Factors Associated With Unqualified Success After Trabecular Bypass Surgery: A Case-control Study

Ricardo A. Paletta Guedes, MD, MPH, PhD,* Daniela M. Gravina, MD,* Vanessa M. Paletta Guedes, MD,* and Alfredo Chaoubah, PhD†

Glaucoma surgical treatment has evolved dramatically over the past decade.1,2 Although traditional filtering surgery (trabeculectomy) has been the gold standard surgical technique for a long time, it presents some potential serious and sight-threatening intraoperative and postoperative complications.3–8 Because of this high-risk profile, surgeons tend to leave its indication to cases where other types of therapies (medications or lasers) are not possible or would not work properly.1 The need to make glaucoma surgery safer has prompted efforts to improve traditional trabeculectomy. Examples include the Moorfields Safer Surgery System, as well as a newer option, microinvasive glaucoma surgery (MIGS) techniques.9,10

MIGS offers improved safety and reasonable efficacy, with minimal damage to the eye. It often involves an ab interno approach and is commonly combined with cataract surgery.11,12 In addition, MIGS techniques usually use mechanisms or devices to enhance aqueous outflow. These outflow methods can be divided basically into 2 groups: (1) techniques that create a new outflow pathway (subconjunctival or suprachoroidal) and (2) techniques that enhance the natural outflow pathway (trabecular outflow system).12

Among the many MIGS procedures, the most studied and used is trabecular micro by-pass surgery, using first-generation (iStent) or second-generation (iStent inject) stents (Glaukos Corp., San Clemente, CA).13,14 These devices create a direct passage from the anterior chamber to the interior of Schlemm canal, bypassing the main site of resistance for aqueous humor outflow; specifically, the trabecular meshwork. Thus, these devices enhance the natural outflow pathway.14

Many studies have demonstrated the effectiveness and safety of the trabecular micro by-pass technique.13,15 Their indication resides in early-to-moderate open-angle glaucoma cases, usually in combination with cataract surgery, but also as a stand-alone procedure in some circumstances.14

Complications with this procedure are rare and, most of the time, self-resolving (eg, hyphemas). When it does not resolve spontaneously, the complication is usually easy to handle with minor manipulation and tends not to generate any sequelae.14

Efficacy in glaucoma surgical treatments is often measured as the capacity to reduce the intraocular pressure (IOP) and also indicated via a reduction in the number of glaucoma medications. This reduction in medication burden is of particular importance in chronic diseases such as glaucoma. By reducing the need for daily drops, the disease can be better controlled by improving treatment adherence. Studies have shown that the number of glaucoma medications after trabecular by-pass surgery is reduced significantly; furthermore, the majority of patients become medication-free over longer periods after surgery.13

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Precis: An older age, a low number of baseline glaucoma medications, an early glaucoma stage, lower intraocular pressure (IOP) values during the first postoperative month, and combined surgery are possible predictors of unqualified success after a trabecular bypass microinvasive glaucoma surgery (MIGS) procedure.

Purpose: The purpose of this study was to identify the potential predictors of unqualified success (IOP <18 mm Hg with no glaucoma medication) after trabecular by-pass MIGS.

Materials and Methods: We designed a case-control study using logistic regression modeling that included all trabecular by-pass surgeries with at least 3 months of follow-up, performed at a single center from June 2017 to December 2019. Eyes that achieved an endpoint of unqualified success (dependent variable) were considered cases. All other eyes were used as the controls. Cases and controls were paired by sex and postoperative time. We tested the following independent variables: age, race, laterality (right eye or left eye), glaucoma stage, type of surgery (combined or stand-alone), type of trabecular bypass, intraoperative complications, baseline number of medications, baseline IOP, and postoperative IOP on days 1, 15, and 30. Additional analysis using IOP <15 mm Hg as a threshold and including eyes with at least 12 months of follow-up were performed.

Results: One hundred ninety-four eyes were included in the analysis. We observed complete success in 56.7% of cases. The mean follow-up time for the entire population was 12.3 ± 6.8 months. All variables were considered in the first step of the modeling process; however, only age, day-15 IOP, day-30 IOP, baseline number of medications, glaucoma stage, and type of surgery remained until the completion of our model, with adequate significance (P < 0.05). The additional analysis confirmed our results.

Conclusion: We identified that an older age, a low number of baseline glaucoma medications, an early glaucoma stage, lower IOP values during the first postoperative month, and combined surgery were associated with a higher chance of unqualified success at 12 months after a trabecular by-pass MIGS procedure.

Key Words: cataract, iStent, iStent inject, open-angle glaucoma, trabecular micro by-pass

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From the *Paletta Guedes Eye Institute; and †Federal University of Juiz de Fora, Juiz de Fora, MG, Brazil.

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Reprints: Ricardo A. Paletta Guedes, MD, MPH, PhD, 79 Oscar Vidal Street, Juiz de Fora 36010-060, MG, Brazil (e-mail: palettaguedes@yahoo.com).

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Among the many MIGS procedures, the most studied and used is trabecular micro by-pass surgery, using first-generation (iStent) or second-generation (iStent inject) stents (Glaukos Corp., San Clemente, CA).13,14 These devices create a direct passage from the anterior chamber to the interior of Schlemm canal, bypassing the main site of resistance for aqueous humor outflow; specifically, the trabecular meshwork. Thus, these devices enhance the natural outflow pathway.14

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Efficacy in glaucoma surgical treatments is often measured as the capacity to reduce the intraocular pressure (IOP) and also indicated via a reduction in the number of glaucoma medications. This reduction in medication burden is of particular importance in chronic diseases such as glaucoma. By reducing the need for daily drops, the disease can be better controlled by improving treatment adherence. Studies have shown that the number of glaucoma medications after trabecular by-pass surgery is reduced significantly; furthermore, the majority of patients become medication-free over longer periods after surgery.13
Although trabecular bypasses are among the most common and studied MIGS techniques, it is still not clear which group of patients could benefit the most from this technology and which clinical features are most likely to be associated with success or failure with this procedure.

The aim of this study was to assess the factors associated with unqualified success (IOP < 18 mm Hg and IOP < 15 mm Hg, with no glaucoma medications) after surgical treatment of open-angle glaucoma using trabecular bypass implants (iStent and/or iStent inject).

MATERIALS AND METHODS

A case-control study was performed to assess which demographic, baseline, intraoperative or postoperative clinical features were associated with unqualified success after trabecular bypass surgery in a single center by the same surgeon.

Inclusion Criteria

Open-angle glaucoma patients (above 18 y old) submitting to trabecular bypass surgery from June 2017 to December 2019 with at least 3 months of follow-up were included in the study. We included eyes with either primary or secondary (pigmentary or pseudo-exfoliation) open-angle glaucoma. In addition, both combined and stand-alone surgeries were considered, where either one of following trabecular bypass techniques was used: iStent (1 trabecular device), iStent inject (2 trabecular devices), or iStent inject PLUS (a term we created to designate the use of both iStent and iStent inject, meaning 3 trabecular devices). Inclusion criteria also comprised the absence of any other ocular findings and only the first operated eye from each patient.

Exclusion Criteria

Patients with other types of glaucoma, any previous glaucoma surgery or those lacking sufficient data in the records were excluded from the study.

The trabecular microbypass surgical technique was as follows. Implantation of the trabecular micro by-passes was conducted through a clear corneal incision. The surgeon implanted the devices under direct gonioscopic view in the inferonasal quadrant (1 to 2 clock hours apart in cases where > 1 was implanted), looking for areas with blood reflux within the Schlemm canal or higher pigmented areas in the trabecular meshwork. Accurate positioning of the iStent inject was verified by gonioscopic examination, which was performed both during surgery and at all clinical examinations throughout follow-up. Standard phacoemulsification with a foldable intraocular lens was first performed if the surgery was combined with a cataract extraction surgery.

Choice among the different options of trabecular bypasses (iStent, iStent inject or the association of both) was made at the discretion of the examiner. No specific clinical variable drove the indication.

After surgery, patients were seen by the clinician at day 1; day 15 (± 5 d); day 30 (± 7 d); day 90 (± 15 d); day 180 (± 30 d); day 360 (± 30 d); day 540 (± 60 d); and day 720 (± 60 d).

Postoperative medications regimen was usual, with patients receiving both antibiotics and steroids drops for a period of 3 to 4 weeks. We stopped all glaucoma medications since the day of surgery and decision to restart any glaucoma medication was made individually based on the target IOP predefined by the physician. No predetermined criteria existed.

We defined unqualified success as an IOP < 18 mm Hg (criterion 1) and IOP < 15 mm Hg (criterion 2), with no glaucoma medication required at the last visit. Eyes that achieved an endpoint of unqualified success were considered “cases.” All other eyes (IOP > 18 and 15 mm Hg or IOP < 18 and 15 mm Hg with adjunctive medications) were considered “controls.” Cases and controls were paired by sex and postoperative period.

Statistical Analysis

The presence or absence of unqualified success criteria 1 or 2 at the last visit was the dependent variable. The following independent variables were used in the model: age, race, laterality (right eye or left eye), glaucoma stage (early, moderate, or advanced; based on the visual field grading system by Hodapp, Parrish, and Anderson16), type of surgery (combined or stand-alone), type of trabecular bypass (iStent, iStent inject, or iStent inject PLUS), intraoperative complications, baseline number of medications, baseline IOP, and postoperative IOP at days 1, 15, and 30.

A logistic regression model was constructed, which initially involved testing potential predictors of failure (the independent variables) in separate analyses. Comparisons between variables were performed using either a $\chi^2$ test (categorical variables) or Student t test (numerical variables).

Potential predictors with a significance > 90% ($P < 0.1$) were entered into the logistic regression model. Once in the model, the criterion for retention for each independent variable was set at a 95% significance level ($P < 0.05$).

We also assessed the probability of success through Kaplan-Meier survival analyses according to the 2 different unqualified success criteria.

We additionally conducted a regression modeling analysis for both success criteria considering only cases and controls with at least 12 months of follow-up.

All statistical analyses were performed using IBM SPSS Statistics 25 (IBM Corp., Armonk, NY). This study followed the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Santa Casa de Misericordia de Juiz de Fora.

RESULTS

Two hundred eighty-three eyes underwent trabecular bypass implant surgery between June 2017 and December 2019; 194 met the main inclusion criteria and were evaluated in this study.

We observed unqualified success in 56.7% (n = 110) and in 51.5% (n = 100) of eyes for criteria 1 (IOP < 18 mm Hg, with no medication) and 2 (IOP < 15 mm Hg, with no medication), respectively; these eyes were categorized as “cases.” The rest of the operated eyes were part of the “control” group. Table S1 (Supplemental Digital Content 1, http://links.lww.com/IGJ/A434) shows the clinical features of the study population. The mean follow-up time for the entire population was 12.3 ± 6.8 months.

Kaplan-Meier survival analysis are shown in Figure 1.

Unqualified Success Criterion 1 (IOP < 18 mm Hg With no Medication) Results

Table S2 (Supplemental Digital Content 2, http://links.lww.com/IGJ/A435) provides a comparison between cases and controls according to unqualified success criterion 1. The potential predictors of unqualified success were age ($P = 0.052$), baseline IOP ($P < 0.001$), day-1 IOP ($P = 0.061$), day-15 IOP ($P < 0.001$), day-30 IOP ($P < 0.001$), baseline number of
medications ($P < 0.001$), glaucoma stage ($P < 0.001$), type of surgery ($P < 0.001$), and type of trabecular bypass ($P < 0.001$).

All variables were entered into the logistic regression model initially at the first step ($P < 0.1$). Four steps were performed to establish the final model. The relationships among the variables with each step resulted in 1 or more of them exiting the model, until the fourth step (Table S3, Supplemental Digital Content 3, http://links.lww.com/IJG/A436). Only age, day-15 IOP, day-30 IOP, baseline number of medications, glaucoma stage, and type of surgery remained until the last step with adequate significance ($P < 0.05$). Step 4 was considered to produce the final model.

Older patients were more likely to achieve IOP <18 mm Hg with no medication (3.9% increase in chance of success for every additional year). Day-15 and day-30 IOPs had a negative impact on the chance of unqualified success; the higher these values were, the lower the chance of unqualified success (a decrease by 8.7% and 15.3%, respectively). In addition, the chance of success decreased for every mm Hg increase in the IOP. Regarding the baseline number of medications, for every medication added preoperatively, there was a 48% lesser chance of achieving unqualified success.

Medication-free outcomes is more likely with early glaucoma than with moderate or advanced glaucoma. With an early glaucoma stage, the chance of unqualified success increased by 177%, almost 2-fold that of more advanced stages. Conversely, more advanced glaucoma was associated with a lower chance of success.

Combined surgery was the most significant factor related to unqualified success ($P = 0.007$ in the final model), increasing the chance of achieving an IOP <18 mm Hg with no medications by 247% (~2.5-fold).

### Unqualified Success Criterion 2 (IOP <15 mm Hg With No Medications) Results

Potential variables associated with an IOP <15 mm Hg with no medications were the same as in criterion 1. They were age ($P = 0.014$), baseline IOP ($P < 0.001$), day-1 IOP ($P = 0.066$), day-15 IOP ($P < 0.001$), day-30 IOP ($P < 0.001$), baseline number of medications ($P < 0.001$), glaucoma stage ($P < 0.001$), type of surgery ($P < 0.001$), and type of trabecular bypass ($P < 0.001$).

Through the logistic regression modeling analysis, final step was achieved after 3 steps. Final model included the following variables: early glaucoma stage ($\text{Exp } \beta = 2.290$), combined surgery ($\text{Exp } \beta = 2.494$), day-15 IOP ($\text{Exp } \beta = 0.920$), and day-30 IOP ($\text{Exp } \beta = 0.798$). Although age and baseline number of medications remained as a significant predictor of unqualified success for criterion 1, they did not appear as a significant factor at the final model for an IOP <15 mm Hg with no medications.

Early glaucoma stage increases the chance of medication-free outcomes (for an IOP <15 mm Hg) in 129% in comparison to moderate and advanced glaucoma stages. Performing trabecular bypass surgery in combination with a cataract extraction increases the chance of success by 149% versus a standalone procedure.

One mm Hg increase in day-15 and day-30 IOP will generate a decrease in the chances of success by ~8% and 20%, respectively.

Since type of surgery (combined vs. standalone) was the most significant predictor of unqualified success for both criteria, we performed the survival analysis according to this specific variable (Fig. 2).

### Additional Regression Modeling Analysis (Minimum of 12 mo of Follow-up)

When we consider a follow-up time of at least 12 months for both cases and controls, 119 eyes met the inclusion and exclusion criteria. Unqualified success results for an IOP <18 mm Hg and for an IOP <15 mm Hg were 64.7% (cases = 77) and 58.0% (cases = 69), respectively.

In criterion 1 analysis, 4 steps were necessary to achieve the final regression model, which included the following variables: combined surgery ($\text{Exp } \beta = 2.655$), day-30 IOP ($\text{Exp } \beta = 0.840$) and baseline number of medications ($\text{Exp } \beta = 0.429$).
For the criterion 2 analysis, final model was achieved after 6 steps. Only 2 variables remained significant at the final step: combined surgery (Exp $\beta = 3.792$) and day-30 IOP (Exp $\beta = 0.799$).

DISCUSSION

Treating glaucoma may involve several clinical decisions among many different options. The decision-making process should include, from an individual perspective, both ophthalmic practitioners and patients (and sometimes, their caregivers). Identifying the best-case scenario for a given procedure can help with choosing the correct option to achieve the best possible results.

Trabecular MIGS procedures are often indicated for mild-to-moderate open-angle glaucoma. The rationale for indicating trabecular devices for mild cases include the ability to reduce the IOP (in which the target IOP is not so low in early glaucoma) and the viability of the posttrabecular outflow system (ie, the Schlemm canal and collector channels are not permanently damaged). It is also very important that the angle is open and its structures.
accessible through gonioscopic view, preferably in the inferonasal quadrant.\textsuperscript{10,12} Apart from these guidelines, very little is known regarding the best candidate cases for this type of surgery.

We identified the clinical features associated with medication-free outcomes after trabecular by-pass surgery (mean postoperative time of 12 mo). Results for both criteria (IOP < 18 mm Hg with no medication) were similar. Both analysis had the same potential predictors of unqualified success. Final model for both analysis demonstrated the same variables, with the exception of age and baseline number of medications, which were present in the first model and were absent in the second one. It seems that these 2 variables are success predictors for an IOP < 18 mm Hg but not for an IOP < 15 mm Hg.

The most significant factor was combined surgery. Combining cataract surgery with a trabecular by-pass procedure appeared to have a synergistic effect. Performing combined cases increased the chances of medication-free outcomes from 1.5- to 2.5-fold, compared with stand-alone cases.

There is evidence in the literature that cataract surgery alone can reduce IOP in open-angle glaucoma cases; however, the reduction tends to be limited and temporary.\textsuperscript{16-20} Armstrong et al\textsuperscript{18} provided some pooled results from 32 studies, where phacoequilibration alone can induce a reduction of the baseline IOP on average 12\% to 15\% up to 24 months, reducing the effect to 9\% at 36 months. There is also sufficient evidence that the combined procedure (cataract and trabecular by-pass procedures) is more efficacious, both in terms of IOP reduction and a reduction in medication burden, while maintaining similar safety profiles, compared with cataract surgery alone.\textsuperscript{11,20-22} A meta-analysis published by Lavia et al\textsuperscript{13} demonstrated that the use of 1 trabecular bypass in association with cataract surgery is associated with lower final IOP on an average of 1 mm Hg, when compared with phaco alone. Samuelson and colleagues conducted a clinical trial comparing iStent inject combined with phaco versus phaco alone. They have found that using iStent inject combined to the cataract procedure provided an average reduction of 7.0 mm Hg from the baseline unmedicated IOP at 2 years, whereas phaco alone achieved an average reduction of 5.4 mm Hg (P < 0.001).\textsuperscript{22} Our results show that the average reduction between baseline and final IOP was 3.5 mm Hg. Differences in efficacy can be explained by some factors. We did not perform a washout from glaucoma medications before surgery, so our baseline IOP was on glaucoma medications and our analysis included different types of trabecular bypasses and both combined and stand-alone procedures. We did not perform any comparative analysis in efficacy among the different trabecular devices, since this was not the purpose nor the appropriate design of our study.

Our study provided some initial evidence that stand-alone trabecular by-pass surgery may not be as effective as a combined procedure. A possible explanation is the phacoequilibration effect on the IOP. High anterior chamber pressure and aspiration rates during cataract extraction could open, wash, and “prime” the trabecular and post-trabecular outflow system, facilitating the exit of the aqueous humor from the anterior chamber.

Our results should be taken with careful consideration, given that indications for the trabecular by-pass procedure in stand-alone or combined surgeries could have had some influence. There is the possibility that trabecular by-pass surgery was indicated earlier in combined cases (as patients were already being submitted to cataract surgery). Thus, additional comparative studies are necessary to confirm our results.

Early-stage glaucoma and a smaller number of medications preoperatively are other potential factors related to better outcomes. For mild glaucoma cases, the chances of success increased 2-fold compared with those in the more advanced stages.

For each glaucoma medication added at baseline, there was a decrease of \textasciitilde 50\% in the chance of unqualified success (IOP < 18 mm Hg with no medication). This may be an indication of the same pathologic condition: the viability of the posttrabecular outflow system (or the degree of damage in the outflow system).

The more advanced the glaucoma, the higher the probability of permanent damage in the posttrabecular outflow system.\textsuperscript{23,24} As more structures (eg, Schlemm canal and collector channels) are involved in the disease, bypassing only the trabecular tissue is not sufficient to re-establish natural aqueous outflow.\textsuperscript{23}

The number of medications can also be an indirect measure of the viability of the trabecular outflow system.\textsuperscript{23} A higher number of medications needed at baseline indicates that the outflow system is more severely damaged. To illustrate this argument, let us consider 2 hypothetical patients submitting to a combined procedure (cataract–trabecular by-pass surgery). Both of them have IOP levels of \textasciitilde 15 mm Hg at baseline. One of them is using only 1 medication and the other takes 4 medications. It is reasonable and natural to believe that the outflow system is more severely damaged in the patient taking more medications.

Age is usually a risk factor for glaucoma incidence and progression.\textsuperscript{25-27} Our study found that for every additional decade, there is approximately a 40\% increase in the chance of success, when an IOP of 18 mm Hg is used as threshold. A similar positive effect of aging is also present in other glaucoma therapies, such as filtering and laser treatments.\textsuperscript{28}

Our results show that postoperative IOPs at days 15 and 30 are possible reliable indicators of whether medication-free outcome has been achieved after 12 months. The lower the IOP during the first month after surgery, the higher the chance of achieving an IOP below 18 or 15 mm Hg with no glaucoma medications at 12 months. This is most likely due to the immediate re-establishment of the natural aqueous outflow after surgery.

Some patients can exhibit IOP spikes during the first month of the postoperative period.\textsuperscript{29,30} Researchers believe that a steroid-induced reaction, or even an inflammatory reaction, may cause this,\textsuperscript{23} or possibly both. Although steroid-induced and inflammatory reactions are both treatable and reversible, it is possible that some permanent damage in the outflow structures may occur, as patients who do not experience spikes in IOP during the first month are more likely to achieve complete success at 1 year.

In an additional analysis, where only cases and controls with a minimum of 12 months of follow-up were considered, results were also very similar with the same main predictors (combined surgery, day-30 IOP and baseline number of medications) remaining significant at the final regression model.

Other clinical variables, which could potentially have had some influence on the outcome, are intraoperative and postoperative complications and the type/number of stents.

In theory, complications are expected to lower the efficacy of the procedure. In our study, they did not interfere with achieving complete success at 12 months. This may be because the rate of complications was low and the majority...
of complications were self-limited or easily dealt with, requiring only minor adjustments.

The number of stents may influence the chance of achieving complete success at 12 months. Previous studies have shown that a higher efficacy is expected with an increase in the number of stents per eye.\textsuperscript{31} In addition, a second-generation trabecular by-pass is generally more efficacious than a first-generation procedure.\textsuperscript{32,33} Our present findings were not able to correlate the number of stents with complete success at 12 months, due to indication and selection bias. We indicated first-generation or second-generation trabecular by-pass or both on an individual basis and as specified on clinical presentation.

The main strengths of this study are its large sample size and that it is a single-center study based on actual patient data. The study also included both combined and stand-alone procedures and both first-generation and second-generation trabecular bypasses.

Although our study shows some interesting results, there were several limitations. Majority of our population was White, thus limiting the external validity of our findings. Regression models have limited clinical generalization capability; therefore, these results can vary on an individual basis. The model shows the relationship between independent variables as a whole and the dependent variable; thus, relationships with individual independent variables require additional examination. Further investigations are needed to confirm these findings.

CONCLUSION

Our study identified that an older age, a low number of baseline glaucoma medications, an early glaucoma stage, lower IOP values during the first postoperative month, and combined surgery were associated with unqualified success at 12 months after a trabecular by-pass MIGS procedure.

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