Glaucoma Surgery Calculator: Limited Additive Effect of Phacoemulsification on Intraocular Pressure in Ab Interno Trabeculectomy

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Abstract

Purpose  
To compare intraocular pressure (IOP) reduction and to develop a predictive surgery calculator based on the results between trabectome-mediated ab interno trabeculectomy in pseudophakic patients versus phacoemulsification combined with trabectome-mediated ab interno trabeculectomy in phakic patients.

Methods  
This observational surgical cohort study analyzed pseudophakic patients who received trabectome-mediated ab interno trabeculectomy (AIT) or phacoemulsification combined with AIT (phaco-AIT). Follow up for less than 12 months or neovascular glaucoma led to exclusion. Missing data was imputed by generating 5 similar but non-identical datasets. Groups were matched using Coarsened Exact Matching based on age, gender, type of glaucoma, race, preoperative number of glaucoma medications and baseline intraocular pressure (IOP). Linear regression was used to examine the outcome measures consisting of IOP and medications.

Results  
Of 949 cases, 587 were included consisting of 235 AIT and 352 phaco-AIT. Baseline IOP between groups was statistically significant (p<0.01) in linear regression models and was minimized after Coarsened Exact Matching. An increment of 1 mmHg in baseline IOP was associated with a 0.73±0.03 mmHg IOP reduction. Phaco-AIT had an IOP reduction that was only 0.73±0.32 mmHg greater than that of AIT. The resulting calculator to determine IOP reduction consisted of the formula -13.54+0.73 × (phacoemulsification yes:1,
no:0) + 0.73 × (baseline IOP) + 0.59 × (secondary open angle glaucoma yes:1, no:0) + 0.03 × (age) + 0.09 × (medications).

Conclusions
This predictive calculator for minimally invasive glaucoma surgery can assist clinical decision making. Only a small additional IOP reduction was observed when phacoemulsification was added to AIT. Patients with a higher baseline IOP had a greater IOP reduction.

Introduction
Cataract surgery is often associated with a moderate intraocular pressure (IOP) reduction of 1.5–3 mmHg in patient with ocular hypertension or glaucoma [1–3]. Minimally invasive glaucoma surgery (MIGS) allows to combine IOP lowering with vision improvement from cataract surgery in an age group often affected by both. Such a practice pattern has become more common because it is standardized, safe [4] and also cost effective [5]. The first randomized controlled trials comparing phacoemulsification alone to phacoemulsification combined with implantation of trabecular bypass microstents, a form of MIGS, (iStent, Glaukos, Laguna Hills, CA), showed a relatively small additional effect of these implants on IOP reduction [6]. Ab interno trabeculectomy with the trabectome (Neomedix Corp; Tustin, CA), another MIGS modality, lowers IOP by plasma-mediated ionization and ablation of trabecular meshwork (TM) of up to 180° thereby increasing aqueous outflow in eyes with an intact downstream drainage system [4]. Both ab interno trabeculectomy (AIT) and phacoemulsification combined with ab interno trabeculectomy (phaco-AIT) can be used in patients with different angle opening [7] and surgical status [8,9]. The purpose of the comparison in this study was to assess reduction of IOP after AIT performed in pseudophakic patients versus phaco-AIT in phakic patients using a Coarsened Exact Matched cohort. Based on results with microstents [10], we hypothesized that in this matched comparison the benefit of adding phacoemulsification to AIT would be associated with a greater reduction in IOP and medications during 12 month follow-up. The resulting calculator can help clinicians to predict the IOP reduction.

Methods
Participants
Data for this study were collected with approval by the Institutional Review Board of the University of Pittsburgh, in accordance with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. No informed consent was necessary for this retrospective, observational cohort study. Patient records were anonymized and de-identified prior to analysis. Subjects were divided into pseudophakic patients who received AIT and phakic patients who received phaco-AIT. Outcomes were determined for all patients with a diagnosis of glaucoma with or without a visually significant cataract, who had 12 months of follow-up. The specific target IOP was set on a case-by-case basis by the individual treating physician and was the maximum IOP estimated to prevent further nerve damage. Patients who were followed for less than 12 months or diagnosed with neovascular glaucoma were excluded. Indications for AIT consisted of worsening glaucoma on maximally tolerated topical therapy while indications for phaco-AIT were the same or stable glaucoma with desire to reduce medications plus a visually significant cataract with visual brightness acuity testing equal or worse than least 0.4 logMAR
The postoperative medications consisted of 1% pilocarpine four times per day for 1 month, then three times per day for 1 month, 1% prednisolone acetate four times per day for 1 week to be tapered by one drop each week, and a third or fourth generation fluoroquinolone four times per day for 1 week. Glaucoma medications could be continued as deemed necessary to achieve target pressures. Visual field status of all patients was categorized as early, moderate, or advanced by individual glaucoma specialists based on the most recent Humphrey visual field exams (Zeiss, Jena, Germany). All patients had a comprehensive slit lamp, gonioscopy and dilated ophthalmoscopy exam prior to surgery.

Statistics
Demographics were compared by Mann-Whitney U test and chi-squared test for continuous and categorical variables, respectively. To avoid eliminating data with missing values multiple imputation was used. Missing values of the incomplete dataset were imputed \( m > 1 \) times, thus creating \( m \) completed datasets. Second, each of the \( m \) completed datasets were independently analyzed. Finally, the results from each of the \( m \) analysis were pooled into a final result. Missing data such as age, gender and race were imputed by generating 5 similar but non-identical datasets. Groups were then matched by utilizing Coarsened Exact Matching [11–13] based on age, gender, type of glaucoma, race, preoperative number of glaucoma medications and baseline IOP. Univariate linear regression was performed first and those variables that were statistically significant were included in the final multivariate regression model. A p-value of less than 0.05 was considered statistically significant. Continuous variables were expressed as mean±SD. All analyses were performed using R [14].

Results
Baseline Demographics
After applying exclusion criteria and matching, a total of 587 patients were included in the study consisting of 235 AIT and 352 phaco-AIT (Fig 1). Baseline demographics are shown in Table 1.

ACG (angle closure glaucoma); POAG (primary open angle glaucoma); SOAG (secondary open angle glaucoma).

Primary open angle glaucoma (POAG) comprised 86% and 89% of AIT and phaco-AIT, respectively. Secondary open angle glaucoma (SOAG) included 14% and 11% of AIT and phaco-AIT, respectively. From the matched subjects, 75% in AIT and also in phaco-AIT were Caucasian, followed by Asian, African American, and others. These values were not statistically significant. Additionally, age, gender, baseline number of glaucoma medications, and baseline IOP were found to be statistically different (p<0.01) between groups (Table 1). Following Coarsened Exact Matching, these preoperative differences between treatment groups were minimized (Table 2).

Multiple Imputation and Coarsened Exact Matching
Missing data in each category are recorded. Data missing from baseline number of medications, type of glaucoma, and IOP were 0% for both groups. Conversely, age, gender, and race had missing data among both groups. Six percent of AIT had an unknown age, 4% were without defined gender and 8% without defined race. Two percent of phaco-AIT had an unknown age, 2% were without defined gender, and 11% without race.
Fig 1. Trabectome Surgeries. Cases analyzed after accounting for exclusion criteria (AIT, ab interno trabeculectomy; phaco-AIT, AIT combined with phacoemulsification; IOP, intraocular pressure; POAG, primary open angle glaucoma; SOAG, secondary open angle glaucoma).

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Linear Regression Models

Linear regression of the multiple imputed, matched data was used to identify the influence of the parameters above on the IOP lowering effect of surgery. Univariate linear regression was performed first (Table 3) using the variables phacoemulsification, baseline IOP, SOAG, age, number of medications at baseline, race and gender (male).

Of these variables, phacoemulsification, baseline IOP, SOAG, age and number of medications at baseline were found to be statistically significant and included in the final multivariate regression model (Table 4). Only baseline IOP and phacoemulsification were statistically significant in both models ($p = 0.02$ and $p < 0.01$, respectively).

Each increment of 1 mmHg in baseline IOP was associated with an IOP reduction of 0.73 ±0.03 mmHg ($p<0.01$). After adjusting for baseline IOP, age, baseline number of glaucoma medications, and type of glaucoma, phacoemulsification conferred an additional IOP reduction of 0.73±0.32 mmHg IOP. Preoperative IOP was 22.6±6.4 mmHg in AIT and 19.9±5.8 mmHg in phaco-AIT with 2.8±1.1 medications in AIT and 2.4±1.1 in phaco-AIT. At one year, IOP in AIT was reduced to 16.9±4.5 mmHg (mean±SD) and in phaco-AIT to 15.4±3.6 mmHg ($p<0.01$), while medications in AIT declined to 2.3±1.3 and in phaco-AIT to 1.7±1.2 (p<0.01). Postoperative AIT and phaco-AIT were significantly different at all time points for both IOP and medications due to the large sample sizes with a narrow confidence interval and small standard error (Fig 2).

Table 1. Raw data demographics of study population. Demographics for AIT-only and phaco-AIT show significant difference ($p < 0.05$) for age, gender, baseline IOP, and baseline number of medications in unmatched data.

|                        | AIT (n = 368) | Phaco-AIT (n = 581) | p-value |
|------------------------|---------------|---------------------|---------|
| **Age**                |               |                     |         |
| Mean±SD                | 75±10         | 74±9                | <0.01   |
| Range                  | (50, 96)      | (51, 94)            |         |
| **Gender**             |               |                     | 0.01    |
| Male                   | 130 (35%)     | 248 (43%)           |         |
| Female                 | 223 (61%)     | 323 (56%)           |         |
| **Types of Glaucoma**  |               |                     | 0.19    |
| ACG                    | 2 (1%)        | 11 (2%)             |         |
| POAG                   | 289 (78%)     | 442 (76%)           |         |
| SOAG                   | 77 (21%)      | 128 (22%)           |         |
| **Race**               |               |                     | 0.34    |
| African Americans      | 19 (5%)       | 29 (5%)             |         |
| Asians                 | 92 (25%)      | 166 (29%)           |         |
| Caucasians             | 216 (59%)     | 303 (52%)           |         |
| Others                 | 10 (3%)       | 20 (3%)             |         |
| **Baseline IOP**       |               |                     | <0.01   |
| Mean±SD                | 24.1±7.1      | 20.6±6.6            |         |
| Range                  | (10, 51)      | (10, 59)            |         |
| **Baseline Number of Glaucoma Medications** | | | <0.01 |
| Mean±SD                | 2.9±1.1       | 2.4±1.0             |         |
| Range                  | (1, 6)        | (1, 5)              |         |

ACG (angle closure glaucoma); POAG (primary open angle glaucoma); SOAG (secondary open angle glaucoma).

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Glaucoma Surgery IOP Reduction Calculator

The calculator predicting the IOP reduction had the formula:

\[-13.54 + 0.73 \times (\text{phaco}; \text{yes}:1, \text{no}:0) + 0.73 \times (\text{baseline IOP}) + 0.59 \times (\text{SOAG}; \text{yes}:1, \text{no}:0) + 0.03 \times (\text{age}) + 0.09 \times (\text{medications}).\]

For example, a 75-year-old pseudophakic patient with POAG with a baseline IOP of 21 and 2 different medications receiving AIT alone would be expressed as:

\[
13.54 + 0.73 \times (0) + 0.73 \times (21) + 0.59(0) + 0.03 \times (75) + 0.09 \times (2) = 4.22 \text{ mmHg reduction in IOP, with a resulting postoperative IOP of 16.78 mmHg.}
\]

Table 2. Matched data demographics of study population. Matched data is shown for both AIT-only and phaco-AIT group demographics.

|                           | AIT (n = 235) | phaco-AIT (n = 352) | p-value |
|---------------------------|---------------|---------------------|---------|
| **Age**                   |               |                     |         |
| Mean±SD                   | 76±9          | 75±8                | 0.04    |
| Range                     | (51.96)       | (56.94)             |         |
| **Gender**                |               |                     |         |
| Female                    | 156 (66%)     | 212 (60%)           | 0.15    |
| Male                      | 79 (34%)      | 140 (40%)           |         |
| **Types of Glaucoma**     |               |                     | 0.34    |
| ACG                       | 0 (0%)        | 0 (0%)              |         |
| POAG                      | 202 (86%)     | 313 (89%)           |         |
| SOAG                      | 33 (14%)      | 39 (11%)            |         |
| **Race**                  |               |                     | 0.77    |
| African Americans         | 7 (3%)        | 7 (2%)              |         |
| Asians                    | 48 (20%)      | 78 (22%)            |         |
| Caucasians                | 176 (75%)     | 263 (75%)           |         |
| Others                    | 4 (2%)        | 4 (1%)              |         |
| **Baseline IOP**          |               |                     | <0.01   |
| Mean±SD                   | 22.6±6.4      | 19.9±5.9            |         |
| Range                     | (10, 46)      | (10, 42)            |         |
| **Baseline Number of Glaucoma Medications** | | | <0.01 |
| Mean±SD                   | 2.8±1.1       | 2.4±1.1             |         |
| Range                     | (1.6)         | (1.5)               |         |

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Glaucoma Surgery IOP Reduction Calculator

The calculator predicting the IOP reduction had the formula:

\[-13.54 + 0.73 \times (\text{phaco}; \text{yes}:1, \text{no}:0) + 0.73 \times (\text{baseline IOP}) + 0.59 \times (\text{SOAG}; \text{yes}:1, \text{no}:0) + 0.03 \times (\text{age}) + 0.09 \times (\text{medications}).\]

For example, a 75-year-old pseudophakic patient with POAG with a baseline IOP of 21 and 2 different medications receiving AIT alone would be expressed as:

\[
13.54 + 0.73 \times (0) + 0.73 \times (21) + 0.59(0) + 0.03 \times (75) + 0.09 \times (2) = 4.22 \text{ mmHg reduction in IOP, with a resulting postoperative IOP of 16.78 mmHg.}
\]

Table 3. Univariate linear regression of patient parameters of study. A p-value of <0.05 is considered statistically significant.

|                         | Coefficient | Standard Error | p-value |
|-------------------------|-------------|----------------|---------|
| Phaco                   | -1.35       | 0.50           | <0.01   |
| Baseline IOP            | 0.74        | 0.03           | <0.01   |
| SOAG                    | 4.17        | 0.74           | <0.01   |
| Age                     | 0.10        | 0.03           | <0.01   |
| Baseline # of medications | 0.56    | 0.22           | <0.01   |
| Race                    |             |                |         |
| Asian                   | 1.10        | 2.30           | 0.64    |
| Caucasian               | 1.94        | 2.19           | 0.39    |
| Other                   | 4.84        | 3.47           | 0.18    |
| Male                    | -0.75       | 0.50           | 0.14    |

Phaco (phacoemulsification); IOP (intraocular pressure); SOAG (secondary open angle glaucoma).

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Conversely, a 75-year-old phakic patient with POAG with the same baseline IOP and medications receiving phaco-AIT in a combined approach would have an IOP reduction of $-13.54 + 0.73(1) + 0.73\times(21) + 0.59(0) + 0.03(75) + 0.09(2) = 4.95$ mmHg, thus a postoperative IOP of 16.05 mmHg. The linear relationship of pre- and postoperative IOP can be seen in the scattergrams that show every single data point (Fig 3).

**Discussion**

We created a glaucoma surgery calculator to determine the postoperative IOP based on the preoperative IOP, type of open angle glaucoma, age, medications, and type of surgery. This first calculator for minimally invasive glaucoma surgery (MIGS) can help clinicians to estimate outcomes and anticipate the need for postoperative glaucoma medications. Using *Coarsened Exact Matching*, we found only a small additional contribution of phacoemulsification to the considerable IOP reduction from AIT. The impact of baseline IOP on total pressure reduction

| Coefficient | Standard Error | p-value |
|-------------|----------------|---------|
| Intercept   | -13.54          | <0.01   |
| Phaco       | 0.73            | 0.02    |
| Baseline IOP| 0.73            | <0.01   |
| SOAG        | 0.59            | 0.24    |
| Age         | 0.03            | 0.10    |
| Baseline # of Medications | 0.09            | 0.55    |

Phaco (phacoemulsification); IOP (intraocular pressure); SOAG (secondary open angle glaucoma).

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Conversely, a 75-year-old phakic patient with POAG with the same baseline IOP and medications receiving phaco-AIT in a combined approach would have an IOP reduction of $-13.54 + 0.73(1) + 0.73\times(21) + 0.59(0) + 0.03(75) + 0.09(2) = 4.95$ mmHg, thus a postoperative IOP of 16.05 mmHg.

The linear relationship of pre- and postoperative IOP can be seen in the scattergrams that show every single data point (Fig 3).

**Fig 2. IOP and medication plots.** Preoperative and postoperative intraocular pressure (IOP; left) and number of glaucoma medications (Meds; right) over the 12 month follow-up for both groups. Represented as mean ± standard error. Statistically significantly different at all time points for both plots (p<0.05).

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was substantial, adding 0.73 mmHg IOP reduction per 1 mmHg higher baseline IOP. Both groups achieved a significant decline in medications.

Compared to the limited IOP effect of only 0.73±0.32 mmHg by phacoemulsification in our study, a more significant IOP reduction can sometimes be seen after phacoemulsification [1–3]. It has been hypothesized to be caused by TM and Schlemm's canal distension that increase the outflow facility [15,16], activation of a TM stress response pathway from ultrasound and

Fig 3. Phaco-AIT and AIT Scattergrams. Scattergrams of AIT and phaco-AIT after 1 month (left) and 12 months (right). Baseline IOP plotted against IOP at 1 month and 12 months with x = y line. Red line represents linear fit.

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fluids [17], a trabeculoplasty-like effect [18,19] or resolution of relative pupillary block [15].
Our results are consistent with the concept that this may be mediated by the remaining tempo-
ral TM [16,20]. Different from the open angle glaucoma patients examined in this study, angle
closure glaucoma patients often experience a profound IOP reduction from cataract surgery
alone, both in the chronic [21] and the acute form [22].

We caution against use of phacoemulsification alone for the purpose of IOP reduction as
recently advocated [15]. Phacoemulsification on its own does not always lower IOP reliably in
glaucoma patients because of a relatively more diseased TM [23] and can cause potentially dan-
gerous IOP spikes during the postoperative course [23,24]. This can be prevented by combi-
ing AIT with phacoemulsification [24]. A higher than normal IOP before surgery is a risk
factor for IOP spikes even in patients without glaucoma [25]. Eyes with a more decreased out-
flow facility may be more prone to this but also experience a larger IOP reduction from AIT
[26]. The impact of phacoemulsification on IOP in patients with same session TM bypass
microstents may be relatively higher compared to ab interno trabeculectomy because of more
remaining TM [4] and fewer drainage segments accessed in the former [27].

The raw baseline age differences and higher number of medications between AIT and
phaco-AIT groups match the increased incidence of cataracts and glaucoma with age [28]. Fol-
lowing coarsened exact matching, these differences were minimized and allowed a statistically
valid comparison with linear regression [29]. It was previously assumed that IOP reduction fol-
lowing AIT is relatively independent of preoperative IOP [7,8] and only limited by episcleral
venous pressure and other downstream elements [30]. The linear correlation between pre- and
postoperative IOPs seen here suggests that patients with higher baseline IOP may have both a
higher TM-mediated outflow resistance and a somewhat higher outflow resistance that is
downstream of the TM.

This study had limitations. Instead of a randomized controlled trial, we applied newer statis-
tical methods, Coarsened Exact Matching and Multiple Imputation, that belong to the class of
Monotonic Imbalance Bounding (MIB) and make no assumptions about the data generation
process [12,31]. This accounts for missing demographic values and avoids losing data thereby
increasing the validity and sample size of the study. Additionally, the 12 month follow-up is
still a relatively short-term follow-up endpoint for patients with good life expectancy and ongo-
ing ocular disease. The calculator presented here may not apply to the pediatric or juvenile
glaucoma population. Interpretations of IOP outcomes presented here have to take into
account that phaco-AIT patients in reality have a mixed indication of vision improvement (cat-
aract surgery) with often optional IOP or medication reduction (AIT). As a result, IOPs can be
considerably lower if the second of the two average glaucoma medication is not eliminated.

In conclusion, this first glaucoma surgery calculator advises clinicians on IOP after trabec-
tome-mediated ab interno trabeculectomy. Phacoemulsification has only a small additional
IOP lowering effect when combined with trabeculectomy surgery. Patients with higher baseline
IOP are expected to have a greater IOP reduction.

**Author Contributions**
Conceived and designed the experiments: NAL ENB IIB. Performed the experiments: AN ENB
IIB. Analyzed the data: AN ENB IIB NAL. Contributed reagents/materials/analysis tools: JSS
NAL. Wrote the paper: AN IIB JSS NAL.

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