



RESEARCH ARTICLE

# Combined analysis of trabectome and phaco-trabectome outcomes by glaucoma severity [version 1; referees: 3 approved]

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**Abstract**

Prior glaucoma severity staging systems were mostly concerned with visual field function and retinal nerve fiber layer, but did not include intraocular pressure or medications to capture resistance to treatment. We recently introduced a simple index that combines pressure, medications, and visual field damage and applied it to stratify outcomes of trabectome surgery. This microincisional glaucoma surgery removes the primary resistance to outflow in glaucoma, the trabecular meshwork, and has been mostly used in mild glaucoma. Traditional glaucoma surgeries have a relatively high complication rate and have been reserved for more advanced disease stages. In the analysis presented here we include our data of trabectome combined with cataract surgery. This is a common practice pattern as both occur in the same age group with increasing frequency. For patients in higher glaucoma index (GI) groups, the intraocular pressure (IOP) reduction was 2.34+/-0.19 mmHg more than those in a GI group one level lower while holding everything else constant. Those who had undergone trabectome combined with phacoemulsification had an IOP reduction that was 1.29+/-0.39 mmHg less compared to those with trabectome alone. No statistically significant difference was found between genders and age groups while holding everything else constant. Hispanics had a 3.81+/-1.08 mmHg greater IOP reduction. Pseudoexfoliation and steroid glaucoma patients had an IOP reduction that was greater by 2.91+/-0.56 and 3.86+/-0.81 mmHg, respectively, than those with primary open angle glaucoma. These results suggest a role for trabectome-mediated ab interno trabeculectomy beyond mild forms of glaucoma. Additionally, the multifactorial glaucoma index demonstrates a role in staging patients when comparing glaucoma surgical modalities.

**Open Peer Review**

Referee Status:

	Invited Referees		
	1	2	3
<b>version 1</b> published 27 Apr 2016	 report	 report	 report

- 1 **Kristy G. Mascarenhas**, Hartford Hospital/Middlesex Hospital USA
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**Competing interests:** NAL has received honoraria for trabectome wet labs and lectures from Neomedix Corp.

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## Introduction

Due to an increasing human lifespan, chronic diseases that manifest later in life, such as glaucoma and cataracts, have an increasing incidence and often occur in the same individuals<sup>1</sup>. In addition, medications used to treat glaucoma<sup>2</sup> or interventions to reduce intraocular pressure (IOP)<sup>3</sup> can cause cataracts or accelerate their occurrence. Traditional glaucoma surgery consists of trabeculectomy or tube shunt implantation, both of which have a relatively high frequency of serious complications. Ab interno trabeculectomy with the trabectome, a plasma surgical modality that ionizes and aspirates the trabecular meshwork with minimal energy transfer to surrounding tissues, was first introduced in 2004<sup>4</sup> and is considered a more mature microincisional glaucoma surgery. Trabectome surgery, similar to other surgeries in this family, has a favorable safety profile<sup>5</sup> but is often only performed in ocular hypertension or mild glaucoma stages<sup>6</sup>.

The primary outflow resistance in glaucoma is the trabecular meshwork<sup>7</sup>. However, more recent insight has also demonstrated a significant contribution to elevated pressure in glaucoma by an outflow resistance that is downstream of the trabecular meshwork<sup>8-10</sup>. According to the Goldmann equation, the limiting factor in pressure reduction from ab interno trabeculectomy with the trabectome is this residual resistance and the pressure of the episcleral veins<sup>11</sup>, and this may vary depending on glaucoma type<sup>12</sup> and severity. Glaucoma severity can be described by visual field<sup>13</sup>, optic nerve damage, and also by the number of medications needed to achieve a target IOP<sup>14</sup>.

We recently examined the amount of IOP reduction that is due to phacoemulsification at the time of trabectome surgery and found this to be relatively clinically insignificant<sup>9</sup>. We also noted that trabectome surgery performed after failed trabeculectomy caused patients with more advanced visual field damage to have on average a greater pressure reduction despite similar medications<sup>10</sup>. In the current study we have consequently combined data of trabectome and phaco-trabectome surgery patients and stratified them by a glaucoma severity index. By combining both trabectome and phaco-trabectome surgery data, a more complete picture can be obtained to guide surgeons on whether ab interno trabeculectomy may be an appropriate primary intervention.

## Methods

This retrospective analysis was approved (PRO14100026) 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. Because of the retrospective nature, no consent was required. Glaucoma patients who received trabectome with or without phacoemulsification were enrolled, except in the following circumstances: history of glaucoma surgery, any subsequent cataract or glaucoma surgery in the follow-up period, and short term followup (less than 12 months). Patients were divided into four groups (from mild to severe) according to a glaucoma index (GI), an indicator of glaucoma severity based on visual field, numbers of glaucoma medication, and preoperative IOP<sup>14</sup>. GI group 1 = mild, GI group 2 = moderate, GI group 3 = advanced, and GI4 = severe were defined based on glaucoma index scores of “≤4”, “4<GI≤8”, “8<GI≤16”,

and “>16,” respectively. The main outcome measure was the reduction of IOP. Secondary outcome measures included reduction of medication and a Kaplan-Meier survival analysis. Baseline characteristics were analyzed by the Kruskal-Wallis and chisquare tests for continuous and categorical variables between GI groups, respectively. Univariate linear regression was performed first and those demographics found to be statistically significant were included into the multivariate regression analysis. Kaplan-Meier was used for survival-curve analyses. Surgical success was defined as IOP≤21 mmHg or at least 20% IOP reduction from baseline in any two consecutive visits after three months and no secondary glaucoma surgery. Log-rank test was used to compare survival distributions of GI groups.

## Results

A total of 1340 cases of glaucoma patients were enrolled in the study and most of them were primary open angle glaucoma (POAG). The distribution across glaucoma severity groups was relatively even in number and average ages (Table 1). There was a slight preponderance of female patients in the mild and moderate groups. The ethnicity of most patients was Caucasian followed by Asian. POAG and pseudoexfoliation glaucoma were the most common diagnoses. The cup disc ratio increased by glaucoma index group and more patients were phakic than pseudophakic. More patients in the higher GI groups had a trabectome surgery that was combined with cataract surgery. Patients with a higher GI group had a more profound IOP reduction (Figure 1). At one year, the mean IOP reduction was 3.57±5.01, 5.34±5.40, 7.75±7.40, 12.09±8.08 mmHg for GI group 1 to 4, respectively. This pressure decrease occurred already on day 1 and remained relatively stable (Figure 2). Similarly, patients with more severe glaucoma experienced a larger reduction in medications which were tapered more gradually (Figure 3). When we stratified the overall IOP reduction by glaucoma severity, patients with worse glaucoma had the largest decrease.

In the univariate regression analysis, age was slightly negatively correlated with the amount of IOP reduction (Table 2) but this was not noted in the multivariate regression (Table 3) while male gender had a positive correlation in the univariate but not anymore in the multivariate regression. For patients in the higher GI group, the IOP reduction was 2.34±0.19 mmHg more than those in one level lower GI group while holding everything else constant. Hispanics experienced a pressure drop larger by 3.81±1.08 mmHg than other ethnicities as did patients with a diagnosis of pseudoexfoliation and steroid induced glaucoma (Table 3). IOP reduction was 2.91±0.56 and 3.86±0.81 mmHg more than in POAG patients. Interestingly, cataract surgery was associated with a slightly worse IOP reduction by 1.29+/-0.39 mmHg (Table 3).

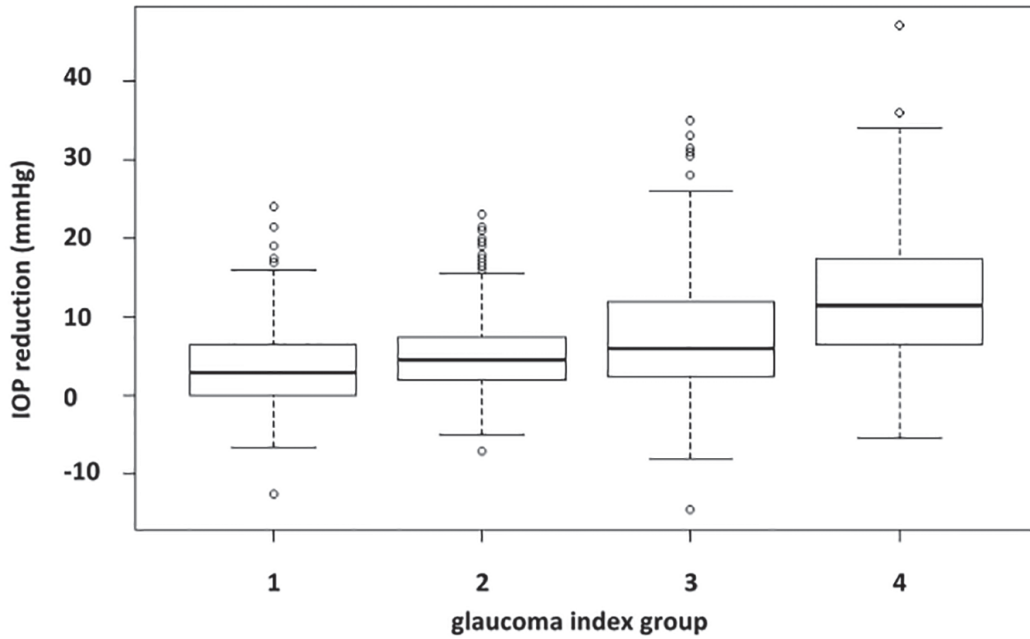
Survival rate at 12 months was 93%, 84%, 82% and 74% for GI group 1 to 4 (Figure 4). Log-rank test indicated statistically significant differences between the GI groups and patients in the lower GI groups had a higher survival rate than those in higher GI groups.

## Discussion

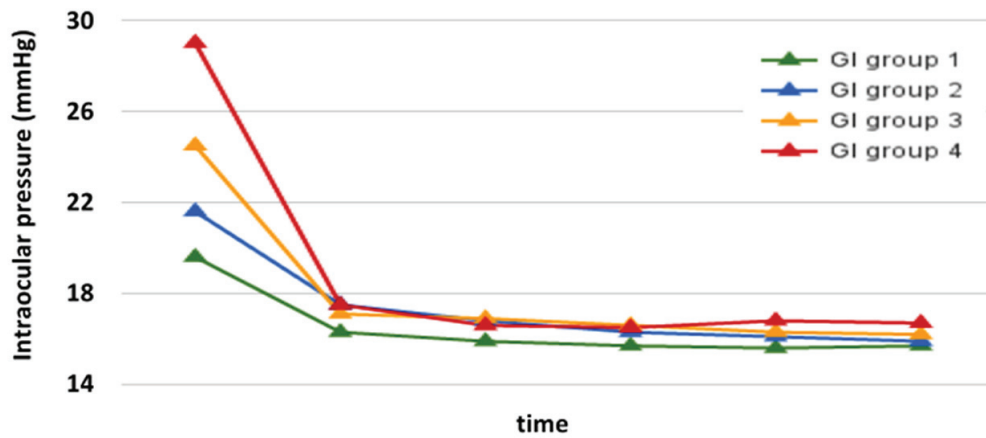
The results of the current study are confirmatory of our prior study where we examined the impact of a glaucoma severity index on the

**Table 1. Demographics.** Glaucoma index (GI); GI1 Mild:  $GI \leq 4$ ; GI2 Moderate:  $4 < GI \leq 8$ ; GI3 Advanced:  $8 < GI \leq 16$ ; GI4 Severe:  $GI > 16$ .

	GI Group 1 n=368	GI Group 2 n=322	GI Group 3 n=370	GI Group 4 n=280	p-value
<b>Age</b>					0.02
Mean±SD	71±11	68±13	69±15	66±18	
Range	18 – 92	18 – 90	18 – 96	18 – 96	
<b>Gender</b>					<0.01
Female	225 (61%)	181 (56%)	183 (49%)	135 (48%)	
Male	139 (38%)	139 (43%)	184 (50%)	136 (49%)	
NR	4 (1%)	2 (1%)	3 (1%)	9 (3%)	
<b>Race</b>					<0.01
African American	29 (8%)	16 (5%)	17 (5%)	14 (5%)	
Asian	98 (27%)	86 (27%)	115 (31%)	107 (38%)	
Caucasian	203 (55%)	177 (55%)	202 (55%)	124 (44%)	
Hispanic	23 (6%)	16 (5%)	17 (5%)	21 (8%)	
Other	15 (4%)	27 (8%)	19 (5%)	14 (5%)	
<b>Glaucoma Diagnosis</b>					<0.01
Primary open angle	288 (78%)	241 (75%)	257 (69%)	179 (64%)	
Pseudoexfoliation	28 (8%)	37 (11%)	59 (16%)	41 (15%)	
Pigment Dispersion	18 (5%)	10 (3%)	11 (3%)	6 (2%)	
Steroid	10 (3%)	18 (6%)	28 (8%)	39 (14%)	
Open angle type not specified	24 (7%)	16 (5%)	15 (4%)	15 (5%)	
<b>Visual Acuity (logMAR)</b>					<0.01
Mean±SD	0.31±0.34	0.28±0.35	0.37±0.52	0.47±0.61	
Range	-0.19 – 2.12	-0.19 – 2.00	-0.19 – 3.00	-0.19 – 3.00	
<b>Cup/Disc Ratio</b>					<0.01
Mean±SD	0.69±0.18	0.74±0.15	0.75±0.17	0.83±0.12	
Range3	0.1 – 1.9	0.3 – 1.00	0.1 – 1.00	0.25 – 1.00	
<b>Lens Status</b>					<0.01
Phakic	296 (80%)	231 (72%)	240 (65%)	159 (57%)	
Pseudophakic	56 (15%)	78 (24%)	116 (31%)	104 (37%)	
Aphakic	1 (0%)	1 (0%)	0 (0%)	3 (1%)	
Not recorded	15 (4%)	12 (4%)	14 (4%)	14 (5%)	
<b>Shaffer Grade</b>					0.47
I	5 (1%)	6 (2%)	4 (1%)	2 (1%)	
II	23 (6%)	25 (8%)	20 (5%)	27 (10%)	
III	107 (29%)	99 (31%)	121 (33%)	85 (30%)	
IV	192 (52%)	146 (45%)	172 (46%)	134 (48%)	
NR	41 (11%)	46 (14%)	53 (14%)	32 (11%)	
<b>Combined Surgeries</b>					<0.01
Trabectome+Phaco	164 (45%)	202 (63%)	260 (70%)	216 (77%)	
Trabectome Alone	204 (55%)	120 (37%)	110 (30%)	64 (23%)	

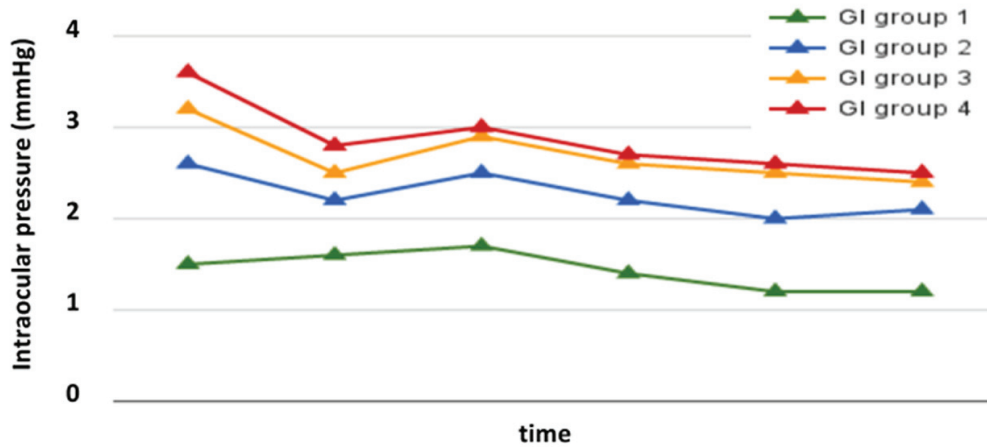


**Figure 1.** Reduction of intraocular pressure at 1 year. More severe glaucoma was associated with a larger pressure reduction.



IOP	Baseline	1D	1M	3M	6M	12M
GI1	19.6±5.2	16.3±7.5	15.9±4.7	15.7±4.1	15.6±3.5	15.7±3.4
GI2	21.6±5.9	17.5±8.8	16.8±5.6	16.3±4.9	16.1±4.0	15.9±3.7
GI3	24.5±7.8	17.1±8.5	16.9±5.8	16.6±5.3	16.3±4.3	16.2±4.4
GI4	29.0±7.3	17.5±8.7	16.6±5.9	16.5±5.0	16.8±4.6	16.7±4.7

**Figure 2.** Intraocular pressure over time by glaucoma index group. Patients with a higher group had the largest decrease (average and standard deviation).



IOP	Baseline	1D	1M	3M	6M	12M
GI1	1.5±1.0	1.6±1.2	1.7±1.2	1.4±1.1	1.2±1.1	1.2±1.1
GI2	2.6±1.1	2.2±1.6	2.5±1.4	2.2±1.4	2.0±1.3	2.1±1.3
GI3	3.2±0.9	2.5±1.6	2.9±1.4	2.6±1.2	2.5±1.3	2.4±1.2
GI4	3.6±0.8	2.8±1.8	3.0±1.5	2.7±1.5	2.6±1.3	2.5±1.4

**Figure 3. Medications by glaucoma index group.** Patients in the severe and advanced groups had the largest medication reduction (average and standard deviation).

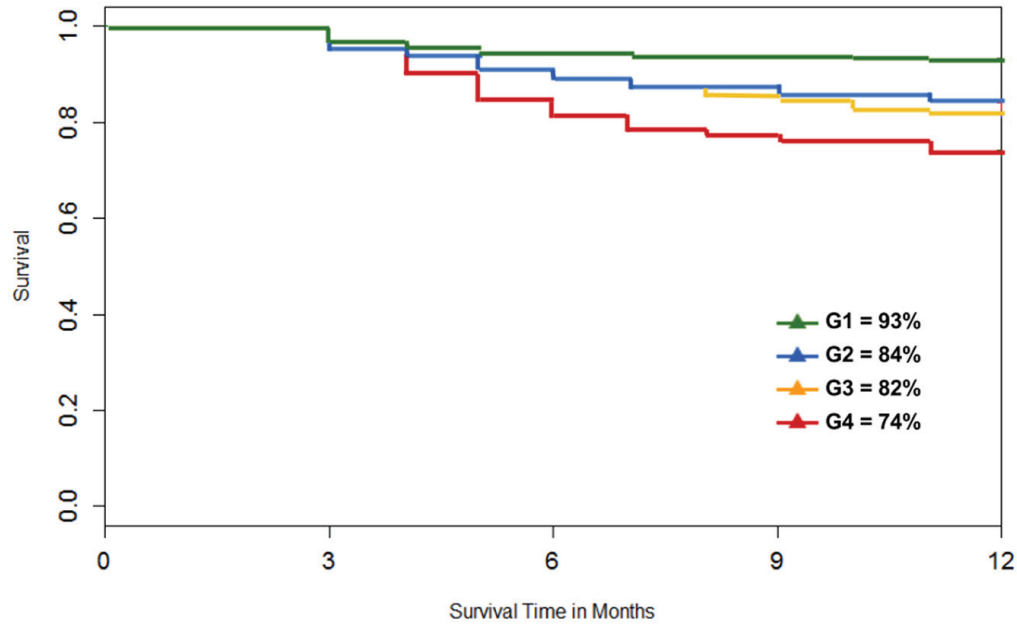
**Table 2. Univariate regression.**

	Coefficient	Standard Error	p-value
<b>Age</b>	-0.06	0.02	<0.01
<b>Male</b>	1.12	0.40	0.01
<b>Ethnicity</b>			
Asian	0.45	0.90	0.61
Caucasian	0.12	0.87	0.89
Hispanic	4.45	1.16	<0.01
Other	-0.57	1.26	0.66
<b>Diagnosis</b>			
Open angle type not specified	0.78	0.90	0.39
Pigmentary Dispersion	0.41	1.12	0.71
Pseudoexfoliation Glaucoma	3.44	0.59	<0.01
Steroid Glaucoma	5.38	0.88	<0.01
<b>Cup/Disc Ratio</b>	-2.30	1.34	0.09
<b>Shaffer Grade</b>	-0.38	0.31	0.21
<b>Lens</b>			
Aphakic	0.59	3.10	0.85
Pseudophakic	0.66	0.49	0.18
<b>Combined with phaco</b>	-3.20	0.41	<0.01

**Table 3. Multivariate Regression.**

	Coefficient	Standard Error	p-value
<b>Glaucoma index group</b>	2.34	0.19	<0.01
<b>Age</b>	-0.02	0.02	0.11
<b>Male</b>	0.60	0.38	0.12
<b>Ethnicity</b>			
Asian	-0.57	0.84	0.50
Caucasian	0.10	0.84	0.90
Hispanic	3.81	1.08	<0.01
Other	-0.30	1.05	0.78
<b>Diagnosis</b>			
Open angle type not specified	1.30	0.79	0.10
Pigmentary Dispersion	0.54	1.10	0.62
Pseudoexfoliative Glaucoma	2.91	0.56	<0.01
Steroid Glaucoma	3.86	0.81	<0.01
<b>Combined with phaco</b>	-1.29	0.39	<0.01

results of trabectome surgery when done as a standalone procedure<sup>14</sup>. The larger number of patients involved here allowed discovery of additional factors. We included here phaco-trabectome patients, who have a different, mixed indication that often includes visually significant cataract as the primary motivator while presenting with



**Figure 4. Survival plot by GI groups.** The highest GI group with more advanced glaucoma (GI4, red) had the worst survival.

a relatively stable glaucoma. We did so after demonstrating by a rigorous statistical matching method, coarsened exact matching<sup>15</sup>, that phacoemulsification does not contribute significantly to IOP reduction when done at the same time<sup>9</sup> or in a surgery prior to trabectome surgery<sup>16</sup>.

The results of this study match established risk factors and findings from other studies. Steroid glaucoma and pseudoexfoliation often produce very high IOPs and the primary pathology is located in the trabecular meshwork. As a result, ablating the meshwork reduces intraocular pressure very effectively<sup>17</sup>.

In that study we found that a larger pressure reduction is achieved in more severe glaucoma consisting of a more advanced visual field damage, a higher pre-intervention IOP and more medications. We had previously found that cup disc ratio, Hispanic ethnicity and diagnosis of steroid-induced glaucoma are related to a larger IOP reduction<sup>14</sup>. In addition to steroid induced glaucoma, pseudoexfoliation glaucoma confers a larger IOP reduction in the present study. Although phacoemulsification was negatively correlated with IOP reduction in this analysis, something that has been described for combined traditional trabeculectomy<sup>18,19</sup>, it is important to recall that this study was not designed to formally compare outcomes of combined versus trabectome-alone as we have done before<sup>9</sup>. The number of patients analyzed here is significantly higher than in the two separate studies but we note similar results in the regression analysis allowing to discover additional factors.

The Goldmann equation describes that the limiting factor to IOP reduction after removal of the trabecular meshwork, the substrate of the main outflow resistance, is the episcleral venous pressure and uveoscleral outflow<sup>11</sup>. The data presented here indicate that that this is mostly true also for more advanced glaucoma and consistent with two prior studies that demonstrated that significant conventional outflow can be recovered even after failed tube shunts<sup>20</sup>

and after failed trabeculectomy<sup>10</sup>. Small differences of the eventually achieved pressures could be explained by an episcleral venous pressures that is higher in glaucoma<sup>12</sup>. Overall, the data presented here suggest that ab interno trabeculectomy might be an appropriate surgery to attempt to control more than mild glaucoma.

#### Data availability

The raw datasets could not be made available because the data could not be sufficiently anonymised to protect patient confidentiality. No individuals other than the investigators or research staff involved in the conduct of this research study and authorized representatives of the University Research Conduct and Compliance Office (RCCO) are permitted access to research data or documents (including medical record information) associated with the conduct of this research study. Institutional IRB rules are available on the following University of Pittsburgh OSIRIS website: <http://www.osiris.pitt.edu/osiris>. The approval permit number for this study is PRO14100026.

#### Author contributions

YD, PR, RTL and NAL acquired and analyzed the data, all authors participated in writing and reviewing the manuscript, NAL provided funding.

#### Competing interests

NAL has received honoraria for trabectome wet labs and lectures from Neomedix Corp.

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*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

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# Open Peer Review

Current Referee Status:



Version 1

Referee Report 20 May 2016

doi:10.5256/f1000research.9096.r13594



**Steven R. Sarkisian Jr.**

University of Oklahoma College of Medicine, Oklahoma City, OK, USA

This is an interesting study demonstrating that ab interno trabeculectomy is an appropriate surgery to attempt to control more than mild glaucoma. Ab interno trabeculectomy is a growing trend in glaucoma surgery, not just with the trabectome device, but also with the dual blade that is recently on the market from New World Medical, and also the Sight Sciences device called TRAB 360. The trend toward ab interno, non-penetrating surgery in patients with not only mild, but even advanced glaucoma demonstrates our aversion for conventional filtration surgery and the significantly high complication rate seen with it. I am grateful to the authors for writing up their large case series of results that mirror a "real world" practice using this procedure. Glaucoma surgeons need to consider expanding the use of this type of technique, knowing that by doing so, they do not rule out the possibility of doing conventional surgery in the future, if necessary.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Competing Interests:** Dr Sarkisian is a consultant to New World Medical, Sight Sciences, Beaver Vistec International, Glaukos, Alcon, Aeon Astron, and InnFocus. He has received research funding from Glaukos, Transcend, and Aeon Astron.

Referee Report 13 May 2016

doi:10.5256/f1000research.9096.r13591



**William Myers**

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The concept of creating glaucoma index buckets has been validated by the authors in their *PLoS One* paper<sup>1</sup>. They showed that similar patients with and without cataract undergoing ab-interno trabeculectomy can be combined in one study. I found the conclusion that use of the Trabectome would be potentially useful in many cases of procedures combined with cataract surgery, even when the glaucoma is fairly far advanced. As the site of greatest resistance to fluid exit, removing the trabecular membrane alone could potentially lower a high enough pressure gradient, at least temporarily. With the potential to avoid a full thickness filter and its attendant complications, the Trabectome could buy time to ride out a post operative cataract pressure spike.

I would like to see more analysis of when an ab-interno trabeculectomy might be risky such as in severe glaucoma with split fixation where the alternative is an ab-externo filter or tube and then later cataract surgery. If this procedure is more effective than iStent and other bypass procedures, and involves no costly per case costs in comparison, then Trabectome with phacoemulsification may be the most prudent choice.

At the other end of the spectrum in ocular hypertension patients with no current measurable damage, is the risk profile of Trabectome combined with phacoemulsification reasonable, compared to the risk and cost of drops or SLT as alternatives? We know that the effectiveness of only one iStent, the FDA approved norm in the US, is quite often not sufficient to reduce pressures adequately.

There was another issue to be considered. The grading system uses pressure as one of the components and also uses the pressure drop as the metric of success. There be some circular reasoning involved, as the initial pressure head itself is a determinant of the resulting pressure drop using drops, lasers or surgery. Unfortunately the study can not be replicated exactly due to patient confidentiality considerations.

The validated glaucoma severity scale. from their previous paper in PLoS, uses simple-to-obtain inputs: IOP, number of medications and visual field loss; graded using MD and PSD from the visual field testing. The combination of these factors with definable numeric values can be utilized by cataract surgeons without glaucoma subspecialties.

## References

1. Loewen RT, Roy P, Parikh HA, Dang Y, Schuman JS, Loewen NA: Impact of a Glaucoma Severity Index on Results of Trabectome Surgery: Larger Pressure Reduction in More Severe Glaucoma. *PLoS One*. 2016; **11** (3): e0151926 [PubMed Abstract](#) | [Publisher Full Text](#)

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Competing Interests:** No competing interests were disclosed.

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This was an interesting analysis of the use of Trabectome surgery in patients with more severe glaucomas. Comments and questions are as follows, most of which would clarify the methods and data analysis for the reader:

- The abstract and introduction could be clearer about the purpose of the study. You have to wait a long time to find out that this was a retrospective chart review of patients who had received Trabectome and phaco-Trabectome surgeries. Were the authors looking for statistically significant differences in IOP reduction between the glaucoma severity groups, or equivalent effect in mild vs. severe glaucoma? If so, was a power calculation done?

- The abstract makes it sound as though only phaco-Trabectome cases were included, but the introduction states that both Trabectome and combined surgeries were included. Please clarify the abstract?
- The methods section briefly introduces the glaucoma index system that was used, but especially for someone who has not read the previous article evaluating it, a bit more detail about the point system used would be helpful.
- One of the exclusion criteria was prior glaucoma surgery. Is data available about the number of patients who had previously had SLT/ALT?
- Table 1 shows the number of Trabectomes vs. phaco/Trabectomes. Did all phakic patients have cataract surgery, or did any receive Trabectome alone?
- Over what time period did the reviewed patients receive Trabectome? Relatively recently, or closer to the beginning of Trabectome use? How many different surgeons' patients were reviewed? (Is it possible that surgical techniques evolved over time, or that different surgeons' techniques varied significantly?) A sentence like "We reviewed the charts of XXX patients from XXX surgeons who underwent CE/Trabectome or Trabectome alone between 2012-2016" would be very helpful.
- The authors state that patients in the severe GI group and patients with more severe glaucomas like pseudoexfoliation and steroid-response had a greater IOP reduction than other groups. Since IOP is one component of the glaucoma index and Trabectome does lower IOP more significantly with higher pre-op IOP, is it possible to say that Trabectome had a greater effect in these groups independently of pre-op IOP? (To confirm, was this analysis done?)
- Can the authors include a short discussion of limitations of the current study and possibly a bit of speculation on the smaller IOP reduction with phaco/Trabectome than with Trabectome alone, as well as on why the more severe GI groups saw a shorter-lived IOP reduction?

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

***Competing Interests:*** No competing interests were disclosed.

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