-area MMC application might have masked the conjunctival inflammatory changes leading to bleb failure in Group 2. This might have been the reason for similar IOP decrease observed in both groups.

Long-term topical medication has also been implicated in development of encapsulated blebs [16]. We also noted higher cystic bleb formation associated with long-term medication use prior to surgery in our study. The management of patients presenting with advanced visual field loss and optimum time for trabeculectomy in these patients exist as an important problems since the presentation with marked visual field loss and high IOPs are major risk factors for further disease progression and blindness[17-19].

Many ophthalmologists avoid early trabeculectomy because of potential devastating complications especially reported in patients with advanced glaucoma [4,5]. According to the previous reports, initial trabeculectomy was superior to conventional management in newly diagnosed OAG, irrespective of disease severity[9-11]. Jay *et al* [10] divided newly diagnosed primary OAG patients into two groups according to first line treatment; conventional medical treatment followed by trabeculectomy or initial trabeculectomy followed by short term medical therapy. They observed that when medical treatment was preferred as a first line, need for filtering surgery at 1st year was 32% and after 4 years follow-up, it increased to 53%. The mean IOP was found significantly lower in surgery group (15mmHg) than that of medical treatment group (20.8mmHg) at 1st year. Migdal *et al* [11] allocated newly diagnosed glaucoma patients into the one of the medical, laser trabeculoplasty or trabeculectomy groups to compare the outcomes of first line treatments. IOP of less than 22mmHg was accepted cut off point for the successful treatment. Over 5 years follow up, success rates for surgery, medical and laser groups were found as 98%, 83% and 68% and the superiority of primary trabeculectomy was emphasized. They concluded that long term use (>1 year) of glaucoma medications might adversely affect the results of fistulizing surgery.

Studies mentioned above have been referenced as a good evidence for long term medical therapy can adversely affect the surgical results[7,8,10,11]. On the other hand, it's been thought that there are some selection bias in these studies [20]. Lavin *et al* [8] compared primary trabeculectomy group with more advanced multiple treatment group.

In the current study, we evaluated the results of trabeculectomy with large area MMC application as a first line treatment in advanced glaucoma. The prospective, randomized trial indicating that the most appropriate initial intervention in patients presenting with highly advanced glaucoma is not available in the current literature. CIGTS interim report showed no different effect on subsequent

visual field loss between initial medication and trabeculectomy [21]. However, a recent report from CIGTS analyzing subgroup of patients who presented more advanced visual field (MD -10dB) or have high IOP variation preoperatively noted that initial surgery was superior to initial medication to prevent further visual field loss over 8 years follow-up[12].

The efficient treatment for glaucoma is lowering IOP. Advanced glaucoma intervention study (AGIS) showed that keeping IOP less than 18mmHg permanently over 6 years follow-up was essential to develop no further visual field loss [22]. However, in this study, patients that did not progress had a mean IOP of 12.3mm Hg over 6 years follow-up [22]. In our practice we usually prefer to set a target pressure as a 15mmHg in moderate to advanced cases [13]. In the current study, most of the patients had cup to disc ratios more than 0.8 with an advanced glaucomatous visual field losses (with mean MD values of 17.4±2.8 (13.3-23) and 17.9±2.4 (13.7-23.2), respectively), so surgical success limit was accepted as 14 mmHg which seems reasonable.

At the end of the second year, complete success was achieved in 18 eyes (90%) *vs* 25 eyes (67.6%) in Groups 1 and 2, respectively. Qualified success was achieved in 19 eye (95%) and 34 eyes (91.9%), respectively (P=0.653; P=0.950; Chi-square test). Complications reported to be associated with advanced glaucoma such as wipe-out phenomenon was not encountered in both groups. Hypotonia was seen in 1 (2.7%) patient in Group 2. Cystic bleb was encountered 4 (10.8%) patients from Group 2 supporting the relationship between cystic bleb formation and multiple anti-glaucoma medication use.

As far as we know "filtration surgery" results in lower IOP with reduced fluctuations so it may be more effective for halting progression than medical therapy in the case of severe glaucoma. Intraoperative MMC application also enhances IOP reduction when used as an adjuctive to trabeculectomy. We have been performing trabeculectomy with large area MMC application with high success rate, more diffuse blebs and lower complication rates [13]. However, trabeculectomy with MMC have some potential and severe complications such as cataract development, bleb-related problems (bleb leak and blebitis) and endophthalmitis. Early complications of trabeculectomy include hypotonia with the development of hypotonous maculopathy, choroidal effusions. Wipe-out is an irreversible loss of central vision but this severe complicaton occurs in a very small percentage of patients after the filtration surgery and it is usually considered as exceptional with the current modern surgical techniques. Reported incidence of this devastating complication ranged between 0 to 0.95% of surgeries[23].

To minimize these early and late complications, alternative surgical methods have been popularized. They are usually designed to increase outflow by using a new channel (Ex-PRESS glaucoma implant) or augmenting conventional trabecular outflow (canaloplasty, Trabectome, trabecular micro-bypass stent) [24]. However, most of these techniques need to be supported by future studies. Moorfields safer surgery system is also another alternative technique that has been recommended for increasing surgical success while minimizing surgical complications[25,26].

In the current study, we have shown that large area MMC application in highly advanced glaucoma as a first line treatment seems to be safe without visually devastating complications such as hypotonia and wipe-out phenomenon. It has also the advantages of more diffuse bleb morphology which is desired for long-term IOP control. Similar IOP values were also found in Group 2 might have resulted from large area MMC application. On the other hand, need for additional therapy was significantly higher and MD values were tended to be progressive in Group 2.

There are some limitations of our study. The postoperative IOP values and MD values were not significantly different in both groups. Although cystic bleb was observed in 4 eyes (10.8%) in Group 2, none in Group 1 (P=0.040), assessment of bleb morphology and function remains essentially subjective. Furthermore, retrospective nature of the study also limits the data extraction.

In conclusion, trabeculectomy with large area MMC application as a first-line treatment might be an efficient and safe method compared with long term medical therapy in advanced glaucoma without causing visually devastating complications such as hypotonia and wipe-out phenomenon. On the other hand, future well-designed, controlled, prospective studies are needed to justify the importance of initial surgery in advanced disease.

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