

# The effect of phacoemulsification on late bleb failure or intraocular pressure in patients with glaucoma: a systematic review

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**Abstract:** The purpose of our systematic review is to document the adverse events that follow phacoemulsification in eyes with trabeculectomy due to glaucoma and to determine whether phacoemulsification jeopardizes the survival of the trabeculectomy. Our research was based on English- and non-English-language articles obtained using the Medline, Embase, Web of Science and Scopus databases. Additional studies were identified by searching bibliographies in the British Library and abstracts presented at the Association for Research in Vision and Ophthalmology annual meetings. Search terms included randomized controlled trial, controlled clinical trial, random allocation, double-blind method, matched studies and trabeculectomy failure, glaucoma-filtering operation failure, bleb failure and cataract surgery or phacoemulsification. Only prospective or retrospective matched studies testing the survival of a trabeculectomy alone versus clear corneal phacoemulsification after a trabeculectomy in patients with glaucoma were included. Data were independently extracted by two authors using predefined data fields. PubMed yielded 152 results, Scopus 235, Embase 222, and Web of Science (science citation index) 216. We read the abstracts of all the trials, and after reading the full text of 31 studies, we decided that 13 studies should be comprehensively evaluated. Current evidence does not allow us to draw safe conclusions on the scientific question so far.

**Keywords:** bleb failure, cataract, glaucoma, phacoemulsification, trabeculectomy

## Introduction

In the past, a number of studies<sup>1,2</sup> have given insight into the epidemiology of primary open-angle glaucoma. For Caucasians, it is estimated that almost 2% of the population will suffer from the disease, and for Afro-Caribbeans this percentage goes to almost 8%. According to the World Health Organization, age-related cataract causes 48% of world blindness. In the United States, age-related lenticular changes have been reported in 42% of those between the ages of 52 and 64 years, 60% of those between the ages of 65 and 74 years, and 91% of those between the ages of 75 and 85 years.<sup>3,4</sup> It is therefore almost inevitable that a glaucoma patient will sooner or later need to undergo cataract surgery independently from his chronic disease.

The objective of the following systematic review is to examine whether there is strong evidence in order to draw safe conclusions on the long-term survival of a trabeculectomy performed before phacoemulsification.<sup>5-7</sup>

## Methods

We looked for matched studies that compared in a prospective or retrospective way the adverse events after a trabeculectomy alone versus phacoemulsification after an

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uncomplicated previous trabeculectomy. Participants of any age with open-angle glaucoma were considered. No limits were applied for language, and we were prepared to translate foreign papers as needed. This search was applied to Medline, Scopus, Embase, the Web of Science (science citation index), and the Cochrane database. The last search was run on February 1, 2012. In addition, we searched the online contents of the British Library and abstracts presented at annual meetings of the Association for Research in Vision and Ophthalmology (ARVO). We used the following search terms to search all trial registers and databases: randomized controlled trial, controlled clinical trial, random allocation, double-blind method, matched study and trabeculectomy failure, glaucoma filtering operation failure, bleb failure and cataract surgery or phacoemulsification. Eligibility assessment was performed independently in an unblinded standardized manner by two reviewers. Disagreements were resolved by discussion between the two; if no agreement could be reached, a third author would decide. In designing the study protocol, we searched primarily for randomized controlled trials (RCTs) to be included. Nonetheless, no author was able to identify one, and therefore, the study design had to be changed. We searched the Cochrane database for similar registrations and found none. Information was extracted from each included study on: (1) characteristics of the study participants and the inclusion and exclusion criteria; (2) type of intervention; (3) type of outcome measure (including visual acuity, intraocular pressure [IOP], number of antiglaucoma drugs used, or need for a secondary antiglaucoma surgery). To ascertain the validity of eligible studies, a pair of authors working independently determined the adequacy of allocation. To explore variability in study results (heterogeneity), we specified the following hypotheses before conducting the analysis. We hypothesized that effect size may differ according to the methodological quality of the study. The primary outcome measure was the statistical significance of the progressive IOP modification before and after phacoemulsification in eyes with previous trabeculectomy.

## Results

A total of 13 studies were identified for inclusion in the review. Two abstracts from the ARVO meetings did not provide full texts, which were necessary to assess the eligibility of the studies, and were not included. All of the studies finally selected for the review were nonrandomized matched studies published in English. None of the studies were multicenter. In all studies, the primary outcome assessed was the postoperative variation of IOP. The secondary and additional outcomes

considered were the number of antiglaucoma medications used and the bleb morphology. No study included morbidity and costs as outcomes. The timing of outcome measures was variable and could include monthly investigations, evaluations every 3 months, or a single final evaluation. The first clinical study assessed was from Wang et al.<sup>8</sup> The main outcome measures for this study were the IOP variation after the phacoemulsification in trabeculectomized eyes and the bleb morphology. The study included 27 eyes and concluded that cataract surgery adversely affects trabeculectomy, especially in cases where there is already an initial failure of the bleb. Inal et al<sup>9</sup> published a controlled study that prospectively assessed completed phacoemulsifications in trabeculectomized eyes as compared to isolated cases of trabeculectomy. Nevertheless, the interventions were retrospective and not current. The study and control group each comprised 30 patients with primary open-angle glaucoma. The study demonstrated that the success of filtering surgery gradually diminished, and the degree of IOP control worsened progressively in a time-dependent manner. In 2005, Ehrnrooth et al<sup>10</sup> conducted a retrospective study in order to evaluate risk indicators for cataract surgery and the effect of phacoemulsification on IOP control in eyes that had undergone trabeculectomy. From a pool of 138 trabeculectomized patients, 47 subsequently underwent cataract surgery and were assessed in the long term. The conclusion of the study was that generally the IOP is maintained stable after cataract surgery, even though there can be cases of late bleb failure. Klink et al<sup>11</sup> conducted a prospective study in 2005 with 30 cases and 36 controls. This prospective study concluded that cataract extraction using clear cornea phacoemulsification may be associated with partial loss of the previously functioning filter and with impairment of filtering bleb morphology. Shingleton et al<sup>7</sup> conducted a retrospective analysis of the surgical results in his private practice, evaluating the IOP, best-corrected visual acuity (BCVA), and glaucoma medication requirements in patients who underwent phacoemulsification with preexisting glaucoma filters. The study included 58 patients, some of whom had had their cataracts removed through a scleral tunnel or temporal clear cornea. The conclusion was that temporal clear corneal or scleral tunnel phacoemulsification in the setting of a preexisting glaucoma filter was associated with improved BCVA, a small but statistically significant increase in IOP, and stability in the number of glaucoma medicines required for IOP control. A prospective matched study was also conducted by Casson et al.<sup>12</sup> Two groups comprising 28 patients each were tested for the same working hypothesis, comparing the mean IOP 1 and 2 years after

phacoemulsification, and the surgical success rate in each group was determined by Kaplan–Meier survival analysis. The authors concluded that phacoemulsification may jeopardize long-term IOP control in individual patients. Rebolledo and Muñoz-Negrete<sup>13</sup> also contributed by designing and executing a prospective, nonrandomized comparative (self-controlled) study aiming to evaluate the effect of phacoemulsification on IOP control in eyes with a previous functioning filtering bleb in patients who were not taking glaucoma medications. Their conclusions were that phacoemulsification significantly increased the IOP and the number of glaucoma medications necessary in eyes with preexisting functioning filtering blebs. Eyes with higher IOPs before phacoemulsification exhibited worsened postoperative IOP control and bleb failure. In their retrospective study, Mietz et al<sup>14</sup> concluded that cataract surgery had no markedly negative effect on IOP. Donoso and Rodriguez<sup>15</sup> conducted a retrospective study comparing two groups of patients treated with 5-fluorouracil (5-FU). The conclusion was that combined cataract and glaucoma surgery with intraoperative 5-FU was associated with good long-term IOP control. This study focused on the effect of phacoemulsification on trabeculectomy survival and therefore the progression of glaucoma. This represents a good example of whether phacoemulsification adversely affects trabeculectomy over the long term. A study by Caprioli et al<sup>16</sup> assessed the safety of temporal clear corneal phacoemulsification in eyes with previous trabeculectomy. In this retrospective case-control study, two groups were matched and assessed. The authors concluded that cataract surgery by temporal clear corneal phacoemulsification in eyes with filtering blebs after trabeculectomy does not adversely affect long-term IOP control. Park et al<sup>17</sup> conducted a retrospective case control study where they attempted to assess the effect of temporal clear corneal phacoemulsification on IOP in eyes with a prior trabeculectomy. After a careful statistical analysis, the authors concluded that cataract surgery by temporal clear corneal phacoemulsification in eyes with filtering blebs does not adversely affect long-term IOP control. Another study that we assessed was published by Swamynathan et al.<sup>18</sup> In this retrospective case-control study, the main outcome measure was the IOP before and after phacoemulsification, at various times postoperatively. This study showed that temporal corneal phacoemulsification can affect the long-term IOP control after trabeculectomy with 5-FU or mitomycin C. Halikiopoulos et al<sup>19</sup> published a prospective case-control study where 68 trabeculectomized patients underwent extraction of their cataracts, either by phacoemulsification or by the extracapsular method. The conclusion of this

study was that in the long term, the complication rate of the phacoemulsification was not statistically significant in respect to the extracapsular method with regard to the glaucoma progression.

## Discussion

A review of the literature resulted in a large number of potentially eligible studies that needed to be assessed for inclusion against predetermined criteria; only a small proportion of these were eventually included in the review (Tables 1 and 2). The process for selecting the studies was explicit and conducted in such a way as to minimize the risk of errors and bias. The process by which decisions on the selection of studies were made was specified in a preliminary meeting of the authors that clarified these issues, including who would carry out each stage and how it would be performed. The aim of the selection process was to ensure that all relevant studies would be included in the review. As already known, the types of study used to assess the effects of interventions can be arranged into a hierarchy, based broadly on their susceptibility to bias. Although the RCTs are considered the best study design with which to evaluate the effect of an intervention, in cases where it is unworkable or unethical to randomize participants, a quasi-experimental or an observational design may instead have to be used. Simply grading studies using this hierarchy does not provide an adequate assessment of study quality, because it does not take variations in quality among studies of the same design into account. Even RCTs can be implemented in such a way that findings are likely to be seriously biased and therefore of little value in decision-making. Therefore, it is important to consider the individual aspects of the study design that may introduce bias rather than focusing on the descriptive label used. This is particularly important for the description of nonrandomized studies. Wang et al<sup>8</sup> presented a prospective study where preoperative IOP and two parameters of the ultrasound biomicroscopy images, including visibility of a route under the scleral flap and reflectivity inside the bleb, were evaluated for an association with postoperative success rate, using Kaplan–Meier survival analysis. An important advantage of the Kaplan–Meier curve is that the method can take some types of censored data into account, particularly if a patient withdraws from a study, ie, is lost from the sample before the final outcome is observed. The same statistical method was also used by Mietz et al.<sup>14</sup> In the study by Inal et al,<sup>9</sup> the data were collected retrospectively, even though success rates were investigated by Kaplan–Meier survival analysis, and the factors influencing final success were submitted to logistic

**Table 1** Summary of studies included

Authors	Number of participants	Number of matched participants	Antimetabolites used	Study design
Wang et al	27	Self-control	Yes, not specified	Prospective
Inal et al	30	30	No	Prospective controlled
Ehrnrooth et al	46	98	No	Retrospective controlled
Klink et al	30	Self-control	Yes, in six cases	Prospective
Shingleton et al	58	Self-control	Mitomycin C (MMC) in 51 eyes	Retrospective
Casson et al	28	28	5-fluorouracil (5-FU)	Prospective controlled
Rebolleda and Muñoz-Negrete	49	Self-control	MMC in six eyes	Prospective, nonrandomized comparative (self-controlled) trial
Mietz et al	107	Self-control	MMC in six eyes	Retrospective
Donoso and Rodriguez	22	18	5-FU	Retrospective matched
Caprioli et al	40	40	5-FU in 18 eyes	Retrospective case-control study
Park et al	40	40	5-FU	Retrospective case-control study
Swamynathan et al	29	29	5-FU or MMC	Retrospective case-control study
Halikiopoulos et al	68	Self-control	No	Prospective

regression analysis. This latter approach is used extensively in the medical sciences to predict a patient's propensity to a certain event. The study by Ehrnrooth et al<sup>10</sup> was a retrospective case-control investigation; the paper from Klink et al<sup>11</sup> and the case-control study by Halikiopoulos et al<sup>19</sup> were prospective studies. Their statistical analysis was based upon standard deviation calculation and extrapolation of the clinical statistical significance (*P*-value), which limited the strength of the results. Shingleton et al<sup>7</sup> used the same statistical methods, but also introduced the best way to clinically assess BCVA using the logMAR scale. The prospective, matched study by Casson et al,<sup>12</sup> the prospective, nonrandomized comparative (self-controlled) study by Rebolleda and Muñoz-Negrete,<sup>13</sup> and the retrospective case-control study by Caprioli et al<sup>16</sup> used the same statistical methods, with the limitations mentioned above. A very good impression comes from the study by Donoso and Rodriguez.<sup>15</sup> They used the log-rank test (sometimes called the Mantel–Cox test), which

is a hypothesis test to compare the survival distributions of two samples. It is widely used in clinical trials to establish the efficacy of a new treatment compared to a control treatment when the measurement is the time to event (such as the time from initial treatment to IOP spikes). Lastly, another source of major bias in the finalization of the results is that during the execution of the trabeculectomy, some surgeons used different antimetabolites and some used none, such as in the studies of Park et al<sup>17</sup> and Swamynathan et al.<sup>18</sup> It is difficult to assess the influence of antifibrotic therapy on the long-term survival of a trabeculectomy when associated with phacoemulsification because statistical variables increase exponentially and add further to the scientific dilemma.

In conclusion, our systematic review sought to gather all the available evidence in favor or against the question of whether phacoemulsification should be performed with or after a trabeculectomy. Evidence to date has not answered this question comprehensively.

**Table 2** Long-term variations of quality controls

Authors	Intraocular pressure	Medications taken	Visual acuity/fields	Bleb survival	Final result
Wang et al	Increased	N/A	N/A	Non modified	Negative
Inal et al	Increased in both groups	Increased	N/A	Compromised	Inconclusive
Ehrnrooth et al	Increased	Increased	N/A	Compromised	Inconclusive
Klink et al	Increased	N/A	N/A	Compromised	Negative
Shingleton et al	Increased	Stable	Improved	N/A	Inconclusive
Casson et al	Increased	Increased	N/A	Compromised	Negative
Rebolleda and Muñoz-Negrete	Increased	Increased	Reduced	Compromised	Negative
Mietz et al	Unchanged on average	Unchanged on average	Improved	N/A	Relatively favorable results
Donoso and Rodriguez	Reduced	None	N/A	N/A	Positive
Caprioli et al	Similar	N/A	N/A	N/A	Positive
Park et al	Similar	N/A	N/A	N/A	Positive
Swamynathan et al	Increased	N/A	Improved	N/A	Negative
Halikiopoulos et al	Increased	N/A	Improved	N/A	Negative

**Abbreviation:** N/A, not applicable.

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