



RESEARCH ARTICLE

REVISED Combined analysis of trabectome and phaco-trabectome outcomes by glaucoma severity [version 2; referees: 3 approved]

Yalong Dang*, Pritha Roy*, Igor I. Bussel, Ralitsa T. Loewen, Hardik Parikh,

Nils A. Loewen








Department of Ophthalmology, School of Medicine, University of Pittsburgh, Pittsburgh, USA

* Equal contributors

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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. In the analysis presented here, we combined data of trabectome alone and trabectome with same session cataract surgery to increase testing power and chances of effect discovery. 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.

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	1	2	3
REVISED			
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version 1 published 27 Apr 2016	 report	 report	 report

- Kristy G. Mascarenhas**, Hartford Hospital/Middlesex Hospital USA
- William Myers**, Northwestern University USA
- Steven R. Sarkisian Jr.**, University of Oklahoma College of Medicine USA

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Corresponding author: Nils A. Loewen (loewen.nils@gmail.com)

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

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REVISED Amendments from Version 1

We have completely rewritten the Introduction to better explain the purpose of combining trabectome and phaco-trabectome data and the idea behind the glaucoma index – and explained the index in more detail in the Methods. In the Discussion we have expanded on the limitations of the study and added a better explanation why phaco-trabectome patients have a lesser IOP reduction

See referee reports

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 individuals¹. Medications² and surgeries³ for glaucoma can induce or worsen cataracts. As a result, combining both cataract and glaucoma surgery is increasingly common, especially since the introduction of safer, microincisional glaucoma surgeries^{4,5}. We recently examined the amount of intraocular pressure (IOP) reduction due to phacoemulsification at the time of trabectome surgery and found this to be clinically relatively insignificant⁶. 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 and medication reduction despite similar medications⁷. In the current study we have consequently combined data of trabectome and phaco-trabectome surgery patients and stratified them by a glaucoma severity index. The idea behind developing a glaucoma index was twofold: 1) to control for different indications for surgery and 2) to stratify outcomes by glaucoma severity.

Because indications for surgery may be a reduction of IOP, elimination of medications, or vision improvement either alone or, more commonly, a combination of those, we recently created a simple glaucoma index⁸ that combines IOP, number of medications and visual field status to gauge relative clinical glaucoma severity but also describes resistance to treatment. Combining IOP and number of medications controls for treatment patterns. For instance, because glaucoma eye drops reduce IOP, a patient with an IOP of 16 mmHg on one medication might have a glaucoma that is clinically similarly challenging as one with an IOP of 24 mmHg off treatment.

Plasma-mediated ab interno trabeculectomy with the trabectome, the surgery examined here, removes the nasal trabecular meshwork (TM) that is thought to be the primary outflow resistance in glaucoma⁹. However, more recent insight has demonstrated a significant contribution by unidentified elements downstream of the trabecular meshwork^{6,7,10} as half of the outflow resistance might remain unaccounted for^{11,12}. Since removal of TM is achieved in all patients regardless of glaucoma severity, outcome differences have to reflect differences in the outflow tract distal to the TM. We included the visual field status to investigate whether IOP reduction from trabectome surgery might be correlated to glaucoma severity. 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). A history of laser trabeculoplasty did not lead to exclusion. 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, number of glaucoma medications, and preoperative IOP⁸. Baseline IOP was divided into 4 groups, <20 mmHg, 20–29 mmHg, 30–39 mmHg, and above 40 and assigned with 1 to 4 points. Glaucoma medications (meds) were divided into 4 groups: ≤1, 2, 3, or ≥4, and assigned values of 1 to 4. Visual field (VF) was separated into 4 groups with points from 1 to 4: mild, moderate, advanced and end stage. GI was then defined as VF*meds*IOP and separated into GI group 1 = mild, GI group 2 = moderate, GI group 3 = advanced, and GI4 = severe 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.

Table 1. Demographics. Glaucoma index (GI); GI1 Mild: GI≤4; GI2 Moderate: 4<GI≤8; GI3 Advanced: 8<GI≤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
Age					0.02
Mean±SD	71±11	68±13	69±15	66±18	
Range	18 – 92	18 – 90	18 – 96	18 – 96	
Gender					<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%)	
Race					<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%)	
Glaucoma Diagnosis					<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%)	
Visual Acuity (logMAR)					<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	
Cup/Disc Ratio					<0.01
Mean±SD	0.69±0.18	0.74±0.15	0.75±0.17	0.83±0.12	
Range ³	0.1 – 1.9	0.3 – 1.00	0.1 – 1.00	0.25 – 1.00	
Lens Status					<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%)	
Shaffer Grade					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%)	
Combined Surgeries					<0.01
Trabectome+Phaco	164 (45%)	202 (63%)	260 (70%)	216 (77%)	
Trabectome Alone	204 (55%)	120 (37%)	110 (30%)	64 (23%)	

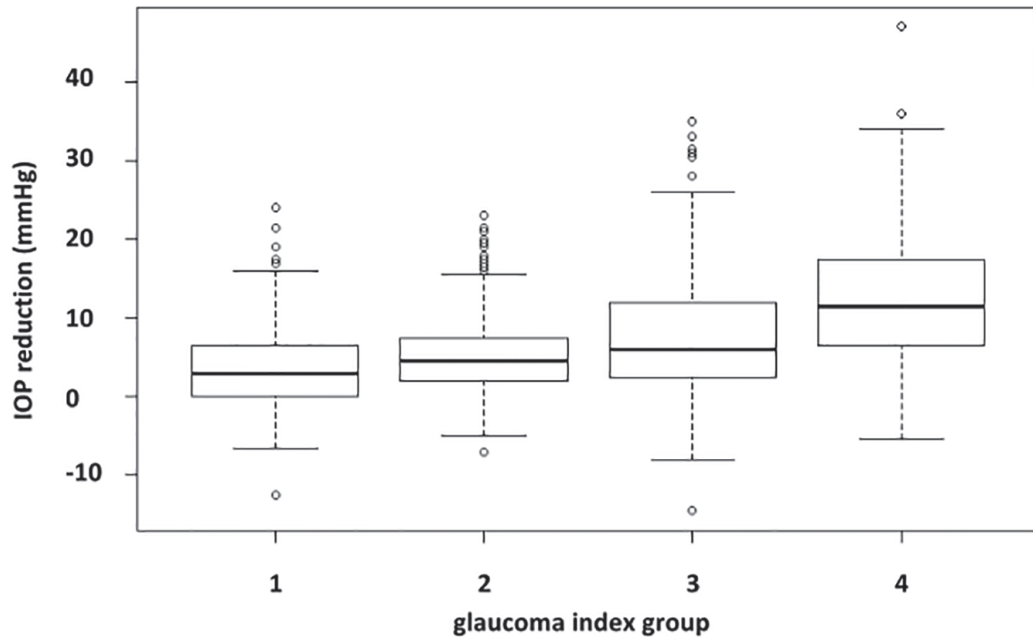
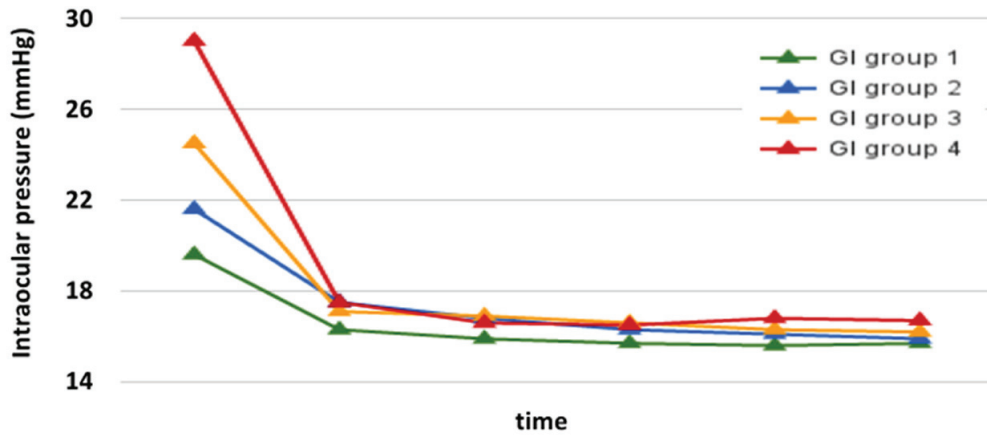
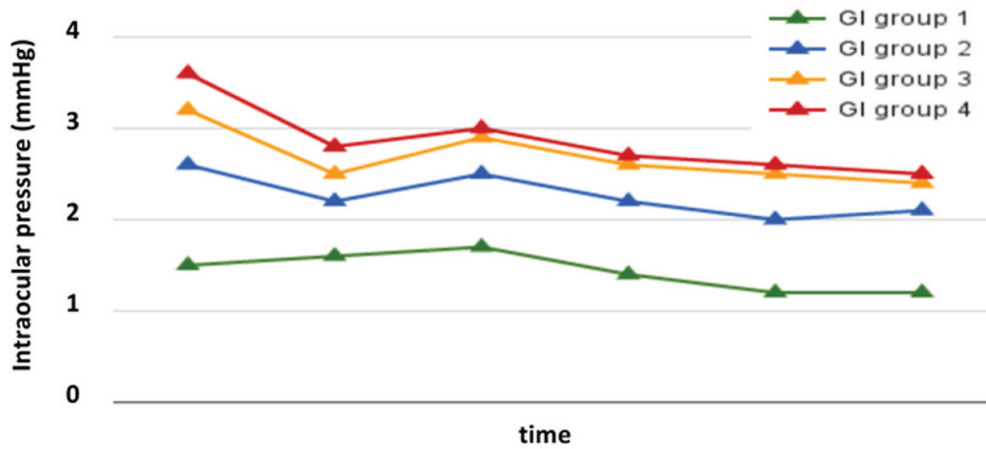


Figure 1. Reduction of intraocular pressure at 1 year. More severe glaucoma was associated with a larger pressure reduction.



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
Age	-0.06	0.02	<0.01
Male	1.12	0.40	0.01
Ethnicity			
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
Diagnosis			
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
Cup/Disc Ratio	-2.30	1.34	0.09
Shaffer Grade	-0.38	0.31	0.21
Lens			
Aphakic	0.59	3.10	0.85
Pseudophakic	0.66	0.49	0.18
Combined with phaco	-3.20	0.41	<0.01

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 results of trabectome surgery when done as a standalone procedure¹⁴. 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

Table 3. Multivariate Regression.

	Coefficient	Standard Error	p-value
Glaucoma index group	2.34	0.19	<0.01
Age	-0.02	0.02	0.11
Male	0.60	0.38	0.12
Ethnicity			
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
Diagnosis			
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
Combined with phaco	-1.29	0.39	<0.01

presenting with a relatively stable glaucoma. without the need for pressure reduction but a motivation to reduce medications. We did so after demonstrating by a rigorous statistical matching method, coarsened exact matching¹³, that phacoemulsification does not contribute significantly to IOP reduction when done at the same time⁶ or in a surgery prior to trabectome surgery¹⁴. As in our prior studies¹⁴, phaco-trabectome patients had a lower preoperative IOP. This study focused on stratification of outcomes by glaucoma index and did not apply advanced matching strategies that we applied elsewhere^{6,14,15} to compare two groups. Hence, one cannot conclude from this study that cataract surgery is causatively linked to a diminished IOP reduction when compared to trabectome-only patients. On the contrary, an IOP reduction in many of our phaco-trabectome patients is simply not necessary to the same degree.

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 effectively¹⁷.

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

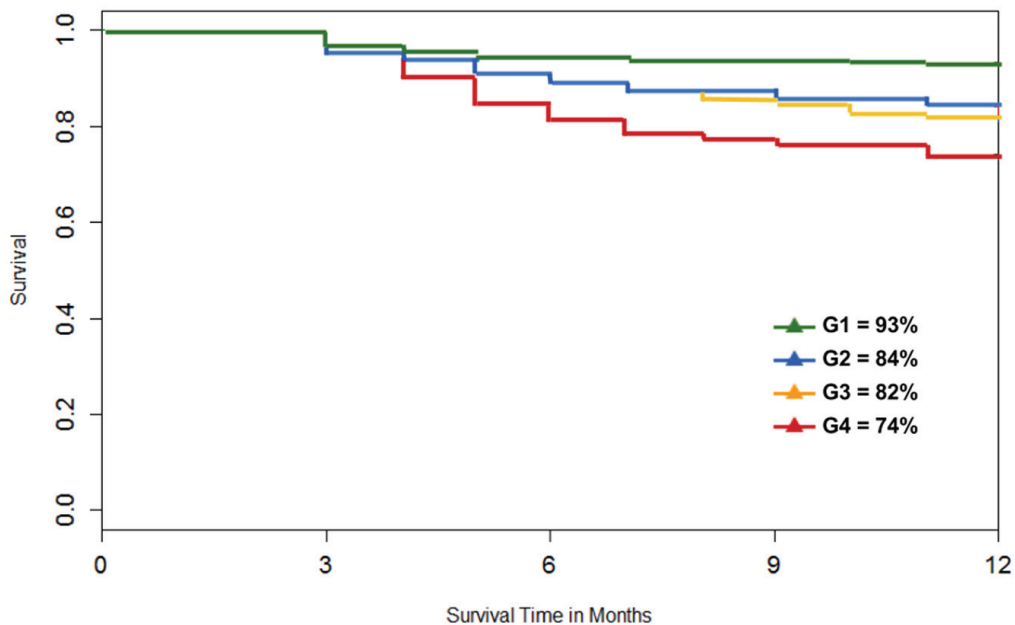


Figure 4. Survival plot by GI groups. The highest GI group with more advanced glaucoma (G14, red) had the worst survival.

had previously found that cup disc ratio, Hispanic ethnicity and diagnosis of steroid-induced glaucoma are related to a larger IOP reduction¹⁴. 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^{18,19}, it is important to recall that this study was not designed to formally compare outcomes of combined versus trabectome-alone as we have done before⁹. 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 outflow¹¹. 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 shunts²⁰ and after failed trabeculectomy¹⁰. Small differences of the eventually achieved pressures could be explained by an episcleral venous pressures that is higher in glaucoma¹². This study has several limitations: to maximize patient number, we included all trabectome surgeries regardless of lens status or lens-cosurgery because our prior studies indicated that neither had a clinically relevant impact^{14,22,23}. This study was limited to only one year when follow up and data integrity was most amenable to automated retrieval and analysis. As a retrospective analysis, this study cannot discover causality and is only able to advise that patients with more severe glaucoma had a similar postoperative IOP and a comparable reduction in medications as those with mild glaucoma. 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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William Myers

Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

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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Steven R. Sarkisian Jr.

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

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.

Version 1

Referee Report 20 May 2016

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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

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William Myers

Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

The concept of creating glaucoma index buckets has been validated by the authors in their *PLoS One* paper¹. 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.

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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](#)

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Competing Interests: No competing interests were disclosed.

Author Response 09 Jun 2016

Nils Loewen,

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.

Authors: This study is designed to analyze how patients with more severe glaucoma fared during the one-year follow-up, and the all-inclusive design maximizes the patient numbers. The results indicate that this microincisional surgery is a viable first option even in more severe glaucoma for many patients, but the resulting pressure is not low enough for many as the survival curve demonstrates. Postoperative complications are surprisingly common after traditional glaucoma surgery. Leakage, endophthalmitis, hypotony, hardware erosion, damage to ocular tissues and other complications that are vision threatening occur with an additive probability of 77% in trabeculectomies and 58% in glaucoma drainage implants.⁹ The surgeon has to discuss with each patient whether the avoidance of postoperative complications of traditional surgeries is worth the risk of an insufficient pressure reduction and the need to move on. In this context, it is important to recall that the postoperative IOP for tubes and trabeculectomies is only approximately 1 to 2 mmHg less than reported here.¹⁰

In forthcoming publications with fewer patients and full data disclosure, we report propensity score matched results of tube shunts and trabectome for a valid comparison of these surgical modalities. Because of the speed and safety of ab interno trabeculectomy, there is also a role for combining the two to achieve a lower IOP with fewer medications.

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.

Authors: It is hard to compare the effectiveness of different surgeries and in various practices without a randomized controlled design. The only way to obtain a high-quality comparison is to perform matching as we have done recently.^{3,5} A cost analysis is similarly specific to the geographical area and practice. Prior cost analyses suggest that SLT is better or similar to eye drops in lowering IOP and more cost effective, even returning more than initially invested.^{11,12} The same can be said about micro-incisional glaucoma surgeries¹³ although this depends on the long-term viability of the chosen surgical modality and costs of anesthesia. SLT is our first line of treatment before use of drops and trabectome surgery presents a sharp step up. It is certainly convenient, fast and safe to combine at the time of cataract surgery. After trabectome surgery, only the distal outflow tract generates pressure causing most patients to drop into the mid-teens while SLT achieves more of a relative reduction that depends on the preoperative IOP. Our study presented here shows that the postoperative results are mostly independent of preoperative IOP (or that a larger IOP reduction is achieved in higher preoperative IOP).

There was another issue to be considered. The grading system uses pressure as one of the components and also use s 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.

Authors: Different from other glaucoma staging systems graded by a defect of visual field or optic nerve injury^{14–16}, the glaucoma index here includes the relative resistance to treatment by individual patients. There is no circular logic, however, because we did not develop a prediction model that would have used a set of normal patients to train an algorithm and control patients within a study that were separated out from progressing patients as we have used elsewhere¹⁷. Both IOP and medications are reduced (or one could say the glaucoma index is reduced) by this procedure.

Unfortunately the study can not be replicated exactly due to patient confidentiality considerations.

Authors: HIPAA concerns are particularly relevant for this study describing many individuals. Fines can quickly climb to millions of dollars:
<https://www.truevault.com/blog/what-is-the-penalty-for-a-hipaa-violation.html> We are very impressed with F1000Research and the compelling benefits of pre-printing and open peer review and will provide full open data with our upcoming publications. Although it is the standard not to release full datasets in clinical ophthalmology publications, we have come to realize that this is a disservice. For instance, one could apply matching strategies to other datasets to compare surgeries and we hope to make ours available for this purpose.

The validated glaucoma severity scale from their previous paper in PLoS, uses simple-to-obtain inputs: IOP, the 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.

Authors: Yes, we agree. We were surprised that this has not been attempted before. Hopefully, better indices will become available. We have a glaucoma risk calculator in our medical record system, a customized version of Epic, and that has been a big step forward.

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

Referee Report 10 May 2016

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Kristy G. Mascarenhas

Hartford Hospital/Middlesex Hospital, Middletown, CT, USA

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.

Author Response 09 Jun 2016

Nils Loewen,

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.

1. *Were the authors looking for statistically significant differences in IOP reduction between the glaucoma severity groups, or equivalent effect in mild vs. severe glaucoma?*
2. *If so, was a power calculation done?*

Authors: Thank you for the opportunity to revise our abstract and introduction.

We have added to the abstract: "In the analysis presented here, we combined data of trabectome alone and trabectome with same session cataract surgery to increase testing power and chances of effect discovery."

We have also completely rewritten the introduction to explain the purpose of combining trabectome and phaco-trabectome data better and the idea behind the glaucoma index. Briefly, we recently created a simple glaucoma index that combines IOP, the number of medications and visual field status to gauge relative clinical glaucoma severity but also describes resistance to treatment. This may control for medication use when trying to gauge IOP results and allow to focus on glaucoma severity related outcomes. We combined trabectome and phaco-trabectome data sets because phacoemulsification is not a significant contributor to IOP reduction in studies with advanced matching strategies.

A power calculation was done and our regression analysis has a power of 0.95. We would require 82 patients to detect a GI IOP difference for a medium sized effect of 0.3 and a power of 80%. As our statistician advises, a power analysis is only needed when no statistical significance is found

and that is why we had not reported it in our original submission. If a statistically significant difference is found as here, then that suggests that the statistical test is powerful enough.

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?

Authors: Thank you for noticing this. Both were included and we have added the following to the abstract: "In the analysis presented here, we combined data of trabectome alone and trabectome with same session cataract surgery to increase testing power and chances of effect discovery."

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.

Authors: We have updated our methods section to explain the individual factors in more detail: "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, the number of glaucoma medications, and preoperative IOP¹. Baseline IOP was divided into 4 groups, <20 mmHg, 20-29 mmHg, 30-39 mmHg, and above 40 and assigned with 1 to 4 points. Glaucoma medications (meds) were divided into 4 groups: ≤1, 2, 3, or ≥4, and assigned values of 1 to 4. Visual field (VF) was separated into 4 groups with points from 1 to 4: mild, moderate, advanced and end-stage. GI was then defined as VF*meds*IOP and separated into GI group 1 = mild, GI group 2 = moderate, GI group 3 = advanced, and GI4 = severe defined based on glaucoma index scores of "≤4", "4<GI≤8", "8<GI≤16", and ">16," respectively."

One of the exclusion criteria was prior glaucoma surgery. Is data available about the number of patients who had previously had SLT/ALT?

Authors: Laser trabeculoplasty is the first line of treatment in our practice pattern, and this was not an exclusion criterion. Nearly all patients will have had this. Trabeculoplasty was not included as a factor in the analysis to reduce complexity. We have added to Methods: "A history of laser trabeculoplasty did not lead to exclusion."

Table 1 shows the number of Trabectomes vs. phaco/Trabectomes. Did all phakic patients have cataract surgery, or did any receive Trabectome alone?

Authors: We have analyzed the effect of trabectome in phakic patients before in two different studies^{2,3} and found that even in narrow angles there does not seem to be a significant difference. Consequently, we included here all patients, including trabectome patients who remained phakic, to focus on the glaucoma index without further break down into subgroups.

It is important to recall that differences in phaco versus no phaco are merely based on averages. Because of a mixed indication for these patients (many cataract surgery patients do not need a pressure reduction and merely want to reduce medications) and because no formal matching was done, one cannot conclude from this study that cataract surgery is causatively linked to a diminished IOP reduction when compared to trabectome-only patients. On the contrary, an IOP reduction in many of our phaco-trabectome patients is simply not necessary to the same degree. *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.

Authors: The study period included data from 2011 up until the end of 2015. We did not analyze outcomes by individual surgeons. We concede that a majority of surgeries was performed by the senior author of this study and after 2012. Unfortunately, is not easily possible to provide the exact breakdown due to how data is extracted from the EMR data cloud. Manual curation of thousands of patient operative reports would be necessary.

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?)

Authors: Thank you very much for this inquiry. Without conducting a prospective, randomized controlled study or applying an advanced matching strategy, it is not possible to detect a strong, likely causative, correlation between glaucoma type and the amount of resulting IOP drop. The multivariate regression analysis we have done here does show that pseudoexfoliation and steroid glaucoma are significantly associated with a larger IOP reduction. This would be expected since both are obvious trabecular meshwork diseases. It is not clear what the substrate is that prevents IOP from reaching the theoretical limit of episcleral venous pressure after trabecular ablation or bypass.

The glaucoma index already captures resistance to medical treatment and these eyes require an IOP that is considerably lower than what can be achieved by trabecular ablation. This may reflect a tipping point.⁴

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?

Authors: Thank you. We would like to add to the discussion the following: "This study has several limitations: to maximize patient number, we included all trabectome surgeries regardless of lens status or lens-cosurgery because our prior studies indicated that neither had a clinically relevant impact.^{2,3,5} This study was limited to only one year when follow-up and data integrity was most amenable to automated retrieval and analysis. As a retrospective analysis, this study cannot discover causality and is only able to advise that patients with more severe glaucoma had a similar postoperative IOP and a comparable reduction in medications as those with mild glaucoma."

We have also added a better explanation why phaco-trabectome patients have a lesser IOP reduction: "We included here phaco-trabectome patients, who have a different, mixed indication that often includes a visually significant cataract as the primary motivator while presenting with a relatively stable glaucoma without the need for pressure reduction but a motivation to reduce medications. We did so after demonstrating by a rigorous statistical matching method, coarsened exact matching⁶, that phacoemulsification does not contribute significantly to IOP reduction when done at the same time⁷ or in a surgery prior to trabectome surgery⁵. As in our prior studies⁵,

phaco-trabectome patients had a lower preoperative IOP. This study focused on stratification of outcomes by glaucoma index and did not apply advanced matching strategies that we applied elsewhere^{5,7,8} to compare two groups. Hence, one cannot conclude from this study that cataract surgery is causatively linked to a diminished IOP reduction when compared to trabectome-only patients. On the contrary, an IOP reduction in many of our phaco-trabectome patients is simply not necessary to the same degree.”

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