

# DOES MEDICAL TREATMENT INFLUENCE THE SUCCESS OF TRABECULECTOMY?

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BY *Allan Joseph Flach PharmD MD\**

## ABSTRACT

*Purpose:* Many ophthalmologists believe that long-term use of topically applied glaucoma medications can adversely affect results of fistulizing surgery. This presentation critically analyzes the published studies most often cited in support of this view to determine whether this conclusion is justified.

*Methods:* Morphologic effects of long-term treatment with antiglaucoma drugs on the conjunctiva and Tenon's capsule in glaucomatous patients have been studied. The results of these studies encouraged investigators to examine the influence of prior therapy on the success of trabeculectomy performed in patients with open-angle glaucoma. From this work, many have concluded that long-term use of topically applied glaucoma medications can adversely affect the results of fistulizing surgery. These results and conclusions are summarized and critically analyzed to determine whether this conclusion is justified.

*Results:* Morphologic studies describe increased numbers of macrophages, fibroblasts, lymphocytes, and mast cells in conjunctival and Tenon's capsule specimens taken from patients receiving long-term antiglaucoma drugs. These findings suggest a potential for more inflammation and subsequent scarring following trabeculectomies in these patients. Efforts to confirm the clinical relevance of these histologic findings in open-angle glaucoma patients with a history of long-term antiglaucoma medication prior to surgery have been published. These retrospective, nonrandomized, unmasked studies of open-angle glaucoma patients include treatment groups and surgeries that are not comparable. In addition, the medical treatments within these studies do not reflect our current approaches to the medical management of open-angle glaucoma.

*Conclusions:* At present, there is no convincing clinical evidence that long-term medical treatments influence the success of contemporary trabeculectomy surgery performed on open-angle glaucoma patients.

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## INTRODUCTION

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Many ophthalmologists believe that long-term administration of topically applied glaucoma medications can adversely affect the results of subsequent fistulizing surgery. This belief is based on the results of histologic examinations and clinical studies of patients with open-angle glaucoma with and without prior long-term medical treatments.<sup>1-5</sup> These studies provide histologic evidence that long-term medical treatment of open-angle glaucoma induces a subclinical conjunctival inflammation that may predispose to scarring.<sup>1,2</sup> Furthermore, subsequent clinical studies provide results that have encouraged investigators to conclude that long-term medical treatment of open-

angle glaucoma patients is detrimental to the outcome of trabeculectomy surgery.<sup>3,5</sup> The purpose of this presentation is to summarize and critically review the results and conclusions of these studies in an effort to determine whether this conclusion is justified.

## METHODS

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The morphologic effects of long-term glaucoma drug treatment on the conjunctiva and Tenon's capsule in open-angle glaucoma patients have been studied.<sup>1,2</sup> The results of these studies indicate that long-term medical therapy, administered before fistulizing surgery is performed, increases the number of tissue inflammatory cells. These histologic observations suggest that extensive medical treatment induces a subclinical inflammation that may enhance the risk of external bleb scarring and filtration surgery failure. This clinical speculation encouraged investigators to study the influence of prior medical therapy on the success of trabeculectomy performed in

From the Department of Ophthalmology, University of California, San Francisco, Medical Center, San Francisco, California.

\*Presenter.

Bold type indicates **AOS** member.

open-angle glaucoma patients in an attempt to link the histologic laboratory observations with an undesirable surgical outcome.<sup>3,5</sup>

Two groups of patients with open-angle glaucoma, one group with a history of long-term medical treatment (1 year to 17 years) and the other with less than 8 weeks of treatment, were carefully examined after glaucoma filtering surgery. The intraocular pressures (IOPs) of all of these open-angle glaucoma patients were measured and compared 18 months after surgery. The results of this retrospective, unmasked clinical study encouraged investigators to conclude that the use of topically applied glaucoma medications for 1 or more years can adversely affect the results of fistulizing surgery.<sup>3</sup>

Furthermore, a second clinical study reports confirmation that long-term topical therapy has adverse effects on the conjunctiva and that these detrimental changes correlate with failure of trabeculectomies.<sup>4</sup> These results and the associated conclusions are summarized and critically analyzed in an effort to determine whether it is justified to conclude that the success rate of contemporary trabeculectomy performed in open-angle glaucoma patients is jeopardized by long-term medical treatment.

## RESULTS

Conjunctival and Tenon's capsule biopsies from patients with and without long-term medical treatment were analyzed by light microscopy.<sup>1</sup> Group A consisted of 20 patients with a mean age of 58, all with open-angle glaucoma and a history of no more than 3 weeks of treatment with pilocarpine. These patients represent the primary surgical treatment group. Patients within group B had a mean age of 65 and were treated with at least two glaucoma medications for at least 1 year (mean, 7.7 years) before surgery. Both groups of patients submitted biopsy specimens for histologic examination by masked observers who were unaware of the patients' prior treatments. Specimens taken from the patients who received long-term glaucoma medication (group B) demonstrated increased numbers of macrophages, fibroblasts, lymphocytes, and mast cells within conjunctiva and Tenon's capsule as compared to specimens from patients receiving minimal treatment. In addition, there appeared to be a decrease in goblet cells in group B. Subsequently, the results of a more extensive histologic study of 126 patients comparing various medical treatment regimens and their influence inducing subclinical inflammation within the conjunctiva prior to filtration surgery supported this observation.<sup>2</sup>

These histologic observations demonstrate that more subclinical inflammation exists within the conjunctiva of patients who have received extensive medical therapy as

compared to minimal medical treatment. These histologic results have encouraged speculation that the subclinical inflammation induced by long-term medical therapy may increase the chance of bleb failure after filtration surgery. This potential conclusion, in turn, suggests important questions regarding the optimum time for filtration surgery and the use of medications in the management of patients with open-angle glaucoma.

Therefore, these clinically relevant speculations prompted investigators to design clinical studies to investigate the effect of previous medical therapy on the outcome of subsequent glaucoma filtration surgery in an effort to correlate the observed histologic observations of subclinical inflammation with clinically significant scarring and fibrosis resulting in failed trabeculectomies.<sup>3,5</sup> A pivotal clinical study compares two groups of open-angle glaucoma patients 18 months after filtration surgery.<sup>3</sup> One group consists of 47 eyes of 47 patients with less than 8 weeks of medical treatment. This is the primary trabeculectomy (PT) group. The subjects within the PT group are taken, retrospectively, from a prior clinical study that compared the results of medical, laser, and surgical treatments of open-angle glaucoma patients.<sup>5</sup> The second group is composed of 43 eyes of 34 patients with 1 to 17 years of medical treatment. This group is identified as the multiple treatment (MT) group. An IOP of less than 21 mm Hg without treatment is considered a surgical success, whereas an IOP greater than 21 mm Hg without treatment is considered a failure. The results of this study show a significant difference in surgical success between the MT group (9/43 failed) and the PT group (1/47 failed) with  $P < .005$ . In addition, at 3 months following surgery, the PT group had IOPs of  $13.5 \pm 5.7$  mm Hg as compared to the MT group, which had IOPs of  $18.1 \pm 9.9$  mm Hg ( $P = .008$ ). The investigators conclude that long-term use (>1 year) of topically applied glaucoma medications can adversely affect the results of fistulizing surgery. These conclusions have influenced the clinical use of glaucoma medications during the medical treatment of open-angle glaucoma patients. Furthermore, this speculation suggests that early trabeculectomy may be a more conservative and less risky alternative to long-term medical treatment of open-angle glaucoma patients.

## DISCUSSION

Medical treatment of open-angle glaucoma can induce undesirable changes within the conjunctiva and Tenon's capsule. In addition to the transient conjunctival changes related to allergy and toxicity that most topically applied eye drops can induce, the parasympathomimetics and sympathomimetics can be associated with cicatricial pemphigoid.<sup>6,5</sup> Early developed beta blockers such as

practolol commonly caused scarring of the conjunctiva, and even commercially available timolol has been associated with drug-induced ocular pemphigoid in at least two cases.<sup>7,8</sup> Furthermore, carbonic anhydrase inhibitors are known to occasionally induce Stevens-Johnson syndrome with severe conjunctival scarring.<sup>9,10</sup> Finally, investigators have reported that exposure to topical antiglaucoma medications for more than 3 years is associated with a significant foreshortening of the inferior fornix secondary to conjunctival fibrosis.<sup>11</sup> These clinical observations suggest that a possibility for enhanced postoperative scarring of surgically created filtering blebs might be more likely in patients receiving long-term antiglaucoma medications. In fact, many believe that the continuing use of miotics prior to filtering surgery increases the likelihood of surgical failure.<sup>12</sup> In spite of these reports and studies, there has been general agreement that surgical treatment of open-angle glaucoma is indicated only after maximally tolerated medical treatment has failed.

However, in recent years studies of conjunctiva and Tenon's capsule have demonstrated increased inflammatory cells in patients receiving long-term open-angle glaucoma therapy as described above.<sup>12</sup> These results suggest that extensive medical therapy before surgery may enhance the risk of external bleb scarring and filtration surgery failure. Therefore, investigators and clinicians have awaited a well-designed clinical study to support this speculation. Such an investigation might link the laboratory finding of subclinical inflammation within the conjunctiva to an enhanced scarring of the surgical bleb with failure of filtering surgery. This would change the approach to the medical treatment of open-angle glaucoma.

During the past 10 years, the results of clinical studies have been referenced with authority as good evidence that long-term medical therapy of open-angle glaucoma (>1 year) can adversely affect the results of fistulizing surgery.<sup>3,5</sup> The suggestion that medical therapy for open-angle glaucoma patients may be counterproductive and encourage the failure of filtering procedures represents a major change in thinking that essentially redefines conservative treatment of open-angle glaucoma patients. This dramatic change in therapeutic attitude requires a rigorous, properly controlled, well-designed clinical study as support. However, this study does not exist.

The most commonly quoted clinical study that concludes that long-term treatment can adversely affect the results of fistulizing surgery is not randomized, prospective, or masked.<sup>3</sup> Therefore, the potential for bias has not been properly controlled. In fact, there is clear evidence for bias within this study because the subjects within the PT group, patients with minimal medical treatment, were selected from a group of subjects reported

within a prior study. More specifically, the 47 subjects used in this pivotal study as the minimally treated control are selected from a group of 57 subjects that were reported in a prior study.<sup>5</sup> It remains unclear how and why the 10 subjects present within the initial study but absent from the subsequent study were eliminated.

In addition to potential subject-selection bias, this pivotal study is weakened because there is evidence that the two groups being compared in terms of postoperative IOP after 18 months are not comparable at baseline in several important ways. As summarized in Table 1, the MT group demonstrates more advanced visual field defects and a greater duration of disease and has more subjects with a history of laser surgery than does the PT group. Furthermore, all of the subjects in the MT group are by definition medical treatment failures. The PT group, which consists of newly diagnosed open-angle glaucoma, may have, at best, only 20% of its subjects that will ultimately become treatment failures.<sup>3</sup> These differences suggest that open-angle glaucoma is present in a more advanced form in the MT group compared with the PT group. In addition, the presence of subjects with a history of laser treatment within the MT group may influence the results of trabeculectomy surgery in these patients, because eyes treated with laser trabeculectomy before filtration surgery have been reported to have a decreased probability of successful surgery.<sup>13</sup>

Although these important differences between the two groups significantly weaken the integrity of the study, an even more critical consideration is whether all of the subjects within the PT group really have open-angle glaucoma. The likelihood that this disease is not present is greater in subjects having had the diagnosis for 8 or fewer weeks than in subjects having had the diagnosis for 1 to 17 years. This possibility seems particularly reasonable in light of recent studies showing that visual field defects observed in open-angle glaucoma patients require confirmation to ensure their presence.<sup>14</sup> This diagnostic requirement is much more likely to have been fulfilled within the MT group than the PT group, because the subjects within the PT group, by definition, had their diagnosis of open-angle glaucoma for only 8 or fewer weeks prior to their surgery. This limited time period is hardly sufficient to confirm visual field defects in potential open-angle glaucoma patients on three separate occasions.

It is recognized that preoperative use of miotics can influence the success of glaucoma filtering procedures.<sup>12</sup> Although the anticholinesterase agents are most clearly implicated, all of the parasympathomimetics are capable of disrupting the blood-aqueous barrier and changing the chemical composition of the aqueous humor. It is possible that more of the filtering procedures within the medically treated group would have been successful if the miotics

TABLE 1. PREOPERATIVE COMPARABILITY OF PRIMARY TRABECULECTOMY (PT) AND MULTIPLE TREATMENT (MT) GROUPS\*

VARIABLE	PT GROUP	MT GROUP
Presenting visual field defects	Early	Advanced
Duration of disease	Days/weeks	1-17 years
History of failed medical treatment	20% of group destined to fail treatment	100% of group
History of prior laser surgery	No	Yes (25% of group)

\*PT group has less than 8 weeks of medical treatment. MT group has 1 to 17 years of medical treatment.

TABLE 2. PREOPERATIVE, OPERATIVE, AND POSTOPERATIVE COMPARABILITY OF SURGICAL PROCEDURES IN PRIMARY TRABECULECTOMY (PT) AND MULTIPLE TREATMENT (MT) GROUPS\*

VARIABLE	PT GROUP	MT GROUP
Preoperative intraocular pressures	Higher	Lower
Consultant performed surgery	8%	20%
Shallow postoperative anterior chambers	23%	6%

\*PT group has less than 8 weeks of medical treatment. MT group has 1 to 17 years of medical treatment.

TABLE 3. GLAUCOMA MEDICATIONS USED BY SUBJECTS IN MULTIPLE TREATMENT (MT) GROUP\*

MEDICATION	DRUGS USED BY ALL SUBJECTS IN MT GROUP	DRUGS USED BY ALL SURGICAL FAILURES IN MT GROUP
Pilocarpine	91%	100%
Epinephrine	60%	89%
Timolol	74%	67%
Guanethidine/epinephrine	27%	56%

\*MT group has 1 to 17 years of medical treatment with multiple medications.

had been discontinued at least 3 days prior to surgery, as some have recommended.<sup>12</sup>

In addition to concerns about the comparability of the two groups prior to surgery, it appears that the surgeries provided the two groups might not be comparable. The presenting IOPs are higher in the PT group. Furthermore, consultants performed more than twice as many of the surgeries in the MT group. Finally, there were almost four times as many shallow chambers following surgery in the PT group, compared with the MT group (Table 2). These differences may have influenced the long-term results of surgery, including the number of failures observed 18 months following surgery.

A final consideration is whether the results of this study and its subsequent conclusions can be extrapolated to the current treatment of open-angle glaucoma patients. Table 3 summarizes the medications used in the MT group and, in particular, the medical treatment that the surgical failures received prior to trabeculectomy.

Pilocarpine and epinephrine were used in 100% and 89%, respectively, of the surgical failures in this study. These parasympathomimetic and sympathomimetic drugs are used much less extensively as part of the current medical treatment of open-angle glaucoma. Furthermore, the guanethidine-epinephrine combination, which was used in 56% of the surgical failures, has never been used in the United States. Therefore, it is clear that the current medical therapy for open-angle glaucoma is different from the medical treatments used within this study.

A subsequent study of 124 patients was published in support of the findings of the pivotal study discussed above.<sup>4</sup> This study concludes that its results show that topical therapy has an adverse effect on the conjunctiva and that these changes correlate with the failure of trabeculectomies. However, this investigation has the most worrisome of the shortcomings within the previously published study.<sup>3</sup> In addition, the more recent study has fewer subjects in the minimal treatment group, has a shorter

follow-up period, and includes a group with minimal treatment that is even more highly selected than the previous study. Therefore, it is difficult to accept the publication's conclusion that good evidence exists showing that early surgery is more likely to be successful and more likely to reduce disease progression in open-angle glaucoma patients.<sup>4</sup>

In summary, there is no convincing evidence that long-term medical treatment as used today influences the success of contemporary trabeculectomy surgery. Existing evidence makes it appropriate to agree with investigators who believe that preoperative use of topical medication does not influence the outcome of surgery.<sup>13</sup> The studies that attempt to justify early surgery are all potentially biased, based on postoperative comparisons of groups that are not comparable at baseline, and include medical treatments that do not reflect current treatment regimens. Therefore, it seems only prudent to employ long-term medical treatment of open-angle glaucoma in our open-angle glaucoma patients, delaying filtering surgery until maximal tolerated medical treatment fails.

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## DISCUSSION

DR MAX FORBES. Although the inflammatory changes in the conjunctiva reported by the Moorfields group are quite real, the comparative surgical outcomes are unreliable and probably overblown as Dr Flach indicated. There is no reason to change the conventional therapeutic strategy in open-angle glaucoma from medication-first to trabeculectomy-first on the basis of unproven results.

The case seems closed, but not quite. Just because an adverse effect of chronic topical antiglaucoma medical therapy on filtration surgery has not been proven does not necessarily mean that such an effect is not true. In fact, there is a current ongoing prospective, randomized, controlled clinical investigation, the Collaborative Initial Glaucoma Treatment Study, that is comparing the long-term outcomes of trabeculectomy-first versus medication-first, laser trabeculoplasty-next, and then trabeculectomy, if needed. Dr Paul R. Lichter, the Study Chairman, is the co-author of an interim five-year report.<sup>1</sup> When a sufficient number of the medication-first eyes have undergone filtration surgery to permit comparison, it will be very interesting to learn whether or not they responded as well as the trabeculectomy-first eyes bearing in mind that interim deployment of laser trabeculoplasty will be a confounding variable.

An additional issue to consider is the subsequent finding by the same Moorfields group that both the conjunctival inflammatory changes and the impaired success of trabeculectomy could be reversed by preoperative treatment with topical fluorometholone combined with cessation of sympathomimetic agonists for a period of one month.<sup>2</sup> That reversal was also accomplished without even resorting to antifibrotic agents that reduce the rate of failure of filtration surgery in eyes that are prone to postoperative scarring. Therefore, even if it should turn out that medical therapy does adversely influence the success of trabeculectomy, the means to overcome that effect are available, and there would appear to be no reason to alter therapeutic strategy on that account. On the other hand, this does not preclude the possibility of switching to surgery as the initial step on the basis of some other devel-

opment, such as a major advance in operative methodology and efficacy.

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DR ALLAN J FLACH. I want to thank Dr Forbes for his kind comments. I certainly agree with him that the results of the Collaborative Initial Glaucoma Treatment Study Trial will be of great interest to all of us.