Issue 2

CUTTING EDGE

Glaucoma

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In Primary Open Angle Glaucoma & Ocular Hypertension

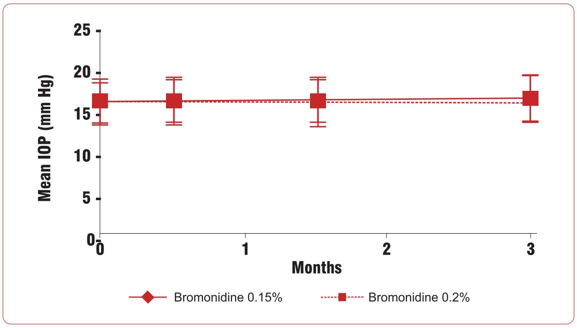
Rx

BRIMOLOL

Brimonidine Tartrate 0.15% + Timolol Maleate 0.5%

Combined power, Greater benefits

Brimonidine 0.15% shows equal IOP lowering to Brimonidine 0.2%[1]



- IOP - lowering effect was maintained over the 3 month with Brimonidine 0.15% and Brimonidine 0.2%
- Lower concentration of Brimonidine in Brimonidine 0.15% may lower the incidence of allergic conjunctivitis

SUN PHARMA

1. Tom M etal, Journal of ocular pharmacology and therapeutics Volume 19, Number 1, 2003,37-44

Preserved with Polyhexamethylene biguanide • BKC - Benzalkonium Chloride • IOP - Intraocular pressure * Data on file

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CUTTING EDGE
Glaucoma

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Contents

WHAT'S NEW

CLINICAL VIGNETTE

Videos available online:

1. Video showing excerpts of the surgical technique implemented in the study.
2. The Video presenting Visco-Trab operation combined with clear cornea temporal phacoemulsification and in-the-bag foldable intraocular lens implantation in a patient with advanced primary open-angle glaucoma and posterior subcapsular cataract. Steps of combined Visco-Trab operation include fornix-based conjunctival flap and subconjunctival Mitomycin C 0.3 mg for 3 min followed by thorough wash with BSS. A 4x4mm lamellar scleral flap (1/3-1/2 of thickness) extending 1mm in clear cornea. Deep scleral flap dissection 0.5 mm inside edge, leaving thin scleral over choroid. Exposure & deroofing of Schlemm's canal. When the glaucoma procedure is combined with phacoemulsification, once the canal is deroofed, the surgeon moves to the temporal side to do the cataract operation through a clear-cornea incision. At the end of the phaco procedure, the AC is reformed and the corneal wound is secured by one 10/0 Nylon suture and the surgeon reverts back to upper position to complete the filtering operation. Excision of deep scleral flap creating a scleral lake. Dilation of SC on either side with sodium hyaluronate. Penetrating trabeculectomy (1x2 mm) and wide peripheral iridectomy were done followed by water tight closure of lamellar scleral flap and conjunctival flap.

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WHAT'S NEW

Outcomes of Adjusted Trabeculotomy in Cases with Juvenile Glaucoma

Ahmad K. Khalil[1,2]

Abstract

Purpose: To evaluate surgical and visual outcomes of modified adjusted trabeculotomy in juvenile glaucoma (JG) cases.

Methods: A retrospective case series; medical records of 43 patients (69 eyes) JG cases operated by adjusted trabeculotomy between 2011 and 2018. Those who completed a minimum of 1 year of regular follow-up, and up to 5 years were included in the study. Intraocular pressure (IOP), number of medications, cup/disc ratio (CDR), and visual acuity (VA) at baseline, postoperative 1, 3, 5 years were evaluated. Success required IOP ≤ 18 mmHg and a minimum of 20% reduction, without medications (full), or with medications (qualified).

Results: Numbers of patients (eyes) who completed 1, 3, and 5 follow-up years were as follows: 26 (43), 15 (27), and 11 (19). Median (range) age at surgery was 21.5 (8–43) years. Mean (range) IOP was significantly ($P < .001$) reduced from 23.4 ± 8.8 (11.0–46.0) mmHg to 11.5 ± 3.5 (7.0–28.0), 10.9 ± 3.6 (6.0–24.0), and 11.4 ± 3.0 (7.0–17.0) mmHg at 1, 3, and 5 years, with reduction of medication scores. At years 1, 3, and 5, complete success rates were 89.5%, 86.8%, and 89.5%, and qualified success rates were 97.4%, 94.7%, and 97.4%. Median (range) LogMAR VA significantly ($P < .001$) improved from 0.3 (0–2.8) to 0.17 (0–2.8) and 0.17 (0–2.8) at 1 and 5 years. Median (range) CDR was significantly ($P < .001$) reduced from 0.85 (0.3–1.0) to 0.85 (0.1–1.0), 0.7 (0.05–1.0), and 0.7 (0.05–0.9) at 1, 3, and 5 years.

Conclusions: Adjusted trabeculotomy could effect remarkable IOP lowering for up to 5 years postoperatively in JG eyes, and seems to be an effective, low-risk surgical modality for treating such eyes. It can be associated with cupping reversibility, and visual improvement on the long-term. Good surgical technique and postoperative care are imperative to achieve a successful outcome.

Keywords: Glaucoma, Juvenile, Surgery, Trabeculotomy

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Key messages

- What is known: Trabeculotomy in adult eyes is a safe but weak surgery which does not result in significant IOP lowering and can be useful for mild-moderate IOP elevations.
- Modified adjusted trabeculotomy is a low-risk, not-highly-invasive surgical modality that can result in persistent IOP lowering to low teens regardless of the preoperative IOP through 5 years of follow up, when performed in adult eyes up to 43 years of age, including black patients.
- Surgery can effect optic disc cupping reversibility with improvement of visual acuity in some cases.

Introduction

The first known mention of angle surgery came in 1891 by De Vincentiis in Italy, who described “incision of the iridic angle” for treating his glaucoma patients [1, 2]. The technique fell into disuse. Few decades later, with the added advantage of newly introduced gonioscopy lenses, Otto Barkan introduced his technique of goniotomy, which revolutionized the management of the then incurable, and “*perhaps most hopeless and certainly the most pathetic of ocular conditions requiring surgery*”; congenital glaucoma [3].

Juvenile glaucoma (JG), an uncommon and rather diffusely defined entity, is considered by some as a subset of primary open-angle glaucoma (POAG) with earlier onset, and by others as a developmental glaucoma. Its onset is asymptomatic, with a course more progressive than POAG, and often refractory to medications [4-6]. Commonly performed glaucoma surgeries such as trabeculectomy, and glaucoma drainage devices (GDD) result in inferior outcomes compared to POAG due to the exaggerated healing in younger eyes [7, 8].

There are reports on the use angle surgery in JG with various success degrees [6, 9, 10]. In this study, the author reports on the intermediate-, long-term surgical and visual outcomes of adjusted trabeculotomy in the treatment of acquired JG.

Materials and Methods

This was a retrospective, consecutive, noncomparative, case series. Medical records of 43 cases (69 eyes) diagnosed with JG (aged 8–45 years), who were operated by adjusted trabeculotomy between January 2011 and December 2018 at the Glaucoma Service, Research Institute of Ophthalmology (RIO) Hospital and a private glaucoma practice, were reviewed. Those who completed a minimum of 1 year of regular follow-up, and up to 5 years were included in the study. All surgeries were performed by a single pediatric glaucoma surgeon (A.K.). As of 2001, adjusted trabeculotomy was the standard initial surgery for JG.

In addition to demographic information, preoperative angle examination, and interoperative and postoperative complications, the following information at preoperative and postoperative

1 day, 1 week, and 1, 3, and 6 months, and 1, 3, and 5 years was retained for analysis: IOP, number of medications, C/D ratio (CDR), and visual acuity (VA). Cases were divided into 2 age groups (≥ 18 years, ≤ 17 years), at the time of surgery, and 2 preoperative IOP groups (≥ 30 mmHg, < 30 mmHg). Medical therapy was used for at least 3 weeks to reduce IOP to the lowest possible before surgery. IOP was measured using Perkins handheld applanation tonometer (Haag-Streit, Koniz, Switzerland). VA was converted from Snellen to approximate logMAR for analysis. CDR was evaluated using slit lamp biomicroscopy and a + 90 lens and graded from 0.0 to 1.0. All measurements were taken by a single examiner, with masking of previous data.

Surgical Technique

Surgical technique was described in detail by the author elsewhere [11-13]. Supplemental Digital Content is a video showing excerpts of the surgery in one of the black eyes of this study. In brief, a layered limbal-based conjunctival incision was made; a half thickness pentagonal scleral flap was made to clear cornea. After deroofing Schlemm's canal, two corneal-diameter-adjusted U-shaped handle-less trabeculotomy probes were inserted into both sides of the incised canal (Fig. 1) before rotating them inwards into the AC severing the trabecular meshwork (TM). Scleral flap was closed by 5 sutures tight enough to prevent free seepage of fluid. Conjunctiva was closed in layers using 7–0 continuous polyglactin sutures, and subconjunctival dexamethasone and gentamicin administered inferiorly.

Postoperatively, systemic broad-spectrum antibiotics (1 week), topical antibiotics (4 weeks), cycloplejics (1 week), and steroids (tapered over 2–8 weeks) were prescribed. When IOP spikes occurred, steroids were withdrawn quicker and ocular massage directed upwards was applied through the lower lid.

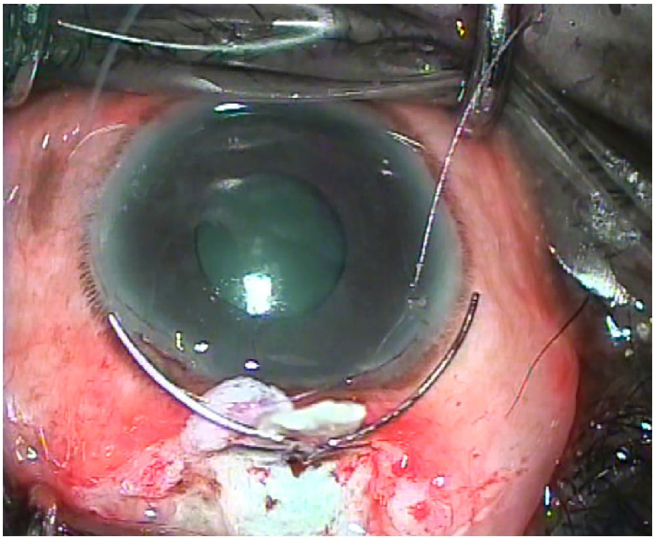

Fig. 1: Corneal-diameter-adjusted U-shaped trabeculotomy probes snugly inserted into the Schlemm's canal on both sides of the incision as seen in one of the 4 black patients reviewed in the study, just before their rotation into the anterior chamber.

Success required IOP ≤ 18 mmHg and a minimum of 20% reduction, without medications (complete), or with medications (qualified), without devastating complications or need for further surgery.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS ver.20 Chicago, IL, USA). Distributions of quantitative variables in different groups were tested for normality using Kolmogorov-Smirnov test, which revealed that data were not normally distributed, so non-parametric tests were used. Quantitative data were described using mean, median, and range. Qualitative data were described using number and percent. Mann-Whitney *U* test was used to compare quantitative parameters between 2 groups. Kruskal-Wallis test was used to compare quantitative parameters between more than 2 groups. Friedman test was used to compare parameters at different time points. Logrank test was used to compare survival functions between groups (age groups, IOP groups). In all statistical tests, level of significance of 0.05 was used, below which the results were considered statistically significant.

Results

A total of 43 patients (69 eyes) were operated by adjusted trabeculotomy during the review period. Seventeen patients (26 eyes) did not complete a minimum of 1 year of regular follow-up and were excluded from the study. Most were from remote places, who would typically show up only for a few weeks of follow-up after surgery, with no or a spotty show afterwards. Twenty-four eyes of these showed success on the short term of 1–3 months and 2 eyes were left on medications.

Twenty-six patients (43 eyes, 16 males, 10 females) completed a minimum of 1-year regular follow-up and were enrolled in the study, fifteen (27 eyes, 11 males, 4 females) completed 3 years, and 11 (19 eyes, 10 males, 1 female) completed 5 years of follow-up. Preoperative gonioscopy showed various degrees of angle dysgenesis (prominent iris processes, and/or high iris insertion) in 39 of 43 eyes (90.7%) (Fig. 2). Median (range) age at surgery was 21.5 (8–43) years. Twelve patients (21 eyes) were ≤ 17 years, and 14 patients (22 eyes) were ≥ 18 years. Twenty-two patients were Egyptian Caucasians, and 4 were black (2 Egyptian Nubians, a Sudanese, and a South Sudanese). Study surgery was the primary procedure in 40 eyes. Schlemm's canal was successfully cannulated in all cases (average arc of both probes: 120–140°).

IOP

Mean (range) preoperative IOP was 23.4 ± 8.8 (11.0–46.0) mmHg on a median (range) of 3 (0–4) medications. Mean (range) postoperative IOP at 1 year was 11.5 ± 3.5 (7.0–28.0) mmHg, on a median (range) of 0 (0–4) medications; at 3 years was 10.9 ± 3.6 (6.0–24.0) mmHg, on a median (range) of 0 (0–1) medications; and at 5 years was 11.4 ± 3.0 (7.0–17.0) mmHg, on a median (range) of 0 (0–1) medications. Mean (range) percentage of IOP reduction from baseline at

1 year was 44.2 ± 23.4% (8.3–75.0%), at 3 years was 49.1 ± 16.5% (26.7–74.1%), and at 5 years was 49.0 ± 18.6% (9.1–73.3%).

There was a statistically significant difference of mean IOP between different readings by Friedman test ($P < .001$). Pairwise comparison revealed statistically significant differences between preoperative and postoperative IOP readings at 1 year, 3 years, and 5 years ($P < .001$), and statistically significant differences between preoperative and postoperative numbers of medications at 1 year, 3 years, and 5 years ($P < .001$). Figure 3 shows IOP results during the first postoperative year.

Success rates

The overall complete success rates at 1, 3, and 5 years were 89.5%, 86.8%, and 89.5%, while the overall qualified success rates at 1, 3, and 5 years were 97.4%, 94.7%, and 97.4%. The complete success rate in the lower IOP group (preoperative IOP < 30 mmHg) was 96.7%, 93%, and 96.7%, while in the higher IOP group (preoperative IOP ≥ 30 mmHg), it was 62.5%, 72.5%, and 72.5% at 1, 3, and 5 years, with a statistically significant difference (logrank test) between the 2 IOP groups at 1 year ($P = .011$), but not at 3 ($P = .44$) or 5 years ($P = .48$). The qualified success rate in the lower

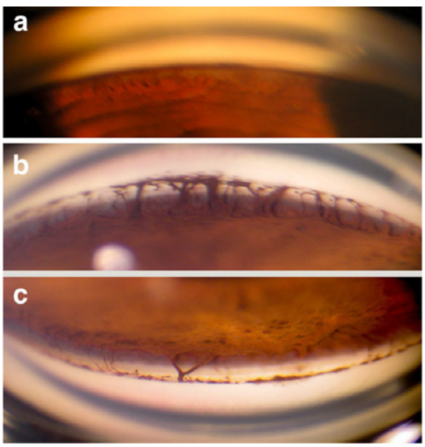

Fig. 2: Gonioscopic appearance showing various degrees of angle dysgenesis/immaturity. (**a**) High iris insertion with minor prominence of iris processes as seen in a 32-year-old case. (**b**) A more extensive form of gonio-dysgenesis seen in the upper angle of a 19-year-old girl showing high iris insertion and a plethora of prominent iris processes connecting between the iris and peripheral cornea/Schwalbe's line area, and spanning a wide area of the angle. (**c**) A less extensive appearance is seen in the lower angle of the same eye. Schwalbe's line area shows a pigmented uveal tissue line.

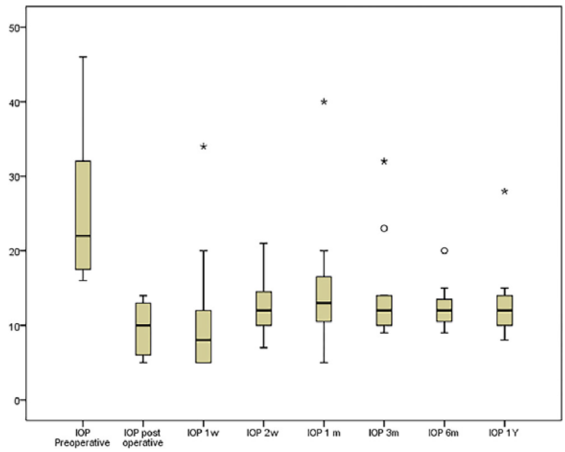

Fig. 3: Boxplot for intraocular pressure (IOP) over different time points in the first year starting by first postoperative day, bold line represents median, lower and upper lines represent minimum and maximum. Circles represent outlier cases; stars represent high IOP spikes (too far from the median).

IOP group was 100%, 100%, and 100%, and in the higher IOP group was 87.5%, 75%, and 88.5% at 1, 3, and 5 years, with no statistically significant differences at 1 year ($P=.08$), 3 years ($P=.62$), or 5 years ($P=.84$) between the 2 groups. There were no statistically significant differences in the success rates at any time point between the 2 age groups, 2 genders, or Caucasian and black patients (Table 1). Three eyes in 2 patients had additional surgery. One had a second adjusted trabeculotomy in a previously untouched area of the limbus. A second patient who had moderate spherophakia associated with the goniodysgenesis had a qualified success with IOP controlled on 2 meds. Bilateral lensectomy was done at year 3 of follow-up, which resulted in pressure control with no meds.

Visual acuity and disc cupping

Median (range) logMAR VA was 0.3 (0–2.8) preoperatively, and 0.17 (0–2.8), 0.3 (0–2.8), and 0.17 (0–2.8) at 1, 3, and 5 years postoperatively, with a statistically significant difference between different readings by Friedman test ($P<.001$). Pairwise comparison revealed statistically significant difference between preoperative reading and the 1-year and 5-year readings ($P<.001$). No eyes showed visual deterioration at 1-, 3-, or 5-year visits.

Table 1: Qualified and complete success rates at 1, 3, and 5 years according to age group, sex, race, and IOP groups as compared by logrank test. There was a statistically significant difference in the complete success rates between the 2 IOP groups at 1 year ($P=.011$), but not at other time points. There were no statistically significant differences in the success rates at any time point between the 2 age groups, 2 genders, or Caucasian and black patients.

	Qualified success 1 year	Complete success 1 year	Qualified success 3 years	Complete success 3 years	Qualified success 5 years	Complete success 5 years
Age						
≤ 17 years ≥ 18 years	94.4% 100% $P=.33$	89% 90% $P=.9$	94.4% 95% $P=.7$	88.9% 85% $P=.38$	94.4% 100% $P=.37$	94.4% 85% $P=.17$
Sex						
Male Female	93.3% 100% $P=.45$	80% 100% $P=.16$	86.7% 100% $P=.44$	80% 89% $P=.95$	93.3% 100% $P=.51$	80% 90% $P=.99$
Race						
Caucasian Egyptian	97.4%	88%	93.9%	84.8%	97%	88%
Black	100% $P=.68$	100% $P=.39$	100% $P=.69$	100% $P=.52$	100% $P=.79$	100% $P=.56$
IOP						
< 30 ≥ 30	100% 87.5% $P=.08$	96.7% 62.5% $P=.011$*	100% 75% $P=.62$	93% 72.5% $P=.44$	100% 88.5% $P=.84$	96.7% 72.5% $P=.48$

*Statistically significant

Median (range) CDR was 0.85 (0.3–1.0) preoperatively, and 0.85 (0.1–1.0), 0.7 (0.05–1.0), and 0.7 (0.05–0.9) at 1, 3, and 5 years, with a significant difference between different readings by Friedman test ($P < .001$). Pairwise comparison revealed statistically significant differences between preoperative reading and each of 1, 3, and 5 years readings. In eyes in which CDR regression was detected, it was noticed to be slow along a course of up to 3 years. A reduction of 0.2 or more occurred in 8 eyes (18%) of 6 patients (3 patients < 18 years, 3 patients ≥ 18 years). Two patients who had bilateral surgery showed this CDR regression only in one eye.

Seventeen eyes of 13 patients had preoperative optic disc cupping ≥ 0.9, nine of these had no visible rim clinically, and 4 of these 9 had VA of light perception (LP) or hand motion (HM). After discussing potential risks with patients and/or their families, these eyes were operated, mostly to relieve pressure, with the understanding and consent of the potential poor visual outcome. None of these 17 eyes had worsened VA at their last visit. Two of the 4 eyes with HM/LP (preoperative IOP: 40, 32) regained noticeably better vision starting 1 month postoperatively (20/400, 20/60 at their last visits), while VA in the other 2 (preoperative IOP: 34, 17) remained unchanged. None of the 4 black patients was among the failures.

Complications

Apart from a tinge of hyphema in the trabeculotomy site, no intraoperative complications occurred. A mild transient hyphema was detected in the second postoperative day in 17 eyes (39.5%), together with an eye of total diffuse hyphema. Hyphema resolved in all cases by the first week. One eye (8 years) showed striate endothelial keratopathy in the first postoperative day, which resolved by week 1. At month 1, one eye showed mild anterior chamber reaction which persisted through month 3 and another showed peripheral shallow choroidal detachment, with AC shallowing and hypotony, which disappeared in 2 weeks' time. IOP spikes (21–40 mmHg) occurred in the first postoperative 3 months in 5 eyes (4 cases) (Fig. 3), with subsequent lowering following quick withdrawal of topical steroids, and applying ocular massage. Application of massage was often associated with a diffuse bleb over the surgical site, which became indistinct by month 3 (Fig. 4).

Discussion

This study detected a success rate of 89.5% with an IOP below 18 mmHg on no medications up to 5 years postoperatively using an adjusted trabeculotomy technique in JG cases with ages up to 43 years at time of surgery, and an overall qualified success rate of 97.4% up to 5 years postoperatively. The mean postoperative IOP was 10.9–11.5 mmHg on a median (range) of 0 (0–4) medications at 1–5 years postoperatively, a significant difference from a preoperative 23.4 mmHg on a median (range) of 3 (0–4) medications. The resulting IOP was generally lower than that reported in other studies which treated JG with angle surgery for a similar duration [10, 14-16]. All cases in this study but two showed angle dysgenesis ranging from mild prominence of iris processes and anterior iris insertion to more advanced forms, similar to that seen in PCG eyes. Both congenital

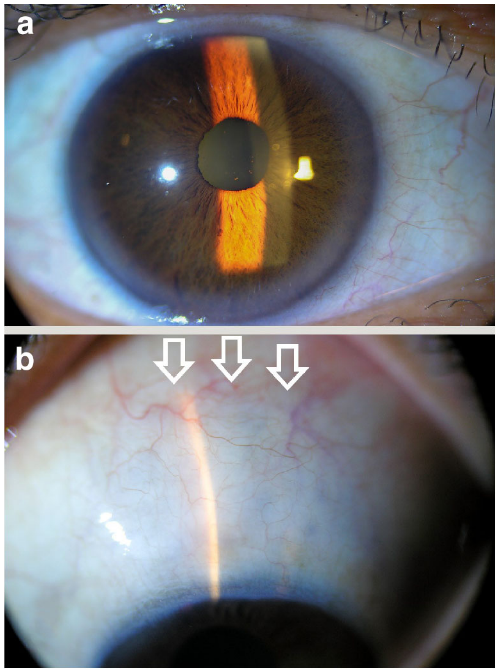

Fig. 4: Appearance of the eye (**a**), and the surgical site (**b**) 1 year postoperatively. Arrows point to the hardly visible conjunctival incision site.

and juvenile glaucoma can occur because of developmental immaturity of the anterior chamber angle area [4, 5]. The more extensive the immaturity, the earlier the glaucoma will become manifest. It would, therefore, be understandable to target the angle when operating on these cases.

Previous studies showed IOP lowering to 15.4–23.0 mmHg with or without medications for 1–7 years following trabeculotomy in JG cases [9, 15]. Newly introduced trabeculotomy-based techniques like gonioscopy-assisted transluminal trabeculotomy (GATT), Trab360 Device, and trabectome were also tried in JG cases with IOP lowering to 14.8–24 mmHg with or without medications [6, 10, 17]. Most literature, however, regard trabeculotomy in adults as a safer yet weaker surgery compared to trabeculectomy and other penetrating surgeries. Though associated with fewer complications, it is believed to be less effective in adults than in children, resulting in high teens IOP with medications, not acceptable for the often advanced glaucoma in juvenile eyes [18-21]. The current study showed high success rates for the described trabeculotomy technique in JG patients up to 43 years of age, with a high safety profile and effective persistent IOP lowering to low teens through 5 years of follow-up, regardless of the preoperative IOP. Though both qualified and complete success rates were higher in the lower IOP group (<30) than in the higher IOP group (≥ 30) at 1, 3, and 5 years, the difference was not statistically significant except for the complete success at 1 year ($P = .011$). An IOP in the high teens in the first postoperative weeks was a concern to be tackled. This rather uniform lowering can be attributed to the surgical technique and perioperative management implemented.

Unlike the commonly used handled trabeculotomy probes, the handle-less probes offer the added advantage of being able to simultaneously and precisely probe both sides of the canal incision before opening the AC and its subsequent frequent collapse. Although these extremely light-weight probes are much more difficult to maneuver compared to the handled probes (with occasional one-way flights into the theater skies), this same light weightiness renders it extremely unlikely to induce false passages all through their full arc length. Once inserted into the incised Schlemm's canal, a correct easy passage along the whole arc is ensured, provided that a suitable curvature probe is used. The slow decompression thus occurring during AC entry is a factor for the high safety profile observed in the high-risk cases who had advanced cupping.

Tight closure of the scleral flap probably helps to rapidly reform and maintain the integrity of the AC and its angle; the target surgical site, keeping the severed lips of the incised trabeculum apart in the first postoperative weeks. Moderate and high IOP spikes (21–40 mmHg) occurred in some cases postoperatively. Subconjunctival steroid injection may have played a role in this IOP elevation. Together with quicker withdrawal of topical steroids in these cases, ocular massage was done in the first 2–3 months, aiming in the beginning to push open potentially collapsed lips of incised trabeculum, and help aqueous into the opened Schlemm's canal. Doing this massage, however, resulted in a diffuse low bleb, implying aqueous seepage through the tightly sutured flap, and breaking the scleral seal. This bleb eventually became indistinct in 2–3 months, but the lowered IOP persisted. Bleb formation is not a strange occurrence with trabeculotomy surgeons. It was deliberately planned for by Hara who, in the 1970s, performed trabeculotomy as a filtration procedure by closing the scleral flap with 2 sutures anticipating aqueous drainage, with 80% of the cases achieving an IOP below 20 mmHg [22]. In the current series, the flap was tightly closed, with bleb formation after massage that remained clinically visible for 3 months. It is probably safe to postulate that IOP lowering, at least in some cases, is caused by a dual mechanism of internal filtration through the Schlemm's canal, and a gentle guarded external filtration through the scleral flap. Despite the realization of this potential external filtration, no trial of argon-laser suture lysis was performed to assist it. Regular timed massage was done in its stead in eyes with IOP spikes. It was thought that massage would maintain gentle seepage of aqueous through the tightly closed flap and possibly breaking micro-fibrous tissue formation in the important first few months, while respecting the tight suture closure of the flap is an attempt against creeping back of fibrous reaction under the flap and into the surgical site. Lastly, the limbal-based conjunctival incision and its layered closure kept the conjunctiva pliable over the surgical site. The successive, least invasive, surgical steps led in most instances to the surgical site being undiscernible a year after surgery (Fig. 4), with persistent functionality.

The canal of Schlemm was successfully cannulated for an average arc of 120–140°. While some authors advocate circumferential surgery [17, 23], others find no difference between a complete 360 trabeculotomy and a partial one [16, 24]. Circumferential trabeculotomy is associated more with cyclodialysis risk and false passage [10, 25]. On the other end, the trabecular micro-bypass stent (iStent, iStent inject), a mini-trabeculotomy 1.0–3.0 mm in length, could produce significant IOP reductions with cataract surgery [26, 27]. It would not, therefore, be entirely surprising that a controlled trabeculotomy technique, spanning 120–140° of the angle, would effect such an IOP lowering in JG cases.

Despite the well-deserved acclaim of the landmark article in which Dr. Barkan described his new operation which he called goniotomy in 1942 for the treatment of PCG, and its not-less-than revolutionary success in this condition, it was actually for adults with chronic glaucoma (what we mostly call today POAG) that Barkan first described his technique in 1936, naming it gonio-*trabeculectomy* [3, 28]. In either instance, his goal was to "*incise the trabeculum to re-establish the outflow from the chamber into Schlemm's canal*." Apparently this goniotomy technique did not achieve the promised results in adults, possibly because of inherent difficulties in ab-interno targeting the TM with low magnification surgery, and for decades to follow, was reserved for the management of PCG.

Alternative therapies for JG are often associated with modest success rates and/or more side effects. Medical therapy is usually insufficient to prevent progression compared to surgery, and most patients, being young, report loss of quality of life [29]. Many of the cases reported in the current study were uncontrolled on maximum tolerable medical therapy, and were declined surgical intervention elsewhere because of the fear of surgery in eyes with advanced cupping, and its potential low success rates in such cases. Trabeculectomy with and without antimetabolites has shown 59–73% success rates, but is generally agreed to be associated with a higher risk of intraoperative and postoperative complications in younger eyes [7, 8, 30]. The risk of bleb-related infections continues for a lifetime of a functioning bleb: an important concern in such young eyes. Similarly, GDD often chosen for medication refractory JG showed success rates of 42–86%, but with frequent need of reoperations for tube-related complications [31, 32].

Optic disc cupping reversal is well recognized in PCG infants following successful surgery, because of the elasticity of the scleral canal, and relatively short duration of IOP rise [33, 34]. Some reports documented cupping reversal related to the degree of IOP reduction in adults, with a higher incidence following surgical rather than medical control [35, 36]. In this study, significant improvement in both median CDR values and logMAR VA for up to 5 years was noticed. This occurred mostly in eyes with remarkably high preoperative IOP, and denotes that the damage was caused in part by mechanical distress rather than neuronal damage, and that optic disc in a glaucomatous adult can retain its elasticity and function for some time under pressure. Contrary to cup reversibility in infants (which the author observes to occur within weeks after congenital glaucoma surgery), that observed here was a slow process for up to 3 years. The improvement of VA could be attributed to relief of a high IOP distressing optic disc nerve fibers and/or a better corneal clarity.

Juvenile glaucoma often presents in an advanced stage. Seventeen eyes (13 patients) presented with optic disc cupping of 0.9 or more, 9 of these eyes had clinical total cupping, and 4 of these 9 had a VA of LP or HM. None of these eyes lost VA lines by their last postoperative visit, and 2 with HM/ LP regained noticeably better vision, starting 1 month postoperatively. These results highlight the safety profile of the technique described, even in cases with advanced cupping, and are in accordance with previous evidence of the higher safety profile of trabeculotomy in general [18, 21].

The 4 failures in this study occurred within the first year postoperatively. This "early failure if it is going to fail" is consistent with previous literature [10, 37]. Noteworthy is that none of the 4 black patients (8 eyes) was among the failures; two are under regular follow-up for well over 5 years now. Although no major conclusions can be drawn from such a small sample number, this might be an indication of a good outcome for black eyes, generally considered to be a high risk for glaucoma surgery.

This study, as well as several studies on JG, detected angle dysgenesis in most of the study eyes, not the open-angle configuration seen in POAG [4, 38]. That is why it opted to use the term juvenile glaucoma (JG), rather than juvenile open-angle glaucoma (JOAG). It is to be noted that the "Guidelines of Glaucoma" produced by the Japan Glaucoma Society, classifies JG under "developmental" rather than "open angle" glaucomas, and mentions "late onset developmental glaucoma" rather than "juvenile open angle glaucoma" [20]. This study proposes the term "primary juvenile glaucoma" (PJG) to set cases apart from secondary juvenile glaucomas. More studies are needed on the angle structure and appearance in eyes with JG to elucidate further the nature, and subsequent treatment strategies of this glaucoma subset.

Owing to the limitations of retrospective data collection and analysis, potential biases cannot be ruled out. Patients were not randomized and there are no controls for comparison. Findings were taken by a single observer, who is a dedicated glaucoma practitioner since 1994. Previous data were masked prior to each examination to reduce the potential for bias. To further validate the findings of this study, future prospective studies are recommended.

Adjusted trabeculotomy significantly lowered IOP in JG eyes, who were mostly refractory to medical therapy. The data presented suggest that this low-risk, not highly invasive modality provides JG cases, even those with vision-threatening disease, with a good option of treatment that is effective and safe for up to 5 years postoperatively. The technique described is less invasive than most "classical" glaucoma surgeries, including trabeculectomy and tubes or valves. We stand short of describing it as a "microinvasive glaucoma surgery," but it is as close as it can get. Entry into the AC is momentary and is with a microdevice which selectively severs the main outflow resistance; the not-infrequently dysgenetic trabeculum in a localized controlled segment. Surgical site is undiscernible a year after surgery (Fig. 4). Surgeries were performed by largely affordable, reusable instruments. The success rates observed can probably be attributed to a triad of surgical, timely withdrawal of topical steroids in these young, often positive steroid responders, and tailored timely ocular massage in the first postoperative 2–3 months that seems to result in some element of guarded external filtration.

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Data availability: All data are available, and support published claims and comply with field standards.

Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflict of interest.

Ethics approval: This study was approved by the "Ethics of Scientific Research Committee" of the Research Institute of Ophthalmology. All the procedures being performed were part of the routine care, and were in adherent to the tenets of the Declaration of Helsinki.

Consent to participate: Informed surgical consent was obtained from all patients/their guardians.

Consent for publication: No identifying information are included in this study. The author is responsible for correctness of the statements provided in the manuscript.

Code availability: Not applicable.

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Ex-Press® Versus Baerveldt Implant Surgery for Primary Open-Angle Glaucoma and Pseudo-Exfoliation Glaucoma

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Abstract

Purpose: To compare surgical outcomes between Ex-Press® (EXP) and Baerveldt glaucoma implant (BGI) surgeries for primary open-angle glaucoma (POAG) and pseudo-exfoliation glaucoma (PEXG) patients.

Patients and methods: This was a retrospective single-facility study. The inclusion criteria were that the patient's preoperative intraocular pressure (IOP) was > 21 mmHg and the post-surgery follow-up was > 1 year. We recruited 161 patients who had undergone a trabeculectomy with EXP (89 eyes) or BGI surgery (72 eyes). We compared these groups' postoperative IOP values and postoperative glaucoma medications, the reduction rate of corneal endothelial cell density (ECD), surgical outcomes, complications, the hospital stay duration, and the number of visits within 3 months post-surgery.

Results: Both the EXP and BGI surgeries could significantly decrease the IOP. When the surgical success was defined postoperative IOP ≤ 21 mmHg, the surgical outcome of BGI was significantly better than EXP ($p = 0.0148$). When the surgical success was defined postoperative IOP ≤ 18, 15, and 12 mmHg, the surgical outcomes between BGI and EXP surgeries were not significantly different ($p = 0.0815$, $p = 0.331$, and $p = 0.910$). The mean ECD reduction rate was significantly faster in the EXP group. The BGI patients had significantly shorter stays in the hospital and fewer visits within 3 months post-surgery ($p < 0.0001$).

Conclusions: BGI surgery could provide comparable surgical outcomes as EXP surgery for POAG or PEXG patients with high preoperative IOP. BGI surgery has some advantages: fewer post-surgery visits, less postoperative interventions, and a lower ECD reduction rate.

Keywords: Ex-Press, Intraocular pressure, Baerveldt, Tube shunt, Surgical outcome

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Introduction

Filtration surgery is widely used to reduce intraocular pressure (IOP) for glaucoma patients. A conventional trabeculectomy is a surgery that removes the trabecular meshwork (TM) and creates an filtration bleb. Today, glaucoma drainage devices (GDDs) are used for filtration surgery. The Ex-Press® Mini-shunt (hereafter, "EXP") (Alcon Laboratories, Fort Worth, TX, USA), the Baerveldt glaucoma implant (hereafter, "BGI") (Johnson & Johnson Vision, Santa Ana, CA), and the Ahmed glaucoma valve are representative GDDs used for filtration surgeries. The EXP is a stainless steel filtration device designed to shunt the aqueous humor from the anterior chamber to the subconjunctival space. A BGI has a long tube to shunt the aqueous humor through a large plate.

In Japan, it is recommended that BGI surgery is performed only for cases of refractory glaucoma such as secondary glaucoma, juvenile glaucoma, and neovascular glaucoma, and for patients who had previously failed trabeculectomy. It is rare to perform BGI surgery as a first surgery for primary open-angle glaucoma (POAG) or pseudo-exfoliation glaucoma (PEXG).

There are many reports comparing the surgical outcomes between trabeculectomy and filtration surgeries using these GDDs. Several research groups reported that the surgical outcomes with EXP surgery were comparable to those of conventional trabeculectomy [1,2,3,4]. In a study comparing primary tube versus trabeculectomy surgery, there was no significant difference in the rate of surgical failure between trabeculectomy and BGI surgeries after 3 years [5]. Few investigations have compared EXP and BGI surgeries [6].

We investigated whether EXP or BGI provides superior surgical outcomes for patients with POAG or PEXG. Since these two surgeries have some different characteristics, we compared their advantages and disadvantages.

Patients and Methods

Patients

This was a single-facility, non-randomized, retrospective comparison study. The inclusion criteria for this study were: (1) the patient's type of glaucoma was POAG or PEXG, (2) the post-surgery follow-up period > 1 year, and (3) the patient's preoperative IOP was > 21 mmHg. We had no explicit definitions for the surgeons' choice between EXP and BGI. We included into BGI group the patients who underwent EXP surgery and required additional BGI surgery. We recruited patients who underwent their surgery at Toyama University during the period from January 2013 to April 2019.

We analyzed the cases of 89 patients who underwent EXP surgery and 72 patients who underwent BGI surgery. We included patients who had undergone glaucoma surgery or cataract surgery. The preoperative IOP was defined as the mean of the IOPs recorded at two of the patient's visits just before surgery. The IOP was measured by Goldmann applanation tonometry (GAT). All patients underwent a comprehensive ophthalmic examination including refraction, Goldmann gonioscopy, fundus examination, optical coherent tomography (OCT) with glaucoma analysis

(RS-3000; Nidek, Nagoya, Japan), automated perimetry (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA) with the 30–2 Swedish Interactive Thresholding Algorithm and the measurement of the corneal endothelial cell density (ECD) with a specular microscope (EM-4000; Tomey Corp., Nagoya, Japan). The measured values of the ECD were obtained by a single measurement at the center of the cornea. We also calculated the postoperative rate of the reduction in the ECD compared to the preoperative ECD.

One glaucoma specialist (N.T.) diagnosed all glaucoma cases, chose the surgical method (EXP or BGI), and performed all of the glaucoma surgeries. The research protocol was approved by the Institutional Review Board of the University of Toyama, and the procedures used conformed to the tenets of the Declaration of Helsinki. After the nature and possible consequences of the study were explained to the patients, written informed consent was obtained from each patient.

EXP Surgical Technique

The EXP surgeries were performed with the standard fornix-based conjunctival incision. The size of the scleral flap was 3.5 mm^2, and the period of the application of Mitomycin C (MMC) solution (0.04 mg/ml) was 4 min. The area treated with MMC was then irrigated with approx. 100 ml of balanced salt solution. The Ex-Press® (model P50) implant was inserted into the anterior chamber at the surgical limbus. The scleral flap was sutured using a 10–0 nylon suture with tension to maintain the anterior chamber depth. The conjunctiva was sutured with 10–0 nylon suture so that aqueous humor would not leak from blebs. In the patients who needed simultaneous cataract surgery, the cataract surgery was performed with a clear corneal incision. We used a Whitestar Signature® phacoemulsification system (Johnson & Johnson Vision) for the phacoemulsification and intraocular lens implantation. There were no clear criteria for simultaneous cataract surgery.

BGI Surgical Technique

The BGI surgeries were performed with the double flap technique. The details of the BGI surgical technique are described elsewhere [7]. For all cases, the Baerveldt® 103–350 implant (Johnson & Johnson Vision; Santa Ana, CA) attached with a Hoffmann elbow was for all of the patients and inserted into the vitreous cavity. For the patients who had not previously undergone a vitrectomy, a pars plana vitrectomy (PPV) was performed along with the BGI surgery. The patients who had not undergone a previous cataract surgery but needed cataract surgery underwent the BGI implantation surgery and cataract surgery in the same surgical session. The PPVs and cataract surgeries were performed with EVA (DORC, Zuidland, Netherlands).

For all of the BGI patients, an incision of conjunctiva was made in the superior-temporal quadrant. The plate was put under the superior rectus muscle and lateral rectus muscle and then fixed to the sclera with 5–0 polyester sutures (Mani, Utsunomiya, Japan) at 12 mm from the limbus. The Baerveldt tube was tied up completely with 8–0 absorbable sutures (Johnson & Johnson Vision) in order to prevent water leakage. A Sharwood slit was created at one site for all patients. A half-thickness, rectangular, 6 × 6-mm limbal-based scleral flap was created. A hole was made with a 20-gauge V-lance for the insertion of the tip of the Hoffmann elbow at the pars plana in the temporal superior quadrant. The Hoffmann elbow was covered first with a half-thickness autologous scleral flap and then with a preserved donor scleral patch. We named this method of covering the elbow with two patches the 'double flap' technique.

The autologous scleral flaps and preserved donor scleral patch were sutured to the sclera at each corner with 9–0 nylon sutures. The conjunctiva was sutured with 9–0 absorbable sutures (Crownjun, Tokyo). A rip cord or suture lysis was not used to decrease the IOP in any of the patients. In other words, the postoperative IOP did not decrease sufficiently until the absorbable sutures had loosened spontaneously.

Postoperative Medication

For both the EXP patients and BGI patients, the postoperative treatments were three types of topical medications: steroids, antibiotics, and non-steroidal anti-inflammatory drugs (NSAIDs). The antibiotics were used 4 times/day for 4 weeks after the surgery. Steroids were administered 4 times/day and reduced gradually over 12 weeks. NSAIDs were used 2 times/day for 12 weeks. Anti-glaucoma medications were added at the discretion of the physicians. We counted a compounding agent as two medications.

Definition of Success And Comparison Items

In this study, we used 4 definitions of failure. We defined 'failure' of either BGI or EXP surgery as a postoperative IOP value > 21, 18, 15, or 12 mmHg on two consecutive visits after 3 postoperative months. We defined 'success' as a postoperative IOP value < 21, 18, 15, or 12 mmHg (on two consecutive visits after 3 postoperative months) with or without the use of glaucoma medications or interventions such as needling. Eyes requiring additional glaucoma surgery and those that developed phthisis or showed loss of light perception were defined as failures.

We compared the surgical outcomes, postoperative IOP, the number of glaucoma medications, the number of visits to the hospital for the first 3 months after surgery, the density of corneal endothelial cells, and the postoperative complications between the EXP and BGI patients.

Statistical Analyses

We used a paired t-test for the comparisons of the EXP and BGI groups. The Wilcoxon signed-rank test was applied for the comparisons of the same patients' IOP values, the number of glaucoma medications, and the density of corneal endothelial cells. We performed a Kaplan–Meier survival analysis. Log-rank tests were used for the comparison of the surgical success rates. All statistical analyses were performed with JMP Pro 14 software (SAS, Cary, NC). Significance was defined as p-values < 0.05.

Results

Ophthalmic Data

We analyzed the cases in the EXP group (89 eyes) and BGI group (72 eyes), comprising a total of 161 eyes. The characteristics of the patients in each group are summarized in Table 1. The mean follow-up period in the EXP group was significantly longer than that in the BGI group ($p < 0.0001$). The gender distribution, patient age, type of glaucoma, number of preoperative glaucoma medications, and preoperative IOP values were not significantly different between the EXP and BGI groups. The preoperative ECD was significantly less in the BGI group ($p = 0.0097$). The BGI group had significantly higher percentages of patients who underwent cataract surgery ($p < 0.0001$), a trabeculectomy (including EXP) ($p < 0.0001$), or a PPV ($p < 0.0001$). Trabeculotomy was performed with Trabectome (NeoMedix, Tustin, CA, USA). Ab interno trabeculotomy can preserve conjunctiva, not effect EXP or BGI surgery.

Postoperative IOP and Glaucoma Medications

The patients' postoperative IOP values, IOP reduction rate compared with preoperative IOP, and numbers of glaucoma medications used post-surgery are shown in Table 2 and Figs. 1 and 2. The results of the eyes that underwent additional glaucoma surgeries were excluded. The mean preoperative IOP values were 29.7 ± 7.0 mmHg in the EXP group and 30.0 ± 7.5 mmHg in the BGI group and were not significantly different ($p = 0.755$). The mean number of glaucoma medications

Table 1: Ophthalmic data of all 161 eyes.

	EXP ($n = 89$)	BGI ($n = 72$)	p value
Gender (male/female)	49/40	50/22	0.0739
Age (yrs)	71.5 ± 9.7	79.1 ± 12.1	0.154
Type of glaucoma: POAG/PEXG	36/53	33/39	0.124
Follow-up period: months	39.0 ± 17.6	26.5 ± 14.9	< 0.001
Preoperative IOP: mmHg	29.7 ± 7.0	30.0 ± 7.5	0.755
Preoperative medications	4.0 ± 1.0	3.8 ± 0.8	0.0829
Preoperative ECD: cell/mm^2	2134 ± 479	1907 ± 623	0.0097
History of cataract surgery	63 (70.1%)	68 (94.4%)	< 0.0001
History of trabeculotomy	29 (32.6%)	33 (45.8%)	0.123
History of trabeculectomy	0 (0%)	22 (30.1%)	< 0.0001
History of PPV	0 (0%)	21 (29.2%)	< 0.001
Simultaneous cataract surgery	26 (29.2%)	4 (5.6%)	< 0.0001
Simultaneous pars plana vitrectomy	0 (0%)	51 (70.8%)	< 0.0001

ECD endothelial cell density, *mos*. months, *PEXG* pseudo-exfoliation glaucoma, *POAG* primary open-angle glaucoma, Preop. preoperative, *PPV* pars plana vitrectomy

Table 2: Postoperative IOP and glaucoma medications.

		EXP	BGI	*p* value
Preop	IOP (mmHg)	29.7 ± 7.0	30.0 ± 7.5	0.755
EXP: 89 eyes, BGI: 72 eyes	Medications	4.0 ± 1.0	3.8 ± 0.8	0.0829
1y Post-op	IOP (mmHg)	11.9 ± 3.6	10.8 ± 3.4	0.063
EXP:89 eyes, BGI:72 eyes	IOP reduction rate (%)	57.9 ± 15.5	62.2 ± 13.6	0.074
	Medications	1.5 ± 1.7	2.3 ± 1.9	0.03
2y Post-op	IOP (mmHg)	12.1 ± 3.6	11.2 ± 3.4	0.197
EXP:69 eyes, BGI:47 eyes	IOP reduction rate (%)	57.5 ± 14.8	59.1 ± 14.3	0.595
	Medications	1.8 ± 1.2	2.4 ± 1.3	0.0643
3y Post-op	IOP (mmHg)	12.2 ± 3.6	11.2 ± 3.9	0.307
EXP:45 eyes, BGI:21 eyes	IOP reduction rate (%)	57.5 ± 15.4	60.0 ± 13.7	0.510
	Medications	2.5 ± 1.5	2.1 ± 1.5	0.316
4y Post-op	IOP (mmHg)	12.7 ± 3.7	8.8 ± 2.3	0.0053
EXP:26 eyes, BGI:9 eyes	IOP reduction rate (%)	57.3 ± 15.9	68.9 ± 11.7	0.103
	Medications	2.7 ± 1.5	2.4 ± 1.5	0.667
5y Post-op	IOP (mmHg)	10.6 ± 3.9	8.5 ± 1.1	0.203
EXP:14 eyes, BGI:6 eyes	IOP reduction rate (%)	63.8 ± 18.4	71.1 ± 14.2	0.399
	Medications	2.7 ± 1.5	2.0 ± 1.6	0.366

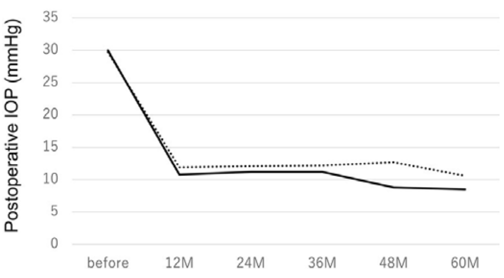

Fig. 1: Postoperative IOP. Solid line: Baerveldt surgery. Dotted line: Ex-Press surgery. Details are provided in Table 2.

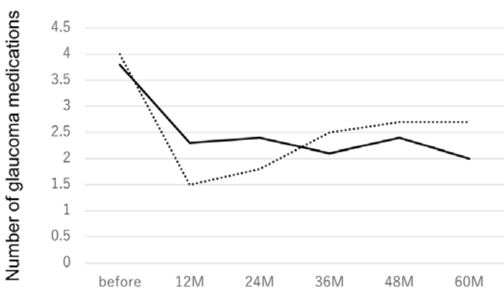

Fig. 2: Number of postoperative glaucoma medications. Solid line: Baerveldt surgery. Dotted line: Ex-Press surgery. Details are provided in Table 2.

was 4.1 ± 1.0 mmHg in the EXP group and 3.8 ± 0.8 mmHg in the BGI group, and these numbers are not significantly different ($p = 0.0829$). The mean postoperative IOP values were not significantly different between the two groups at 1, 2, or 3 years. The mean number of postoperative medications gradually increased in the EXP group but did not increase in the BGI group. During the early postoperative period (i.e., ≤ 1 year), the mean number of glaucoma medications was significantly higher in the BGI group. After 2 years, there was no significant difference between the groups in the mean number of glaucoma medications.

Surgical Outcomes

All patients could be inserted EXP or BGI, and there was no case intraoperative exclusive hemorrhage. In BGI group, there was no case who need tamponade after pars plana vitrectomy. Figure 3 illustrates the Kaplan–Meier survival curves of the BGI and EXP patients. Figure 3a–d shows the results defined surgical success as < 21, 18, 15, and 12 mmHg, respectively. At 5 years after their surgeries, the success rates of the EXP group were 72.4%, 70.3%, 46.1% and 18.2%, and those of the BGI group were 88.9%, 83.7%, 71.4%, and 39.5%. When surgical success was defined < 21 mmHg, the BGI group achieved significantly better surgical outcomes compared to the EXP group ($p = 0.0148$). When surgical success was defined < 18, 15, and 12 mmHg, surgical outcomes of both groups were not significantly different ($p = 0.0815$, $p = 0.331$ and $p = 0.910$).

In the EXP group, 16 eyes resulted in failure, and these patients required additional glaucoma surgeries because postoperative IOP was higher. All 16 of these patients underwent BGI surgery

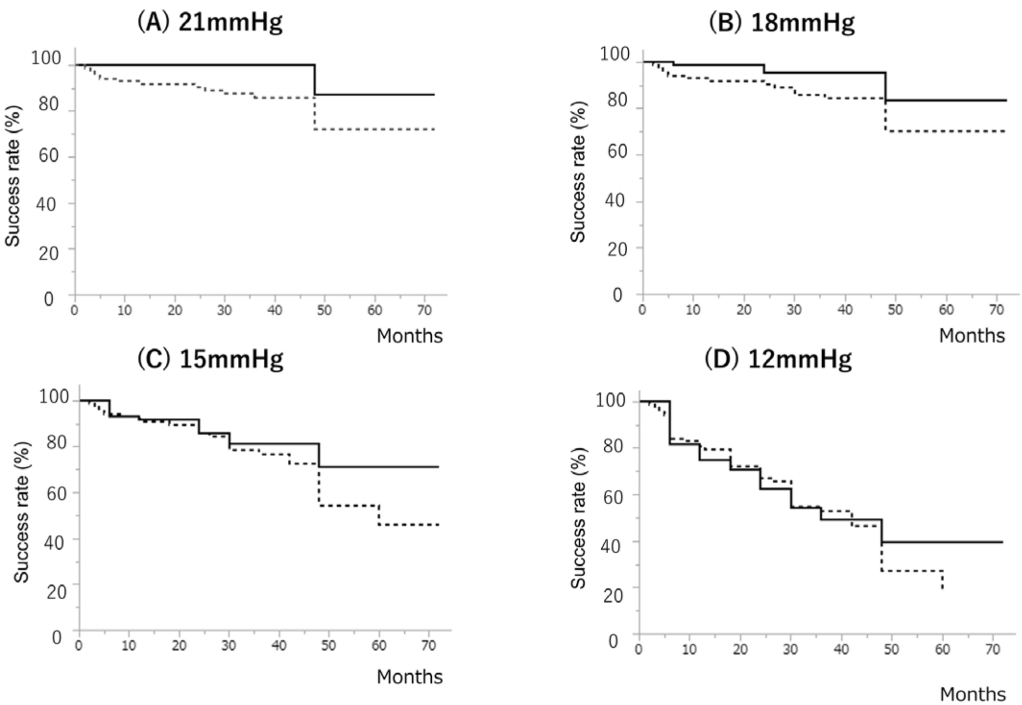

Fig. 3: Kaplan–Meier survival plots of all cases for qualified success. Solid line: Baerveldt surgery. Dotted line: Ex-Press surgery. Success was defined as postoperative IOP ≤ 21 mmHg. The surgical outcomes of Baerveldt surgery were significantly better than Ex-press surgery ($p = 0.0148$). Success was defined as postoperative IOP ≤ 18 mmHg. The surgical outcomes of Baerveldt surgery and Ex-press were not significantly different. ($p = 0.0815$). Success was defined as postoperative IOP ≤ 15 mmHg. The surgical outcomes of Baerveldt surgery and Ex-press were not significantly different. ($p = 0.331$). Success was defined as postoperative IOP ≤ 12 mmHg. The surgical outcomes of Baerveldt surgery and Ex-press were not significantly different. ($p = 0.910$).

as additional glaucoma surgery. In the BGI group, there was one PEXG patient exhibited a loss of light perception after 4 years, despite showing a low postoperative IOP (5–8 mmHg).

The Reduction Rate Of Corneal Endothelial Cell Density (ECD)

Table 3 provides the mean postoperative ECD values. The mean preoperative ECD in the EXP group was significantly less than that in the BGI group ($p = 0.0097$). The groups' "preoperative ECD values were difficult to compare, and we therefore compared the groups' ECD reduction rates (Table 4). In BGI group, the ECD rate decreased very slowly, whereas the ECD rate in the EXP group decreased significantly faster after 4 years ($p = 0.0145$).

Complications

We have summarized the postoperative complications in Table 5. In the EXP group, the rate of complications that are due to low IOP such as choroidal detachment (CD) or a shallow anterior chamber was higher than that of the BGI group. A shallow anterior chamber was defined as an iridocorneal touch in the periphery as revealed by a slit lamp examination. These complications due to hypotony were improved spontaneously within 2 months. There was no case of hypotensive maculopathy.

However, there were more complications involving vitreous hemorrhage (VH) in the BGI group. There were no cases in which irrigation of the VH was required, since the VH disappeared spontaneously within 3 months. There was one case of tube occlusion; we performed an additional intervention to remove the tube occlusion. Persistent corneal edema due to decreased ECD

Table 3: Mean postoperative ECD in the EXP and BGI groups.

	EXP (*n*)	BGI (*n*)	*p* value
Preop. ECD (cells/mm^2)	2134 ± 479 (89)	1907 ± 623 (72)	0.0097
1-yr Post-op ECD	2056 ± 507 (78)	1846 ± 693 (71)	0.0317
2-yr Post-op ECD	2015 ± 533 (65)	1736 ± 713 (43)	0.314
3-yr Post-op ECD	1953 ± 643 (45)	1752 ± 697 (20)	0.259
4-yr Post-op ECD	1802 ± 651 (26)	1869 ± 570 (8)	0.791
5-yr Post-op ECD	1656 ± 696 (14)	17,067 ± 723 (6)	0.884

ECD Endothelial cell density

Table 4: Comparison of the mean of ECD reduction rate between the EXP and BGI groups.

ECD reduction rate (%)	EXP (*n*)	BGI (*n*)	*p* value
1 yr	95.8 ± 18.1 (78)	99.7 ± 29.0 (71)	0.322
2 yrs	89.7 ± 16.0 (65)	99.5 ± 29.0 (43)	0.0717
3 yrs	86.7 ± 19.8 (45)	97.9 ± 30.6 (20)	0.096
4 yrs	77.5 ± 25.1 (26)	101.1 ± 5.7 (8)	0.0145
5 yrs	70.0 ± 24.2 (14)	105.6 ± 11.5 (6)	0.0034

Table 5: Postoperative complications.

Postoperative complications	EXP (%)	BGI (%)
Tube occlusion	0 (0%)	1 (1.4%)
Tube erosion	0 (0%)	0 (0%)
Choroidal detachment	11 (12.4%)	1 (1.4%)
Shallow anterior chamber	4 (4.5%)	0 (0%)
Hyphema	6 (6.7%)	2 (2.8%)
Aqueous misdirection	0 (0%)	0 (0%)
Suprachoroidal hemorrhage	0 (0%)	0 (0%)
Vitreous hemorrhage	3 (3.4%)	10 (13.9%)
Cystoid macula edema	1 (1.1%)	2 (2.8%)
Rhegmatogenous retinal detachment	0 (0%)	1 (1.4%)
Persistent corneal edema	2 (2.2%)	1 (1.4%)
Endophthalmitis	1 (1.1%)	0 (0%)

occurred in two eyes in the EXP group and one eye in the BGI group. Rhegmatogenous retinal detachment occurred in one case in the BGI group. Endophthalmitis occurred in one case in the EXP group.

Other merits and Demerits of Both Surgeries

EXP surgery requires laser suture lysis or needling for the control of the postoperative IOP. The patients in the present EXP group thus require many visits after the early postoperative period, especially within the first 3 months. In contrast, the BGI surgery usually does not need postoperative interventions. We compared the postoperative interventions and the length of hospital stay between the two groups (Table 6), and the results demonstrated that the rate of patients in the entire cohort who required any postoperative intervention such as laser suture lysis or needling was 82 (91.2%). Only one patient required a postoperative intervention (1.4%); the patient's tube had to be reinserted due to tube occlusion with the uvea.

The mean length of hospital stay was significantly longer in the EXP group at 8.6 ± 1.8 days compared to 4.9 ± 1.4 days in the BGI group ($p < 0.0001$). We compared how many visits were made to our hospital within 3 months post-surgery between the groups: the mean number was 7.3 ± 1.4 in the EXP group, which was significantly higher than the 4.1 ± 0.8 visits in the BGI group ($p < 0.001$).

Our data revealed that the EXP surgery decreased the patients' IOP immediately, whereas it took a few months for the patients' IOP to decline after the BGI surgery. The mean IOP value at 1-month post-surgery was significantly lower in the EXP group at 9.8 ± 4.4 mmHg compared to 20.6 ± 10.8 mmHg in the BGI group ($p < 0.0001$). At 3 months, the mean IOP values were not significantly different between the groups (EXP: 12.3 ± 5.3 vs BGI: 12.9 ± 6.8 mmHg) ($p = 0.558$). The number of early postoperative glaucoma medications was significantly lower in the EXP group ($p < 0.001$). These results (Table 6) highlight some advantages of EXP surgery. The advantages and disadvantages of the EXP and BGI surgeries are summarized in Table 7.

Table 6: Mean of early postoperative IOP, glaucoma medications and visits, and number of visits.

	EXP ($n=89$)	BGI ($n=72$)	p value
Postoperative interventions, N/NA	82/7	1/71	< 0.001
Length of hospital stay, days	8.6 ± 1.8	4.9 ± 1.4	< 0.001
No. of visits within 3mos	7.3 ± 1.4	4.1 ± 0.8	< 0.001
1-mos. Post-op IOP, mmHg	9.8 ± 4.4 (89)	20.6 ± 10.8 (72)	< 0.001
1-mos. Post-op IOP, medications	0 ± 0	3.6 ± 0.9	< 0.001
3-mos. Post-op IOP, mmHg	12.4 ± 5.3 (89)	12.9 ± 6.7 (72)	0.558
3-mos. Post-op IOP, medications	0.7 ± 1.3	2.2 ± 1.7	< 0.001
6-mos. Post-op IOP, mmHg	11.3 ± 4.1 (86)	11.2 ± 3.7 (72)	0.823
6-mos. Post-op IOP, medications	1.1 ± 1.7	2.2 ± 1.5	< 0.0001

N/NA necessary/not necessary, *mos.* months

Table 7: Summary of merits and demerits for both surgeries.

	EXP	BGI
Visits, within 3 mos	7.3 visits	4.1 visits
Post-op interventions	Necessary	Unnecessary
Post-op IOP, within 3mos	9.8–12.4 mmHg	20.6–12.9 mmHg
Post-op IOP, after 3mos	11.9–12.2 mmHg	10.8–11.2 mmHg
Medications, within 1 yr	1.5 drops	2.3 drops
Medications, after 2 yrs	2.5–2.7 drops	2.1–2.4 drops
Post-op ECD after 3 years	13.4% decrease	2.1% decrease
Main complications	Hypotony	Vitreous hemorrhage, retinal disease

Discussion

Both of the EXP and BGI surgeries significantly decreased the individual patients' IOP at all time points ($p < 0.001$). The success rate was significantly better in the BGI group ($p = 0.0148$) when surgical success was defined < 21 mmHg. Defined < 18, 15, and 12 mmHg, both of surgical outcomes were not significantly different. The ECD after the EXP surgeries decreased significantly faster than after BGI.

Cases with unsuccessful previous filtration surgery are known to have poor additional surgery results. Considering the fact, BGI surgery was expected poor surgical results in this study. However, the BGI group had comparable surgical outcomes of Express, despite including significantly more patients with a history of filtration surgery. In Japan, there is a tendency to refrain from BGI surgery for POAG or PEXG patients for the first time. However, our study could suggest that BGI surgery might be an option for the initial surgery for POAG and PEXG patients with high preoperative IOP. BGI group had significantly many patients who underwent PPV simultaneously. Some previous studies reported that PPV with small gage could remained stable [8, 9]. In previous reports, the postoperative IOP after EXP surgery was 11.3–14.7 mmHg [1, 2, 4, 10], and that after BGI surgery was 12.4–14.2 mmHg [6, 11, 12]; our present findings are thus almost the same.

The patients who underwent EXP surgery need not use glaucoma medications immediately after the surgery. This is an advantage for the patients who underwent the EXP surgery. In the BGI surgery, the patient's IOP remains high until the absorbent yarn spontaneously melts, and thus, many of the patients in the present BGI group required glaucoma medications at approx. 2 months after their surgeries. However, filtration blebs have a tendency to become smaller over a period of years after EXP surgery [13]. For this reason, in the present EXP group, the use of glaucoma medications increased more as time passed. In addition, the number of patients who required additional glaucoma surgery increased. The EXP group's surgical outcomes were significantly poorer than those of the BGI group.

In the BGI group, the number of glaucoma medications did not change notably. After 2 years, the numbers of glaucoma medications were not significantly different between the BGI and EXP groups. Moreover, there were no cases in which the postoperative IOP was above 21 mmHg under the conditions in which glaucoma medications could be used. In addition, there was no case of hypotonic maculopathy, and BGI surgery poses a low risk of ocular hypertension or hypotony. The BGI surgery could maintain good IOP over a long period of time [14]. The reason for this might be that the plate used in BGI surgery was enough large to lower the IOP.

The reduction in ECD after EXP surgery has been examined [4, 15], but conflicting results regarding whether the ECD decreased after EXP surgery were obtained. In the present investigation, the EXP surgery reduced the patients' ECD significantly. We reported that the insertion of an Ex-Press implant into the cornea (not the trabecular meshwork) was a risk factor for rapid ECD loss [16]. It has been reported that in BGI surgery, the reduction in ECD could be suppressed by inserting the implant into the vitreous cavity [17, 18]. In the present study, the BGI implant was inserted into vitreous cavity for all of the BGI patients. Bullous keratopathy is one of the serious potential complications of glaucoma surgeries that leads to poor vision, and surgery to avoid such risks is desirable.

There were many complications due to hypotony in our EXP group. Netland *et al.* reported that a shallow anterior chamber and choroidal detachment occurred in 6.8% of their patients who underwent Ex-Press surgery [19]. Herein, we observed a slightly higher rate of complications due to hypotony. These complications improved spontaneously within 3 months after the EXP surgery. There were no cases of hypotonic maculopathy. There were six cases in which hyphema was caused by Ex-press insertion, of which three cases had vitreous hemorrhage. There was one case of endophthalmitis due to bleb infection in the EXP group; it occurred at 26 months post-surgery.

Our BGI group had many retinal and vitreous complications. Vitreous hemorrhage was observed in 10 cases (13.9%). Campagnoli *et al.* reported that vitreous hemorrhage occurred in 17% of their BGI patients [20]. The main reason for the present VH rate is that we used a 20-gauge V-lance for the insertion of the Hoffmann elbow at the pars plana, and a 20-ga. V-lance might hit the vessel of sclera or uvea. Another reason for the present VH rate is bleeding from the conjunctiva inflow into the vitreous cavity at the wound for inserting the Hoffmann elbow. All 13 of our patients with vitreous hemorrhage improved spontaneously, and none required additional surgery for the irrigation of the VH. There was one case of rhegmatogenous retinal detachment in the BGI group. Although there appear to be few complications of BGI surgery, clinicians should pay close attention to the possibility of complications after BGI or EXP surgery.

The EXP and BGI surgeries include the same technique in that they drain aqueous humor out of the eye. After EXP surgery, the postoperative IOP can be controlled with laser suture lysis or needling. It is difficult to control the postoperative IOP after BGI surgery. Conversely, BGI surgery does not require postoperative interventions. BGI surgery thus has the characteristics of shorter hospital stays and a smaller number of postoperative consultations. Short hospital stays and fewer consultations provide a lesser burden on physicians and patients, and they are thought to have a positive influence on health-care economics. However, BGI surgery has the disadvantage in that the postoperative IOP cannot be lowered immediately, and the IOP cannot be sufficiently reduced until the absorbent yarn has melted. BGI surgery may not be suitable for patients in whom the IOP must be reduced immediately after surgery.

This study has some limitations. Its design is retrospective, which may involve some bias. This study, we did not clear surgical indications which surgeries we choose. We thought that this is a big problem for comparative studies. In generally, BGI used in refractive glaucoma and EXP for early glaucoma. It was difficult to compare the surgical outcomes. So, we compared only POAG and REXG patients; we excluded the case of refractive glaucoma as NVG, uveitis glaucoma. There were between-group differences in the history of eye surgery and the lengths of the follow-up periods. There were no definitions or criteria for (1) the performance of simultaneous cataract surgery, (2) the number of suturing flaps or the timing of suture lysis in the EXP surgery, (3) the use of/need for glaucoma medications, or (4) the need for additional glaucoma surgery. The ECD was measured only once, at the center area. The patients were not necessarily discharged early when their conditions were improved. We decided the date of discharge based not only on each patient's condition but also the patient's desires. In addition, the follow-up period in this study is short.

We compared the results of the EXP and BGI surgeries using the parameters of postoperative IOP, number of glaucoma medications, ECD reduction rate, success rate, complications, the length of hospital stay, and the number of postoperative consultations. For the POAG and PEXG cases with preoperative IOP values > 21 mmHg, the BGI surgery could provide comparable surgical outcomes as EXP surgery and a lesser reduction in the ECD. BGI surgery has the advantage of requiring shorter hospital stays and fewer consultations. BGI surgery could be appropriate for the first surgery for patients who cannot engage in frequent hospital consultations. However, it is necessary to explain to patients that the BGI surgery cannot lower their IOP immediately after surgery, and the patients might need several glaucoma medications.

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Compliance with ethical standards

Conflict of interest: The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethics approval: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate: Each patient in this study provided informed consent after a thorough explanation of the study.

Consent for publication: We obtained consent for publication from each patient.

Code availability: We used JMP for statistical analysis.

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Combined Visco-Trab Operation: A Dual Filtration Pathway for Management of Advanced Glaucoma—Midterm Results

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Abstract

Purpose: To study midterm efficacy and safety of combined Visco-Trab operation for management of advanced glaucoma.

Methods: 168 eyes of 148 patients with advanced glaucoma had Visco-Trab operation (a merge of both viscocanalostomy and trabeculectomy operations). Mean follow-up was 29.1 ± 22.2 months. Criteria of success were intraocular pressure (IOP) of 14 mmHg or less with or without glaucoma medications, with no devastating complications, loss of light perception, or additional glaucoma surgery.

Results: IOP, number of glaucoma drops, and visual field mean deviation were significantly reduced (11.9 ± 5.6 mmHg, 0.7 ± 1.2, and 14.2 ± 6.3 dB, compared to preoperative values of 24.4 ± 9.9 mmHg, 2.8 ± 1.4, and 17.3 ± 6.3 dB, respectively). Success was reported in 136 of 168 eyes (81%) without (100 eyes, 59.5%) or with (36 eyes, 21.5%) glaucoma medications. A functioning bleb was seen in 2/3rd of eyes; diffuse (59 eyes, 35%) and thin ischemic (54 eyes, 32%). Predictors for failure to achieve the target IOP included previous ocular ($p = 0.01$) or glaucoma ($p = 0.04$) surgery, number of preoperative glaucoma medications ($p = 0.029$), and severity of glaucoma ($p = 0.058$).

Conclusion: Combined Visco-Trab operation proved safe and effective, on midterm follow-up, in reducing IOP to the proposed target level in eyes with severe glaucoma via enhancing internal and external filtration.

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Keywords: Advanced glaucoma, Visco-trab operation, Dual filtration, Midterm results

Introduction

Patients with advanced glaucoma (near total cupping of the optic disc and advanced visual field defect encroaching on fixation) are high-risk surgical candidates [1]. Complications of current surgical interventions, namely subscleral trabeculectomy with mitomycin C application (MMC-Trab), include high incidence of hypotony-related complications after the filtering operation or after suture cutting (flat anterior chamber, choroidal effusion or hemorrhage etc.) or postoperative pressure rise due to tight flap closure. This turbulence of postoperative IOP may endanger the compromised optic nerve and the residual vision [2].

Visco-Trab operation constitutes combining viscocanalostomy and trabeculectomy with Mitomycin C in a single technique in order to increase both internal and external flow of aqueous postoperatively [3]. Surgical technique included lamellar and deep scleral flap dissection, deroofing and viscodilation of Schlemm's canal (SC), penetrating trabeculectomy, peripheral iridectomy, and tight flap closure. The early postoperative IOP reduction after Visco-Trab was mostly attributed to improved internal flow mechanisms, while external filtration is minimized by tight scleral flap closure. Subsequent scleral flap suture cutting, when needed, allows subconjunctival drainage of aqueous. Persistent IOP lowering is attributed partly to improved conventional outflow pathways and partly to external filtration. The controlled hypotony produced by enhancing internal filtration and limiting external filtration plays a major role in reducing IOP to the target level during the early postoperative period without pressure spikes or severe complications related to excessive filtration [3]. In a comparative study of the contralateral eye, comparing combined Visco-Trab operation to MMC-Trab proved a similar efficacy over a longer follow-up period with reduced postoperative complications [4].

In this study we evaluated the midterm efficacy and safety of Visco-Trab operation in terms of controlling IOP to a low and stable level with less eventful postoperative course.

Patients and Methods

A retrospective analysis of collected data for previous prospective studies was conducted. 168 eyes of 148 patients with advanced to end-stage glaucoma surgically treated with Visco-Trab operation in the Glaucoma and Cataract Unit at Magrabi Eye and Ear Center, Jeddah, Saudi Arabia, from 2006 till December 2013 were included in the analysis. A local institutional review board was obtained which meets the tenets of the Declaration of Helsinki, and an informed consent was signed by every patient. Advanced glaucoma in this study was defined as near total cupping of the optic disc, severe visual field defect encroaching on central 5 degrees of fixation in at least one quadrant or tubular field defect [1]. In some patients, reliable visual field cannot be obtained because of poor vision, dense cataract, or unreliability of the test. For these patients, glaucoma severity was judged by degree of damage of optic disc, IOP, and patient's compliance. Surgical treatment for these patients was indicated when there was lack of proper control of IOP to the required target level with maximally tolerated medical therapy. The risk–benefit ratio of surgical management was explained to the patient, and a consent form was obtained. Patients with visually significant cataract had separate-site phacoemulsification combined with the glaucoma procedure.

Surgical technique (Fig. 1)

The procedure was performed under topical or peribulbar anesthesia without application of Honan bulb. General anesthesia was given in young or uncooperative or sometimes in single-eyed patients. The globe is rolled down with superior corneal traction suture with 7/0 silk. The filtering site is located slightly nasal or temporal to the 12 o'clock position. Details of the procedure are explained in previous studies [3, 4]. After preparing the site of surgery and Mitomycin C application, a 4×4 mm rectangular lamellar sclera flap was outlined and dissected anteriorly to within 1 mm of clear cornea. A second deeper rectangular flap was outlined 0.5 mm inside the border of the first and dissected using a special dissecting sclera pocket knife (Grieshaber, Switzerland), leaving only a thin translucent layer overlying the choroid. Forward dissection in this plane continues until Schlemm's canal (SC) is identified and deroofed. Dissection continues through the lumen and extends forward until it exceeds Schwalbe's line and Descemet's membrane is seen. No blunt dissection of Descemet's window is performed as in routine viscocanalostomy. A specially designed viscocanalostomy cannula (Grieshaber, Switzerland), with an outer diameter of 165 μm was introduced into the ostia of SC, right and left, to inject sodium hyaluronate 1% (ProVisc, Alcon) into the canal. The cannula is introduced inside the canal for a short distance, and a small amount of viscoelastic is injected and repeated few times on each side. The trabeculo-Descemet's membrane is incised right at the junction with the anterior border of the floor of SC, and a penetrating deep sclero-corneal block was excised for approximately 1.5 mm in length and 2 mm in width. A wide peripheral iridectomy is performed, and the lamellar sclera flap is closed watertight by 4 10/0 Nylon sutures, 2 at the distal corners and 2 on the vertical limbs. The AC is reformed, and the conjunctiva is closed with 2 corners and 2 transverse-mattress 10/0 Nylon sutures.

When the glaucoma procedure is combined with phacoemulsification, once Schlemm's canal is deroofed, the surgeon switches his position to the temporal side to do the cataract operation through a clear-cornea incision. At the end of the phaco procedure, the AC is reformed and the corneal wound is secured by one 10/0 Nylon suture and the surgeon reverts back to upper position to complete the filtering operation.

Postoperatively patients used antibiotic-corticosteroid eye drops every 2 h for one week and then tapered gradually over 5 weeks. Cycloplegic-mydriatic eye drops were used for one week and may be continued if there were signs of early inflammation, shallow AC, hypotony, or anticipated risk of aqueous misdirection. Patients were examined at day 1 and 3 then at 1, 2, 4, and 8 weeks and after that periodically every 3 months. If the pressure was elevated, digital massage, focal compression, and LSL, needling with flap lift, or bleb revision with subconjunctival MMC injection were performed according to the IOP level and degree of filtration.

A minimal of 3 months follow-up was required to be included in the analysis. Criteria of Success were IOP of 14 mmHg or less at the last follow-up, with no devastating postoperative complications or loss of vision or additional glaucoma surgery.

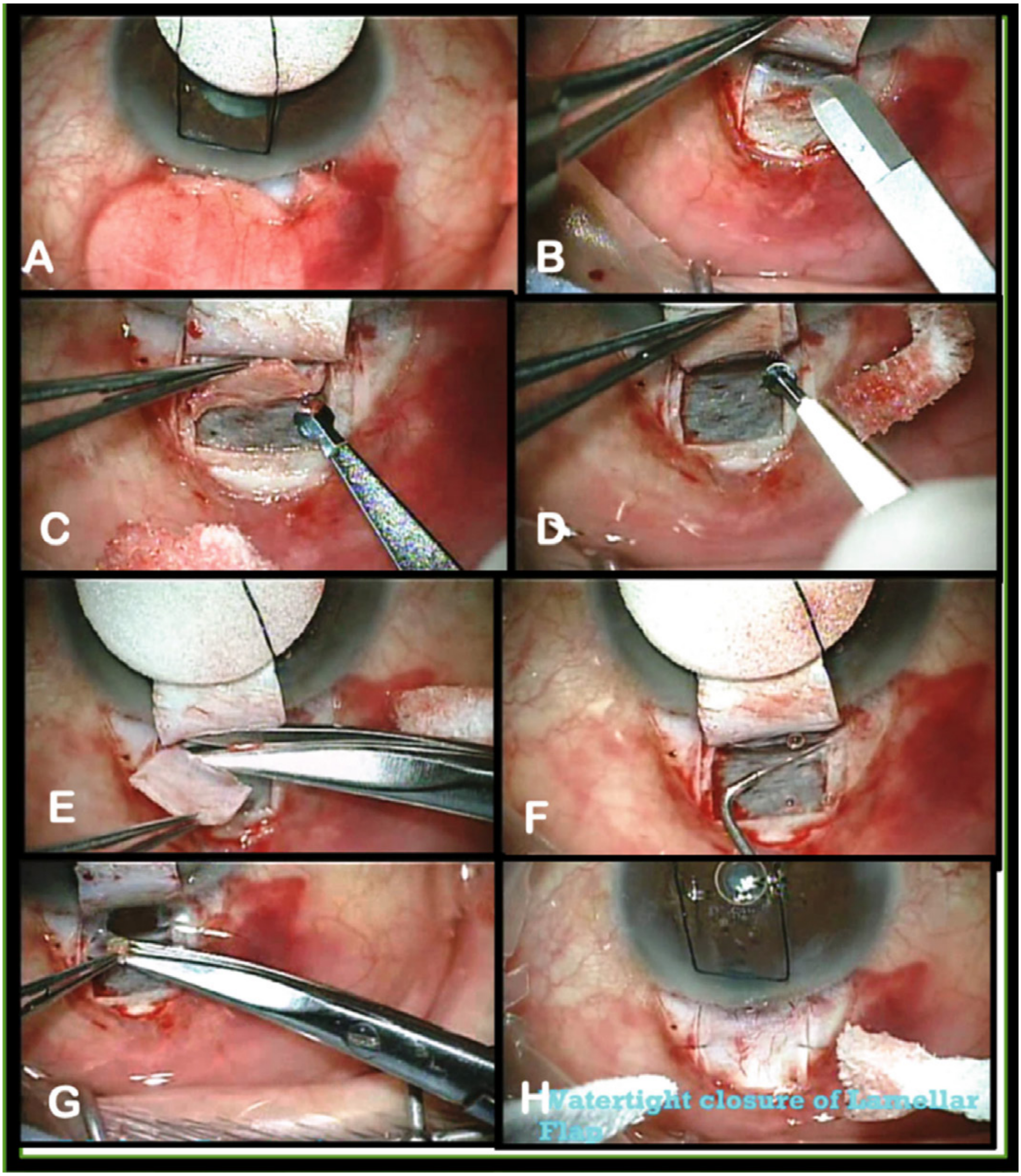

Fig. 1: Steps of combined Visco-Trab operation for advanced glaucoma. **a** Fornix-based conjunctival flap and subconjunctival Mitomycin C 0.3 mg for 3 min. **b** A 4×4 mm lamellar scleral flap (1/3–1/2 of thickness) extending 1 mm in clear cornea. **c** Deep scleral flap dissection 0.5 mm inside edge, leaving thin scleral over choroid **d** Exposure & deroofing of Schlemm's canal (No Descemet's window exposure). **e** Excision of deep scleral flap creating a scleral lake. **f** Dilation of SC with sodium hyaluronate. **g** Penetrating trabeculectomy and peripheral iridectomy. **h** Water tight closure of lamellar scleral flap and conjunctival flap.

Descriptive statistics of numeric (mean ± standard deviation) and categorical (count and percentage) variables for patients' eyes, and glaucoma characteristics, operative data, and postoperative course were listed and tabulated. Paired t-test was used to compare IOP, number of glaucoma medications, visual field mean deviations, horizontal cup-disc ratio, and logMar visual acuity preoperatively and at the last follow-up evaluation. Kaplan–Meier survival analysis of probability of failure of Visco-Trab operation to achieve an IOP of 14 mmHg or less was plotted over the follow-up period. Predictors of failure to achieve the target pressure were studied using logistic regression analysis with a significance level of $p \leq 0.05$.

Results

One hundred ninety-seven eyes were operated with Visco-Trab operation throughout the study period, 25 of them had less than 3 months of follow-up in their records and did not match the inclusion criteria. Additional 4 eyes were converted to classic MMC-Trab and were excluded from the analysis.

Table 1 lists demographic data, characteristics of the study eye and type and severity of glaucoma. Seventy percent of the study patients were males (103 patients) and almost 60% of them (87 patients) were above 50 years of age. More than half of the eyes had primary open-angle glaucoma and 20% (34 eyes) had primary angle closure glaucoma. Three quarters of the eyes received previous glaucoma treatment, and two-thirds of them had a preoperative IOP of 25 mmHg or less. Table 2 describes operative data, intraoperative complications, early postoperative course, postoperative complications and additional surgical interventions. Self-absorbing hyphema was the most common early postoperative complications (21 eyes, 12.5%) followed by shallow to flat anterior chamber (19 eyes, 11.4%; 3 eyes required added maneuvers to reform the anterior chamber). Three eyes (1.8%) suffered from postoperative hypotony with choroidal effusion, two of them required choroidal tap to drain the fluid. Scleral flap lift with a 27-gauge needle on the slitlamp (14 eyes, 8.3%) or bleb revision with additional subconjunctival mitomycin C injection (11 eyes, 6.5%) were done in eyes after failure of laser suture lysis to augment external filtration.

Mean follow-up was 29.1 ± 22.2 months (range 3–86). Mean pre- and postoperative IOP, number of glaucoma medications, visual acuity, and visual field mean deviation are demonstrated in Table 3. Mean IOP and number of glaucoma medications were reduced significantly at the last follow-up evaluation in comparison with their preoperative levels (11.9 versus 24.4 mmHg and 0.7 versus 2.8, respectively, $p < 0.001$). On the other hand, the mean values of cup-disc ratio, visual field mean deviation, and logMar of visual acuity showed stable course over the follow-up length without any significant change from preoperative values.

Table 4 presents the number and percentage of eyes that achieved an IOP of 21 mmHg or less with or without antiglaucoma medications, as well as the number and percentage of eyes that did or did not achieve the target pressure (≤ 14 mmHg) at last follow-up visit. Eighty one percent of eyes (136 of 168 eyes) achieved a target IOP of 14 mmHg or less without (100 eyes, 59.5%) or with glaucoma drops (36 eyes, 21.4%). This percentage of success (both complete and qualified) increased to 95.3% when a pressure of 21 mmHg or less was used as a cutoff value. The recorded appearance of the filtering bleb at last visit examination was counted and is presented in Table 4. Almost two third of the eyes had a functioning bleb either diffuse (59 eyes, 35%) or thin ischemic (54 eyes, 32%) blebs. Cumulative probability of failure of Visco-Trab operation to achieve an IOP of 14 mmHg or less over the extended follow-up period was shown in the Kaplan–Meier analysis chart (Fig. 2).

Table 1: Patients' and eyes' characteristics (*n* = 168).

Variable		**Frequency**	**Percentage**
Sex (*n* = 148)	Male	103	69.6
Age group (n = 148)	> 50 years	87	58.8
Study eye	Right eye	81	48.2
Previous glaucoma treatment		125	74.4
Previous glaucoma surgery (MMC-Trab)		27	16.1
Preoperative visual acuity	> 20/40	93	55.4
	20/40–20/200	53	31.5
	</= 20/400	22	13.1
Preoperative IOP (mmHg)	</= 25	111	66.1
	> 25	57	33.9
Lens status	Clear	116	69.0
	Cataract	24	14.3
	Pseudophakic	28	16.7
Preoperative visual field changes	Double arcuate scotoma	6	3.6
	Hemifield defect	6	3.6
	Advanced defect not affecting fixation	17	10.1
	Advanced defect splitting fixation	64	38.1
	Tubular field defect	21	12.5
	Total field loss	12	7.2
	Not done	42	25.0
Glaucoma diagnosis	Primary open-angle	89	53.0
	Low-tension	4	2.4
	Primary angle closure	34	20.3
	Congenital	14	8.3
	Juvenile	8	4.8
	Angle recession	8	4.8
	Pseudoexfoliative	5	3.0
	Pigmentary	2	1.2
	Steroid-induced	3	1.8
	Uveitic	1	0.6
Glaucoma severity	Advanced	121	72.0
	End-stage	47	28.0

Predictors for failure to achieve the target IOP of 14 mmHg or less at last follow-up evaluation (by logistic regression analysis) included previous ocular ($p = 0.01$) or glaucoma ($p = 0.04$) surgery, number of preoperative antiglaucoma medications ($p = 0.029$), severity of glaucoma ($p = 0.058$). Nonsignificant predictors in the multivariate model included old age ($p = 0.1$) and high preoperative IOP ($p = 0.7$) (Table 5).

Table 2: Operative data and postoperative course of study eyes after Visco-Trab operation.

Variable		Frequency	Percentage
Anesthesia	Topical	82	48.8
	Peribulbar	68	40.5
	General	18	10.7
Intraoperative complications			
	Vitreous loss from sclerostomy	2	1.2
	Descemet membrane detachment during viscodilation	3	1.8
	Choroidal exposure during deep flap dissection	4	2.4
IOP measurement within the first postoperative week			
	</=10 mmHg	133	79.2
	>10 mmHg	35	20.8
Early postoperative complications		38	22.6
	Hyphema	21	12.5
	Shallow anterior chamber	16	9.6
	Flat anterior chamber	3	1.8
	Leaking conjunctival hole	2	1.2
	Choroidal effusion	3	1.8
	Suprachoroidal hemorrhage	1	0.6
Postoperative laser suture lysis			
	Within one week	4	2.4
	Between 1 and 4 weeks	36	21.4
	Between 1 and 3 months	5	3.0
Added postoperative surgical intervention			
	Anterior chamber reformation	3	1.8
	Repair of conjunctival hole Scleral flap lift on slitlamp	2 14	1.2 8.3
	Bleb revision and subconj 5-MMC	11	6.5
	Choroidal drainage	2	1.2
	Repair of Descemet membrane detachment	1	0.6
Cataract extraction during postoperative course		12	7.1

Discussion

Combined Visco-Trab aims, in a single procedure, to lower IOP and lessen the early postoperative complications in patients with severe glaucoma. Surgeons familiar with trabeculectomy and non-penetrating surgery will find no difficulty in performing Visco-Trab without any learning curve. In Visco-Trab, unlike viscocanalostomy, the technique is easier since dissection is not extending over Descemet's membrane where most macro-perforations occur. [5-9].

Table 3: Mean, standard deviation, minimum, and maximum values of numeric variables preoperatively and at the last follow-up in the study.

Variable		Mean	SD	Minimum	Maximum	*P* value
Age (years)		51.1	18.9	4	85	
Length of follow-up (months)		29.1	22.2	3	86	
IOP (mmHg)	Preoperative	24.4	9.9	10	55	< 0.001*
	At last follow-up	11.9	5.6	1	31	
Number of glaucoma drops	Before surgery	2.8	1.4	0	5	< 0.001*
	At last follow-up	0.7	1.2	0	4	
Cup/disc ratio (horizontal)	Before surgery	0.9	0.1	0.5	1.0	0.9
	At last follow-up	0.9	0.4	0	1.0	
Visual field mean deviation (dB)	Preoperative	17.3	6.7	6.2	32.4	0.2
	At last follow-up	14.2	6.3	4.5	24	
LogMar of visual acuity	Preoperative	0.5	0.3	0	1.0	0.9
	At last follow-up	0.5	0.3	0	1.0	

Table 4: Complete and qualified success of achieving a postoperative IOP of 21 mmHg and 14 mmHg and the appearance of the associated filtering bleb at last follow-up evaluation.

Variable		Frequency	Percentage
Filtering bleb appearance at last follow-up			
	Flat bleb	23	13.7
	Localized bleb	28	16.6
	Diffuse bleb	59	35.1
	Thin ischemic bleb	54	32.1
	Cystic bleb	4	2.4
IOP < 21 mmHg at last follow-up			
	Without antiglaucoma drops	130	77.4
	With antiglaucoma drops	30	17.9
	IOP higher than 21 mmHg	8	4.8
IOP </= 14 mmHg at last follow-up			
	Without antiglaucoma drops	100	59.5
	With antiglaucoma drops	36	21.4
	IOP higher than 14 mmHg	32	19.0

The combined Visco-Trab operation reduces IOP by enhancing both internal and external filtration of aqueous fluid. The internal filtration is enhanced by several mechanisms; (1) deep scleral flap dissection and excision creates a scleral lake that accommodates and directs aqueous to orifices of SC or to suprachoroidal space via the remaining thin scleral sheet; (2) dilation of SC with viscoelastic results in circumferential expansion of the canal and collector channels and focal ruptures of the inner wall of SC and juxta canalicular meshwork; (3) tight closure of the superficial lamellar scleral flap limits external flow to the subconjunctival space and directs all aqueous into

Table 5: Predictors of failure to achieve IOP of 14 mmHg or less (logistic regression analysis).

	Regression coefficient	*p* value	Odd's ratio	95% Confidence Interval	
				Lower	Upper
Old age	0.831	0.114	2.295	0.818	6.435
Preoperative IOP (> 25 mmHg)	0.218	0.653	1.244	0.480	3.219
Number of preoperative glaucoma drops	1.014	0.029*	2.757	1.108	8.860
Previous glaucoma operation	1.089	0.040*	2.972	1.048	8.422
Previous ocular surgery	1.380	0.011*	3.974	1.373	11.499
Severity of glaucoma	0.936	0.058	2.550	0.970	6.702

* indicate significant *p* value

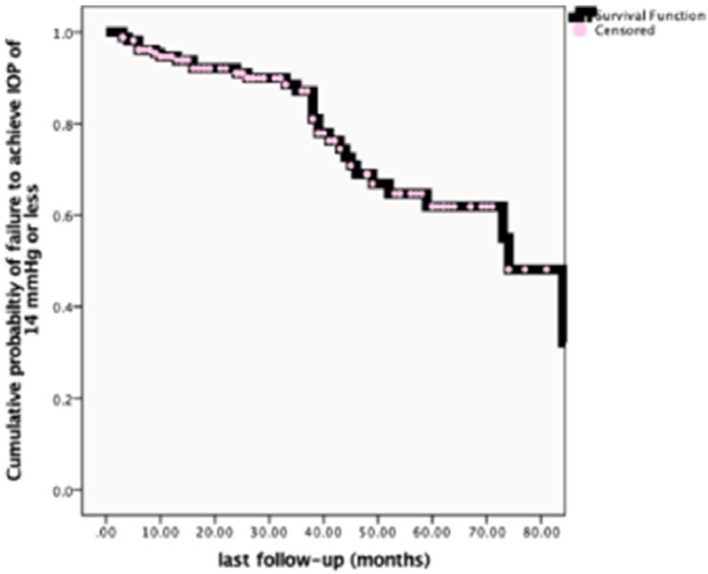

Fig. 2: Kaplan–Meier survival analysis of probability of failure of Visco-Trab to achieve a pressure of 14 mmHg or less necessary for management of advanced glaucoma over the follow-up period.

conventional outflow pathways. On the other hand, subconjunctival flow is guaranteed over the long term via; (1) excision of a penetrating deep sclero-keratectomy (trabeculectomy) creates a guarded external fistula; (2) use of subconjunctival mitomycin C as an antifibrotic agent to reduce episcleral fibrosis; (3) delayed laser cutting of the sutures of the lamellar flap to augment external filtration when needed.

In this study, Visco-Trab operation for management of advanced glaucoma proved midterm efficacy in reducing IOP to 14 mmHg or less in 60% (complete success) and 81% (qualified success) of the eyes at the last follow-up. The total success rate increased to 95.3% when a pressure of 21 mmHg or less was used as a cutoff value. Our results were comparable to those of King and Stead [10]. They reported a success rate of 85% for achieving an IOP of 16 mmHg or less at year 5 follow-up after MMC-Trab for patients with advanced glaucoma. However, Law and associates [11], comparing initial versus repeat MMC-Trab for open-angle glaucoma, reported lower success rate in achieving an IOP of 15 mmHg or less (61% and 41%, respectively). On studying the outcome of viscocanalostomy in patients with advanced glaucoma at 1, 2, and 3 years follow-up by Tsagkataki and associates [12], complete success was 45%, 28%, and 31%, whereas qualified success was 67%, 66%, and 60%, respectively. On the other hand, combination of trabeculectomy with deep sclerectomy had an 83% complete success and 100% qualified success to achieve a 22 mmHg or less IOP after 12 months of follow-up [13]. The success rate was much less in a recent study by Sangtam and associates [14] using combined modified deep sclerectomy and trabeculectomy for various types of glaucoma at different stages of severity. Complete success in their study was 50% (for IOP < 22 mmHg) and 36% (for IOP < 16 mmHg), while qualified success was 70% and 47%, respectively. The difficulty to compare different studies in terms of success rates is due to variability in selection criteria of patient type, glaucoma diagnosis, disease severity; previous ocular surgery; primary versus repeat glaucoma operation; variable success criteria; and follow-up duration. In our Visco-Trab study, we had patients with various ethnicities, different types of glaucomas, and nearly one third of the eyes had previous ocular surgery, but all patients were categorized as advanced disease, operated by one surgeon, all had the same surgical technique, follow-up regimen, and criteria of assessment.

In the meantime, Visco-Trab operation safely reduced postoperative pressure spikes as well as hypotony-related complications that might result from excessive external filtration. Reported intraoperative complications were very few (Table 2) denoting that the procedure can be mastered easily. Micro- or macro-perforations are the most common complications of viscocanalostomy that occur during dissection of the descemet's window, a step not required in Visco-Trab operation. Postoperative complications that required added surgical intervention included flat anterior chamber (3 eyes), choroidal effusion (3 eyes, 2 of them had choroidal tap). None of the eyes lost light perception or had other devastating complications (endophthalmitis, or atrophia). In a previous study [3], early postoperative complications were comparable in number; however, some complications were greater in severity after MMC-Trab than after Visco-Trab, such as anterior chamber shallowness (no eyes with flat chamber in the Visco-Trab group compared to 5 eyes in the MMC-Trab group), choroidal effusion (none required surgical drainage after Visco-Trab compared to 2 eyes after MMC-Trab), and surgically induced astigmatism. Additionally, patients required less postoperative surgical intervention in the Visco-Trab group (3 interventions compared to 8 in the MMC-Trab group). In another contralateral eye-controlled study [4], early postoperative complications were greater and postoperative surgical interventions were more frequent after MMC-Trab than after Visco-Trab operation. In a previous study on 60 eyes with advanced glaucoma having MMC-Trab, a 35% postoperative complication rate was reported (25% of the eyes had excessive filtration and shallow or flat anterior chamber and 15% had choroidal effusion). [15] A similar rate of postoperative complications after Trab with antifibrotic agents was reported in other studies. [16-19].

Several studies reported post-laser suture lysis complication rates between 21 and 42% after MMC-Trab [16, 20]. Viscoelastic dilatation of Schlemm's canal in Visco-Trab was shown to enhance internal filtration early postoperatively. This made suture cutting seldom necessary in the first two weeks after surgery despite tight closure of lamellar sclera flap. This relatively long interval may limit excessive flow of aqueous into the subconjunctival space with less adverse events. Morinelli and associates reported that a longer time interval between surgery and suture lysis may result in both a lesser degree of IOP reduction and a lower incidence of subsequent hypotony [20]. Delayed suture cutting postoperatively after Visco-Trab might be associated with early onset episcleral and scleral fibrosis. This, in some patients, may explain the lack of IOP lowering after laser suture lysis and necessitates invasive maneuvers such as needling and flap lift on the slitlamp (14 eyes) or bleb revision with subconjunctival mitomycin C in the operating room (11 eyes).

Most of the eyes had stable visual acuity and visual fields compared to preoperative level (Table 3). None of the eyes had "wipe-out phenomenon" after Visco-Trab neither in this study nor in our previous report [3, 4]. Costa and associates [21] reported that the risk of unexplained postoperative loss of central visual field does exist but is lower than 1% and is more likely to occur in older patients with macular splitting in the preoperative visual field. In another study, Topouzis *et al.* [22] reported no occurrences of "wipe-out" phenomenon in their series of end-stage glaucoma after MMC-Trab. They concluded that this sudden, unexplained postoperative loss of central vision is, at most, a rare complication and early surgical intervention should be considered in these patients. Stability of the visual filed mean deviation, cup/disc ratio, and visual acuity over the extended follow-up period (Table 3) indicates the importance of a low and stable target IOP for those glaucoma patients with advanced neuronal damage [23, 24].

Combined Visco-Trab, unlike nonpenetrating surgeries, can be performed for all types of glaucoma regardless of the angle appearance. Disadvantages of this technique include added surgical difficulty and time consumption in deep scleral block dissection & Schlemm's canal exposure, extra cost of viscoelastic, a special knife and cannula not routinely used with MMC-Trab. In this study, sodium hyaluronate 1% is used instead of the high molecular weight Healon GV or Healon 5 which may have affected our results [25]. Tanito and coworkers [26] reported a comparable success rate using Healon 1% (Pharmacia, Japan), but they assumed that it may be related to the high incidence of postoperative hyphema.

Two third of eyes had functioning blebs either diffuse (59 eyes, 35%) or thin ischemic (54 eyes, 32%) which may be matching with almost 60% of eyes that achieved complete success. On the other hand, only a quarter of the eyes (45, 26.8%) required postoperative laser suture lysis despite the surgical plan of tight closure of the lamellar scleral flap in Visco-Trab. This significant long-term IOP reduction without suture cutting may be attributed partly to viscoelastic dilation of Schlemm's canal and widening of trabecular pores which may provide long-lasting enhancement of internal filtration. In the meantime, even though the scleral flap is being closed watertight, there could be percolation of aqueous into the subconjunctival space assisted by blinking, ocular pulsation, digital massage, and reduced healing activity induced by antifibrotic agents (mitomycin C and topical steroids). Many of these patients develop a functioning bleb without the need for postoperative suture cutting.

Significant predictors for failure of Visco-Trab operation to reduce IOP to 14 mmHg or less at last follow-up evaluation included previous ocular surgery ($p = 0.01$), previous glaucoma surgical intervention ($p = 0.04$) surgery, and number of preoperative antiglaucoma medications ($p = 0.029$).

Severity of glaucoma (advanced versus end stage) had border line significance ($p = 0.058$), whereas old age ($p = 0.1$) and high preoperative IOP ($p = 0.7$) were not significant predictors for failure to maximally reduce IOP after Visco-Trab technique. Law and coworkers [11] reported that younger age and requirement for laser suture lysis were significant risk factors for failures in eyes with repeated MMC-Trab. Song and associates [27] found increased age, greater baseline IOP, limbus-based conjunctival flaps, and MMC duration > 1 min were associated with decreased risk of surgical failure of MMC-Trab for eyes with primary angle-closure glaucoma.

In conclusion, combined Visco-Trab operation proved safe and effective, on midterm follow-up, in reducing IOP to the proposed target level in eyes with severe glaucoma via enhancing internal and external filtration.

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Data availability: All data available in data collection sheets and in SPSS files.

Compliance with ethical standards

Conflict of interest: Tarek M. Eid Ezz, El-Din M. Ibrahim and Ahmad Zaid declares that he has no conflict of interest with any items related to this study.

Consent to participate: All patients signed an informed consent.

Consent to publish: Approved from authors.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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CLINICAL VIGNETTE

Confocal Scanning Laser Ophthalmoscopy and Glaucoma

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Introduction

Confocal scanning laser ophthalmoscopy (CSLO) to assess optic disc topography was first implemented in the late 1980s (Laser Tomographic Scanner, Heidelberg Instruments). With reductions in cost and the advent of improved hardware, the first practical commercial confocal scanning laser ophthalmoscope was the Heidelberg Retina Tomograph (HRT) introduced in 1991 (Heidelberg Engineering, Heidelberg, Germany).

The HRT is a scanning laser ophthalmoscope designed to acquire images of the optic nerve head, retinal nerve fiber layer, and posterior pole. A rapid scanning 670 nm diode laser is used to acquire images without mydriasis. Both the HRT II and HRT III obtain 16–64 high resolution, reflectance images with a 4 mm depth over an area of 15° by 15°. A three-dimensional topographic representation of the optic disc and peripapillary retina is constructed from multiple two-dimensional slices [1]. Three scans are aligned and analyzed to create the mean topography scan for each patient. Morphologic parameters (such as rim area and volume) are calculated from an arbitrary reference plane 50 μm below the surface of the temporal parapapillary retina along the disc margin included RNFL thickness [1] (Fig. 1). Other parameters such as the cup shape measure (CSM) are independent of the reference plane. The measurements of optic disc topography are highly reproducible and show very good agreement with clinical estimates of ONH structure and visual function [2]. The reproducibility of the local surface height measurement at over the 384 × 384 pixel area is 20 μm for healthy and glaucomatous eyes with an acuity of 20/40 or better and cylindrical refractive error < 1 diopter.

Parameters

Once the optic disc contour is drawn, the software displays the stereometric parameters of the optic disc compared to a range of statistically "normal values." The parameters that are measured by HRT include optic disc area, cup area, cup-disc area ratio, rim area, cup volume, cup depth, retinal nerve fiber layer (RNFL) thickness, and cross-sectional retinal nerve fiber layer area. These parameters are available for the entire optic disc (global) and for segments of the optic disc (Fig. 2).

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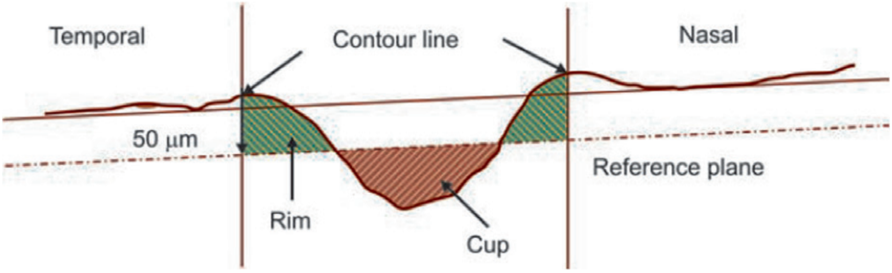


Fig. 1: The reference plane is located 50 µm posterior to the temporal disc margin between 350° and 356° (the papillomacular bundle). The volume enclosed by the contour line and above the reference plane is the rim and is shown in green. The cup is located below the reference plane and is shown in Red.

Parameters	global	normal range	p-value	temporal	tmp/sup	tmp/inf	nasal	nsl/sup	nsl/inf
disc area [mm²]	2.03	1.63 - 2.43	-	0.47	0.26	0.28	0.48	0.28	0.25
cup area [mm²]	0.33	0.11 - 0.68	> 0.5	0.25	0.03	0.05	0.00	0.00	0.00
rim area [mm²]	1.70	1.31 - 1.96	> 0.5	0.23	0.23	0.24	0.48	0.28	0.25
cup/disc area ratio [ ]	0.16	0.07 - 0.30	> 0.5	0.52	0.12	0.17	0.00	0.00	0.00
rim/disc area ratio [ ]	0.84	0.70 - 0.93	> 0.5	0.48	0.88	0.83	1.00	1.00	1.00
cup volume [mm³]	0.02	-0.01 - 0.18	> 0.5	0.02	0.00	0.00	0.00	0.00	0.00
rim volume [mm³]	0.40	0.30 - 0.61	> 0.5	0.02	0.04	0.05	0.12	0.08	0.08
mean cup depth [mm]	0.13	0.10 - 0.27	> 0.5	0.16	0.13	0.16	0.06	0.06	0.06
maximum cup depth [mm]	0.32	0.32 - 0.76	> 0.5	0.33	0.29	0.33	0.16	0.18	0.17
height variation contour [mm]	0.31	0.31 - 0.49	0.34	0.13	0.18	0.17	0.13	0.03	0.08
cup shape measure [ ]	-0.13	-0.28 - -0.15	0.24	-0.02	-0.07	-0.02	-0.15	-0.18	-0.15
mean RNFL thickness [mm]	0.23	0.20 - 0.32	> 0.5	0.09	0.27	0.28	0.24	0.34	0.32
RNFL cross sectional area [mm²]	1.19	0.99 - 1.66	> 0.5	0.11	0.17	0.19	0.29	0.23	0.21
linear cup/disc ratio [ ]	0.40	0.27 - 0.55	> 0.5	-	-	-	-	-	-
maximum contour elevation [mm]	-0.06	-0.21 - -0.04	0.42	-	-	-	-	-	-
maximum contour depression [mm]	0.25	0.17 - 0.39	> 0.5	-	-	-	-	-	-
CLM temporal-superior [mm]	0.18	0.14 - 0.27	> 0.5	-	-	-	-	-	-
CLM temporal-inferior [mm]	0.19	0.13 - 0.29	> 0.5	-	-	-	-	-	-
average variability (SD) [µm]	11	-	-	-	-	-	-	-	-
reference height [µm]	299	-	-	-	-	-	-	-	-
FSM discriminant function value [ ]	1.48	-	-	-	-	-	-	-	-
RB discriminant function value [ ]	1.15	-	-	-	-	-	-	-	-
modified ISNT rule fulfilled	yes	-	-	-	-	-	-	-	-

Fig. 2: The morphometric parameters that are automatically calculated by HRT. These parameters are available for the entire optic disc (global) and for the different sectors.

OU Printout

An informational printout of both eyes is now available and includes the quality of the image, topographic maps, topographic values for each eye, and the asymmetry. The color-coded optic disc image identifies the rim (green), rim slope (blue) and cup (red) (Fig. 3).

Comparison of topographic parameters to a normative database are represented with red crosses denoting 'outside normal limits', yellow exclamation marks denoting 'borderline', and green ticks denoting 'within normal limits'.

When a printout is read (Figs. 4 and 5), the following parameters should be evaluated:

1. Patient information
2. Quality (Fig. 4a): A standard deviation (SD) < 40 µm is acceptable quality while a SD < 30 µm is a good quality image
3. Disc size (Fig. 4b): Discs are classified as small (< 1.6 mm²), average (1.6–2.6 mm²), and large (> 2.6 mm²) depending on cutoffs provided by the manufacturer

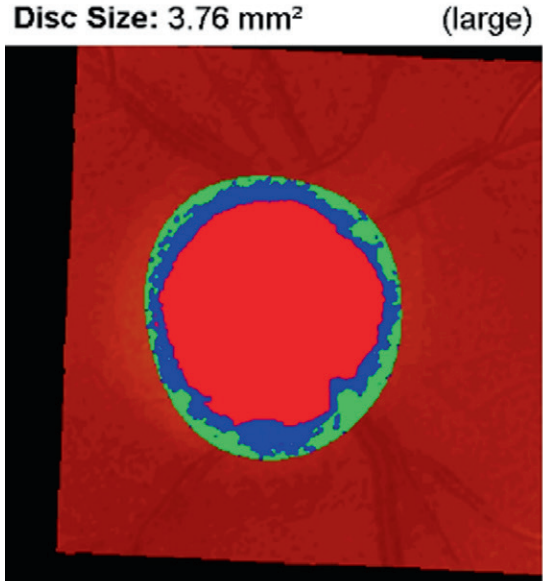


Fig. 3: Color coded optic disc with the rim shown in green, rim slope shown in blue, and cup shown in red.

4. Cup Analysis (Fig. 4c): Shows the configuration of the cup shape measure (CSM) which represents the slope and the cup
5. Rim Analysis (Fig. 4d): Provides the rim area and Moorfields regression analysis based on the rim to disc area globally and for each sector
6. RNFL Analysis (Fig. 4e): Measures the thickness of the RNFL along the contour line and relative to the reference plane. Note that, unlike optical coherence tomography (OCT), it is not the actual measurement of RNFL thickness and suffers from variability as disease progresses.

Moorfields regression analysis (MRA) compares sectoral rim areas to a normative database adjusted for disc area, ethnicity, and age. The optic disc is divided into 6 sectors and each is classified as follows: within normal limits (0–95%), borderline (95–99.9%), and outside normal limits (99.9–100%) [3] (Fig. 6). In a group of early glaucoma patients, the MRA showed a sensitivity of 84% and a specificity of 96% in detecting glaucoma [4].

Glaucoma Probability Score (GPS): The HRT III provides an additional means to analyze the optic nerve head without needing to manually delineate the optic disc margins. This method, the Glaucoma Probability Score, is based on fitting the optic nerve head to a predefined model to provide global and sectoral quantifications of the region [5] (Fig. 7).

Simply put, the GPS compares the shape of the optic disc excavation to a cone (normal) or cup (glaucoma) and classifies the ONH into three different groups based on the value obtained: normal (0–28), borderline or suspect (28–64), and 'outside normal limits' (64–100) group. The GPS has been shown to be more sensitive but less specific than minimum rim width (MRW) in detecting glaucoma. This suggests that an abnormal MRA classification is useful to confirm that a disc is glaucomatous, whereas a 'within normal limits' GPS classification is useful to confirm that a disc is normal [6].

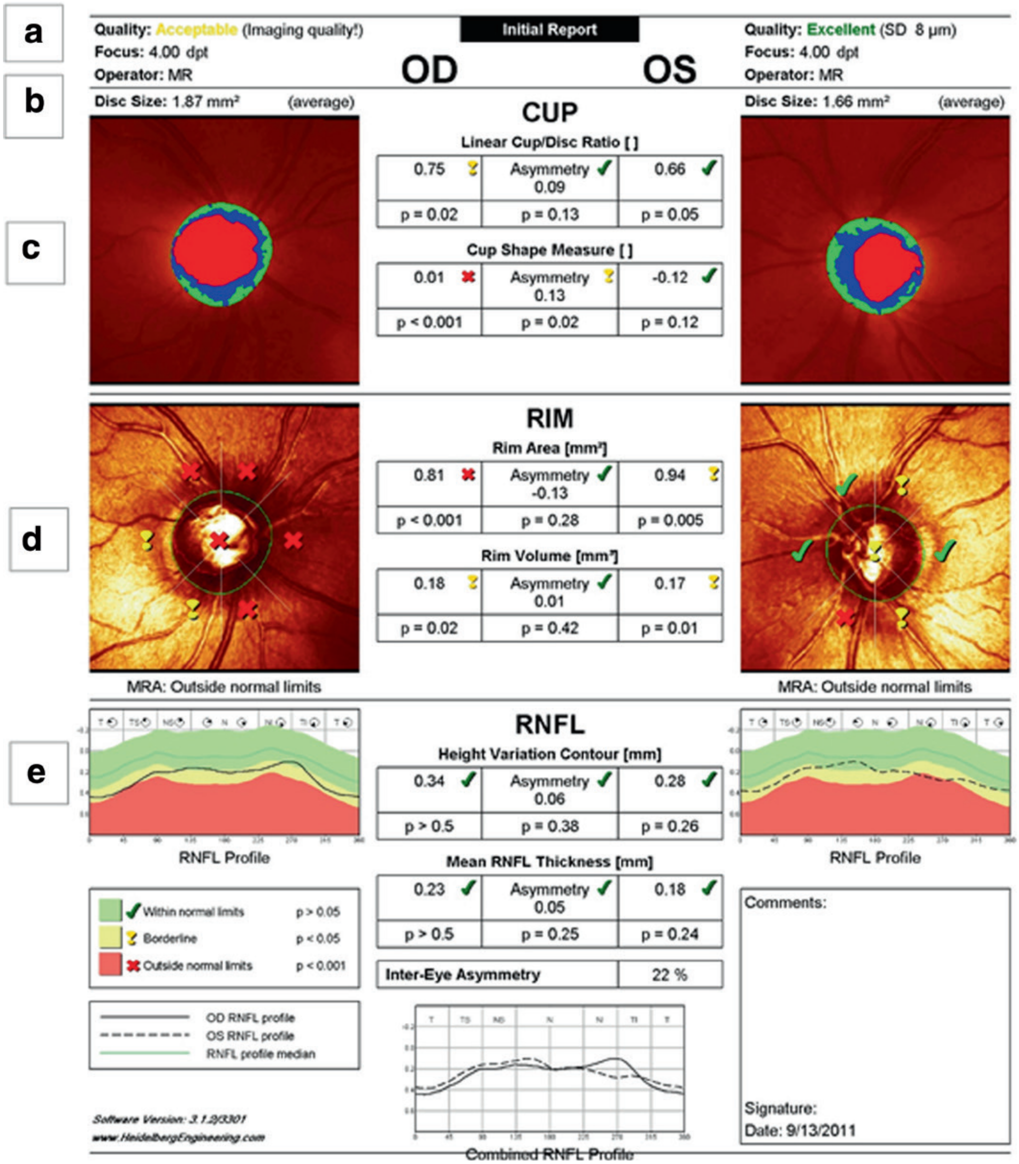


Fig. 4: A confocal scanning laser ophthalmoscopy image of a 68-year-old female with glaucoma. **a** The quality of the image is acceptable in the right eye and excellent in the left eye. **b** The disc size is average with a disc area of 1.87 mm² and 1.66 mm² in the right and left eye, respectively. The disc size is important because the normative values of the other parameters are relative to the disc size. **c** Cup analysis shows increased cupping in the right eye with an abnormal cup shape measure and normal cup shape measure in the left eye. **d** Rim analysis is one of the most important parts of the HRT printout. The Moorfields regression analysis (MRA) classifies most sectors in right eye as "outside normal limits." In the left eye, only significant inferonasal rim thinning is flagged by the MRA. The rim area is outside normal limits in the right eye and borderline in the left eye. **e** In the RNFL analysis, the right eye has a flattened plateau contour line with a loss of the double hump pattern. The left eye has a reduced height of the contour line from the reference plane in the inferior pole. However, the mean RNFL thickness is 'within normal limits' in both eyes. Of note, HRT is not a reliable device to measure RNFL thickness as the plot is the distance of the RNFL contour line to an arbitrary reference plane.

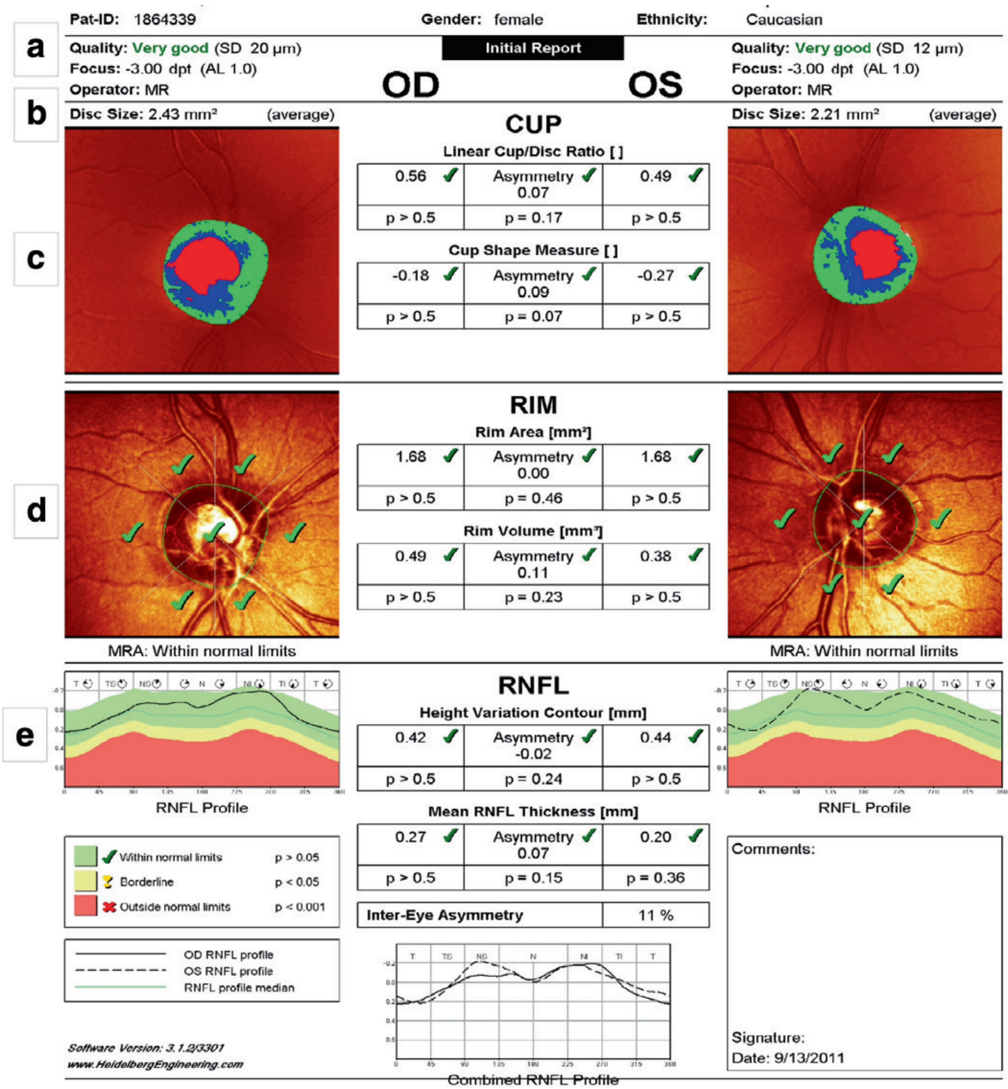


Fig. 5: A confocal laser scanning tomography image of a 55-year-old healthy female. **a** The quality of the image is very good in both the right and left eye. **b** The disc size is average with areas of 2.43 and 2.21 mm^2. **c** Cup analysis shows small cups in both eyes with a cup/disc ratio and cup shape measure 'within normal limits' in both eyes. **d** Rim analysis and the Moorfields regression is 'within normal limits' in all sectors. **e** In RNFL analysis, a double hump pattern can be seen in both eyes with normal values for mean RNFL thickness and height variation contour.

Case 1–Early and Moderate Glaucoma

A 68-year-old woman presented with a visual acuity (VA) of 20/25 in the right eye and 20/50 in the left eye. IOP was 21 and 25 mmHg on latanopost in right and left eye, respectively. Examination of the optic disc showed sloping of the superior neuroretinal rim with decreased visibility of RNFL

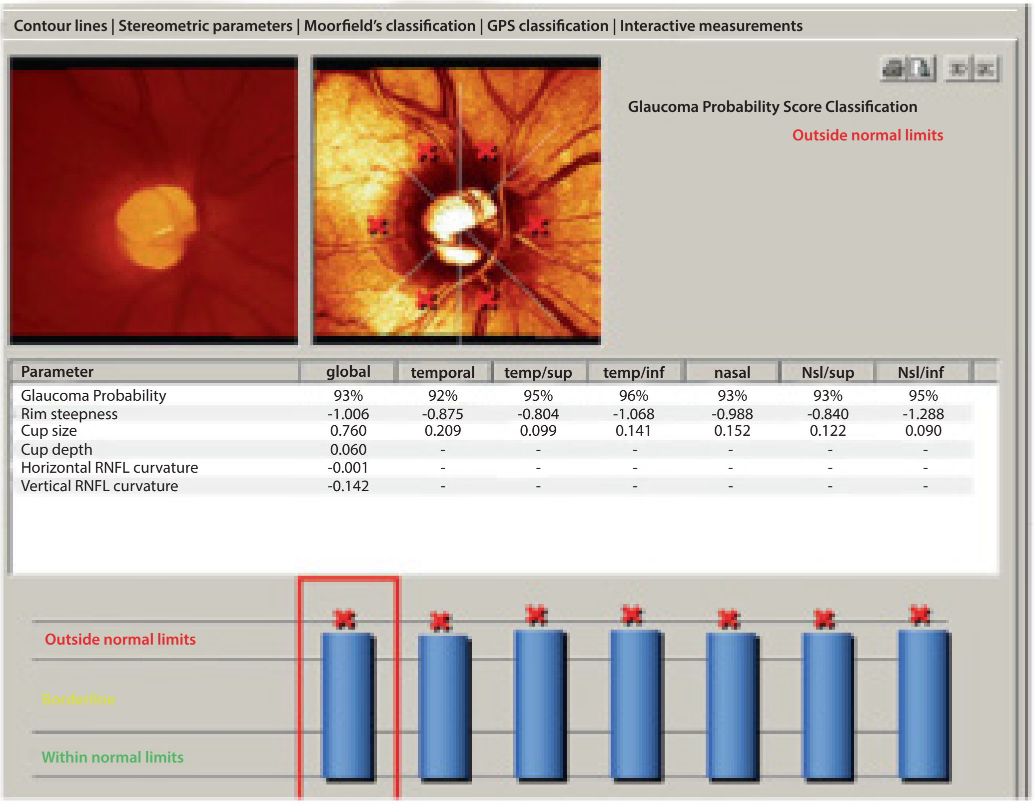


Fig. 6: Moorfields regression analysis of a glaucoma patient. All the sectors and the global rim area are flagged as 'outside normal limits' and depicted with a red "X".

superiorly compared to inferiorly in the right eye and extensive cupping with loss of the neuro-retinal rim and RNFL superiorly and inferiorly in the left eye. Automated perimetry was normal in right eye and revealed superior and inferior altitudinal defects in left eye. Confocal laser scanning tomography showed a Moorfields regression analysis of "borderline" globally in right eye and 'outside normal limits' in supratemporal sector. Cup, rim and RNFL parameters were within normal limit in right eye. Almost all the sectors in the left eye are flagged as "outside normal limits" in left eye (Figs. 8 and 9). Note that the GPS is 'outside normal limits' in both eyes. The GPS is more sensitive and less specific than MRA in diagnosing glaucoma.

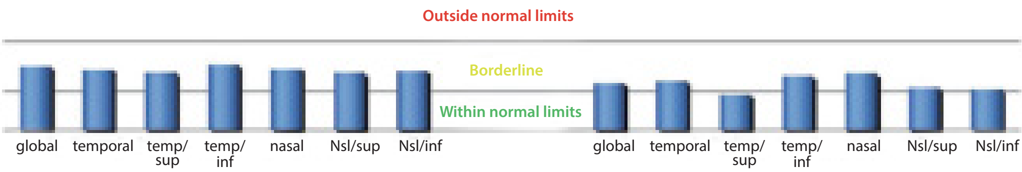
Case 2–Advanced Glaucoma

A 75-year-old man presented with a visual acuity of 20/40 in the right eye and 20/200 in the left eye. IOP was 16 mm Hg in the right eye and 18 mmHg in the left eye. He was using latanopost and Cosopt. The visual field in both eyes revealed dense scotomas in both hemifields. The follow-up HRT scan showed an acceptable image of the right eye but an unacceptable image for the left

Operator: Mi **OD** **OS** Operator: Mi

Glaucoma Probability Score (GPS)

global	temporal	tmp/sup	tmp/inf	nasal	Nsl/sup	Nsl/inf	Parameter	global	temporal	tmp/sup	tmp/inf	nasal	nsl/sup	nsl/inf
0.48	0.44	0.41	0.41	0.44	0.41	0.42	Glaucoma prob.	0.21	0.25	0.25	0.20	0.40	0.20	0.20
-0.18	-0.68	-0.76	-0.52	-0.53	-0.43	-0.55	Rim steepness	0.01	-0.21	-0.12	-0.55	0.56	-0.07	0.12
0.45	0.14	0.05	0.09	0.11	0.05	0.05	Cup size (mm^2)	0.31	0.14	0.04	0.10	0.14	0.06	0.02
0.90	-	-	-	-	-	-	Cup depth (mm)	0.01	-	-	-	-	-	-
-0.04	-	-	-	-	-	-	H.RNFL curv.	-0.01	-	-	-	-	-	-
-0.16	-	-	-	-	-	-	V.RNFL curv.	-0.11	-	-	-	-	-	-



Glaucoma Probability Score Classification
Borderline

Glaucoma Probability Score Classification
Borderline

Fig. 7: Glaucoma Probability Score (GPS) of a patient with a normal intraocular pressure history. The disc is suspicious, and GPS shows the shape of the disc is 'borderline' in almost all sectors.

eye probably due to a cataract (Fig. 10). Although the MRA is abnormal in almost all sectors and the rim area is significantly reduced, RNFL analysis shows only blunting of RNFL profile and abnormal values in inferior region of left eye. As mentioned earlier, in contrast to OCT, RNFL analysis by the HRT is not a direct measure of the RNFL thickness and is not reliable for detecting or monitoring of glaucoma.

Case 3–Large Optic Disc

A 56-year-old woman was suspected of having glaucoma because of the appearance of the optic disc. Her cup-to-disc ratio was high and estimated to be 0.75 and 0.65 in her right and left eye, respectively. Her optic disc was also determined to be large. Visual fields were normal and the IOP

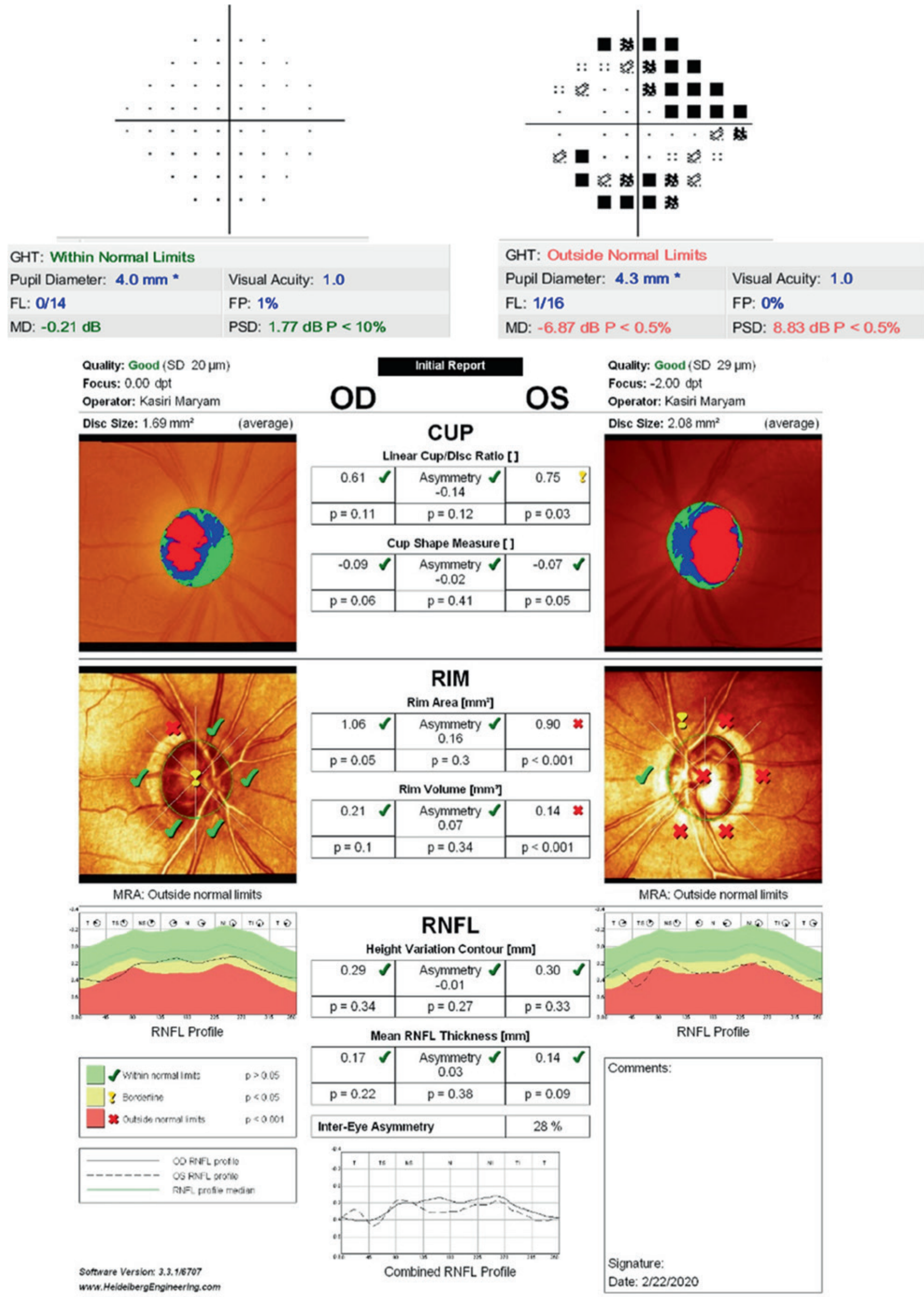


Fig. 8: Confocal laser scanning tomography image of a patient with early glaucoma (right eye) and moderate glaucoma (left eye). The quality of image is good in both eyes. The disc size is average. Cup analysis shows normal cup parameters in right eye and abnormal cup parameters in left eye. Rim analysis is 'within normal limits' in most sectors in right eye but "outside normal limit" in most sectors of the left eye. RNFL analysis shows blunting of RNFL profile. However, RNFL parameters are 'within normal limit' both eyes. Interestingly, the glaucoma probability score is 'outside normal limits' in all sectors in both eyes.

Initial Report

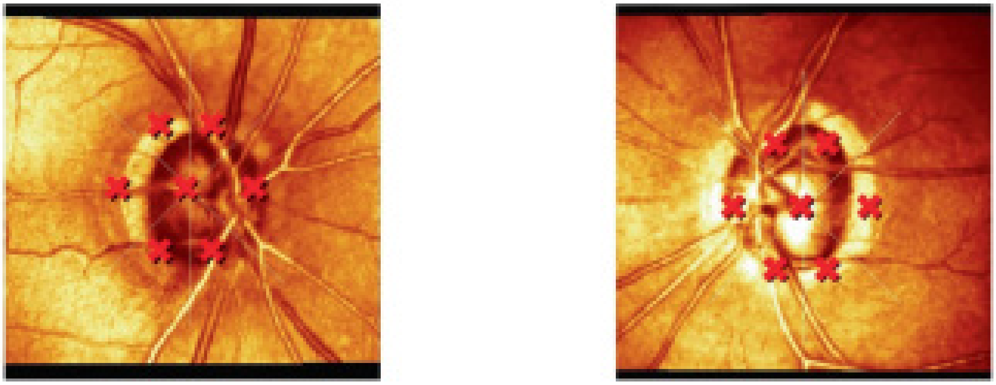
Quality: Good (SD 20 µm)
Focus: 0.00 dpt
Operator: Kasiri Maryam

OD

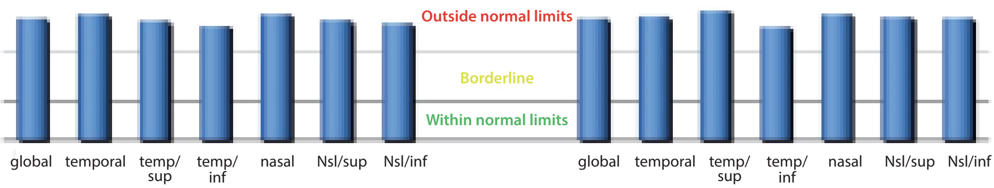
OS

Quality: Good (SD 29 µm)
Focus: -2.00 dpt
Operator: Kasiri Maryam

Glaucoma Probability Score (GPS)



global	temporal	tmp/sup	tmp/inf	nasal	Nsl/sup	Nsl/inf	Parameter	global	temporal	tmp/sup	tmp/inf	nasal	nsl/sup	nsl/inf
0.87	0.90	0.95	0.82	0.9	0.86	0.94	Glaucoma prob.	0.97	0.89	0.93	0.82	0.90	0.89	0.99
0.45	0.34	0.24	0.30	0.45	0.21	0.95	Rim steepness	0.27	-0.20	0.01	-0.10	1.35	0.22	0.03
0.55	0.12	0.11	0.12	0.10	0.09	0.06	Cup size (mm^2)	0.80	0.10	0.16	0.10	0.11	0.13	0.09
0.43	-	-	-	-	-	-	Cup depth (mm)	0.53	-	-	-	-	-	-
-0.10	-	-	-	-	-	-	H.RNFL curv.	-0.11	-	-	-	-	-	-
-0.11	-	-	-	-	-	-	V.RNFL curv.	-0.15	-	-	-	-	-	-
✖	✖	✖	✖	✖	✖	✖		✖	✖	✖	✖	✖	✖	✖



Glaucoma Probability Score Classification
Outside normal limits

Glaucoma Probability Score Classification
Outside normal limits

✔ Within normal limits
! Borderline
✖ Outside normal limits

Comments:

Signature:
Date: 2/22/2020

Fig. 9: The GPS is more sensitive and less specific than Moorfields regression analysis in diagnosing of glaucoma.

was 19 mmHg in both eyes. She was evaluated with the Heidelberg Retina Tomograph (Fig. 11). The right eye had an average optic disc size (2.45 mm^2) and the left eye had a large optic disc size (2.96 mm^2). Moorfields Regression Analysis of both eyes were 'outside normal limits'. Large disc

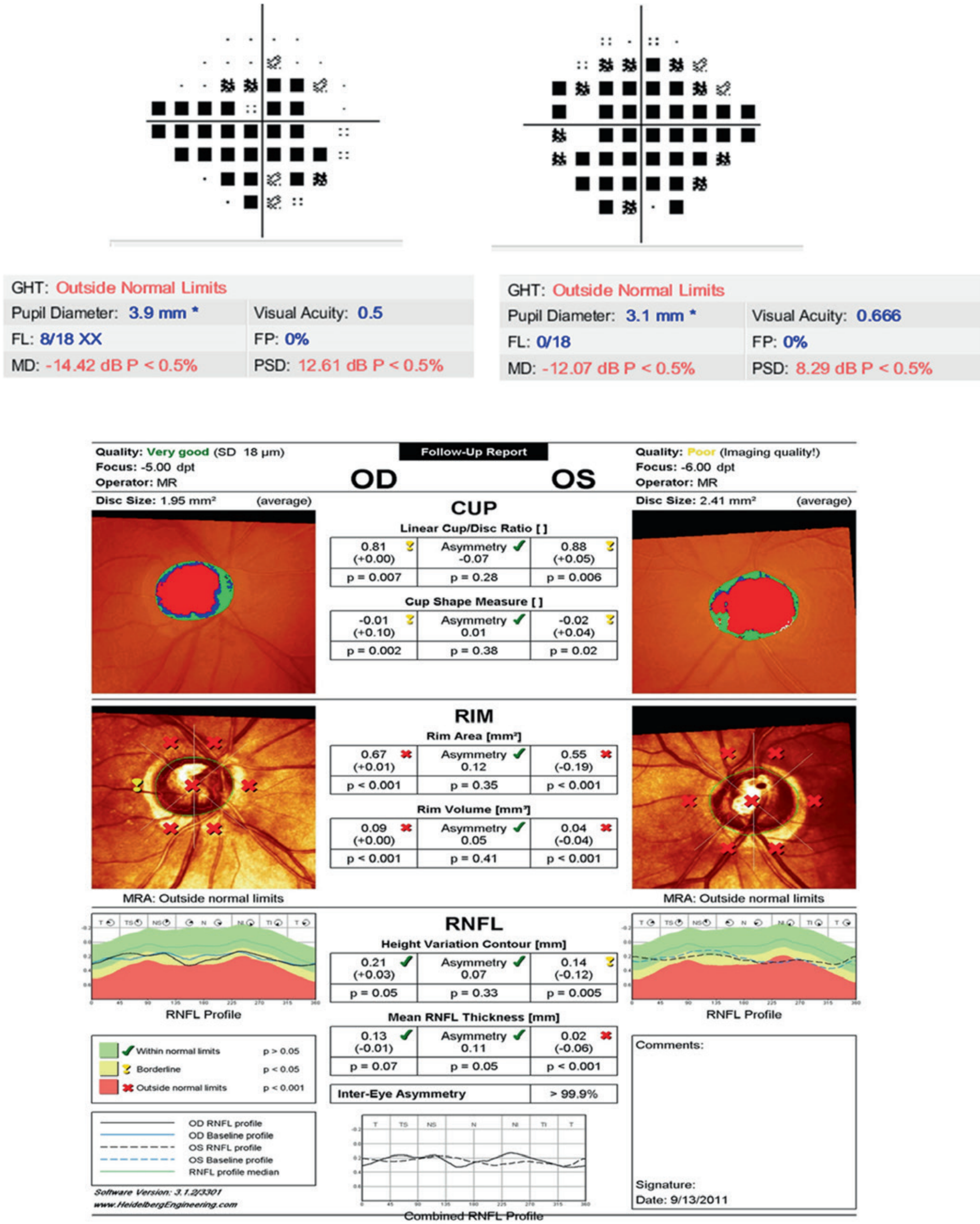


Fig. 10: Confocal laser scanning tomography image of a patient with advanced glaucoma. The quality of the image is very good in the right eye but poor in the left eye. The disc size is average. Cup analysis shows borderline cup parameters. Rim analysis is 'outside normal limits' in almost all sectors in both eyes. Although the patient has advanced glaucoma, RNFL analysis shows only blunting of the RNFL profile with values in inferior quadrant of left eye. Due to the poor image quality, the imaging should be repeated in the left eye.

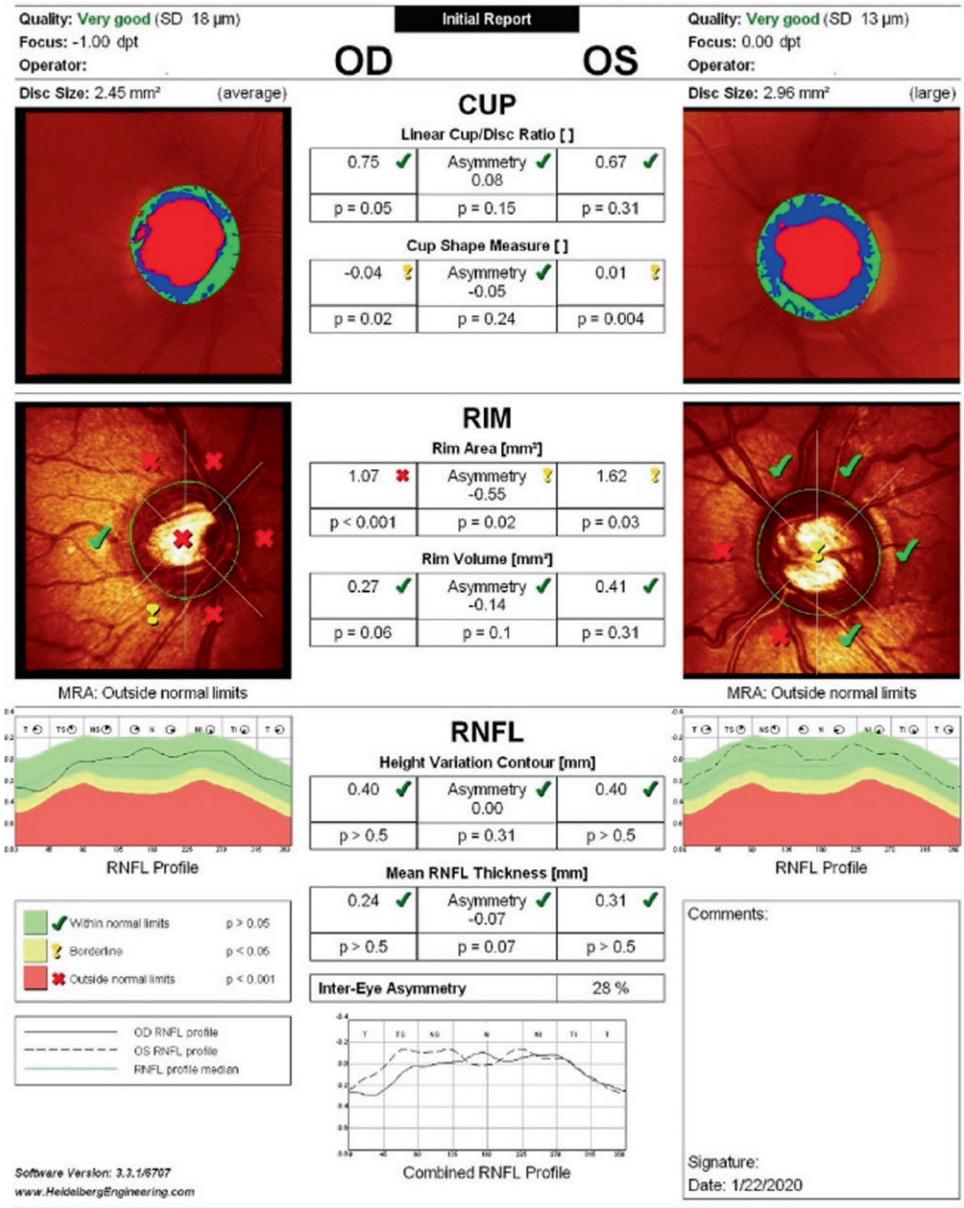


Fig. 11: Confocal laser scanning tomography image of a patient with large discs and physiologic cupping. The image quality is very good in both eyes. The right eye has an average optic disc size (2.45 mm^2) and the left eye has a large optic disc size (2.96 mm^2). Moorfields Regression Analysis (MRA) of both eyes was 'outside normal limits'. In HRT, false positive rates for the detection of glaucoma increase with increasing disc size.

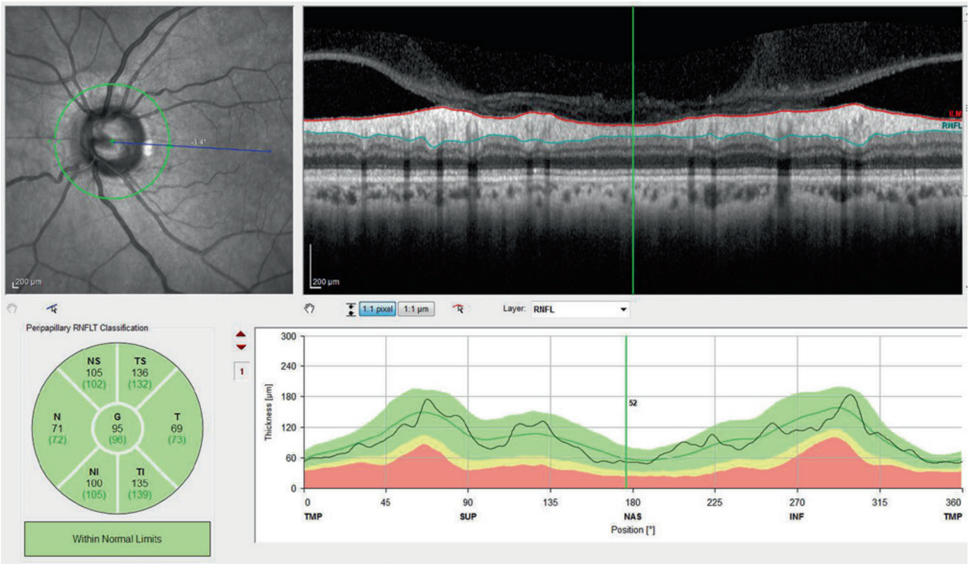


Fig. 12: SD-OCT (Spectralis) RNFL report of the left eye of the patient with large disc and physiological cupping. The patient has a normal RNFL profile in both eyes.

size (2.8 mm^2) can confuse the MRA. There would be increasing variability in rim area and also the specificity loss with larger disc size. The patient had a normal RNFL profile in both eyes using OCT (Fig. 12). The patient was diagnosed with large disc and physiologic cupping. This is a typical case of "Red Disease" for HRT in which false positive results increase with increasing disc size.

Glaucoma Progression

Progression is a hallmark of glaucomatous disease and plays an important role in determining the management of glaucoma. A major strength of the HRT is in monitoring glaucoma disease. HRT applies a robust statistical algorithm in order to differentiate real biological changes from test–retest variability. Another advantage is that each successive version of the analysis software is "backwards compatible" with previous iterations. The HRT II and HRT III software displays two methods for glaucoma progression analysis:

Topographic Change Analysis

With Topographic Change Analysis (TCA), retinal height measurements of super-pixels are used to compare changes between baseline and follow-up examinations. The criterion for significant change is the presence of a cluster of 20 super-pixels with a significant decrease within the ONH

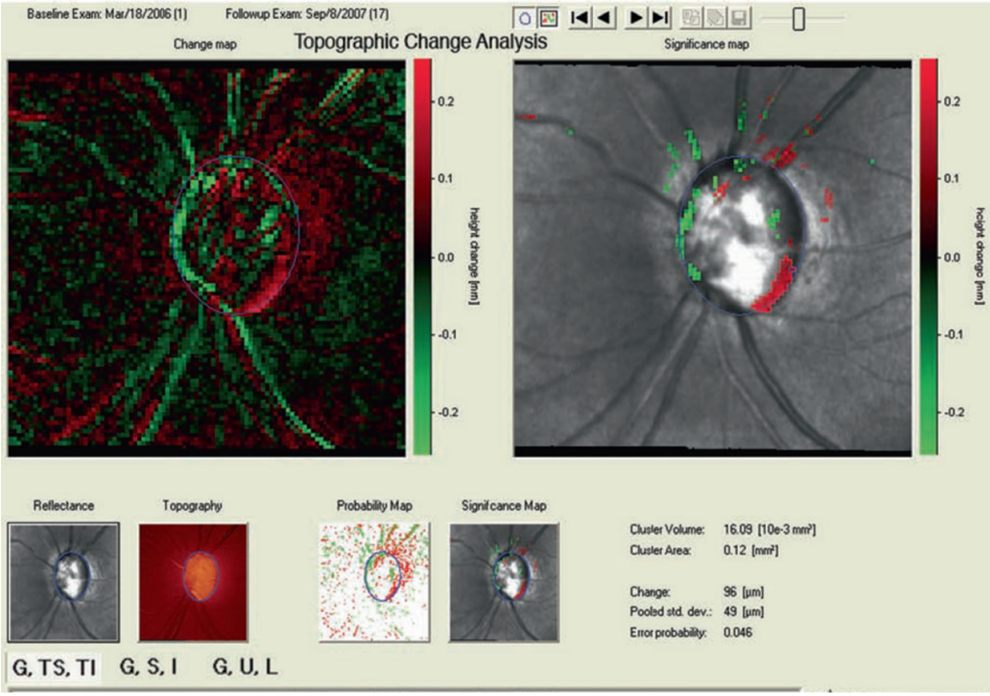


Fig. 13: Topographic Change Analysis of a glaucoma patient after 15 months of baseline HRT showing inferotemporal rim tinning in the left eye. Areas in red are those which show a depression and areas in green are those which show elevation. The red spots located along the superior blood vessels might be due to measurement variability and should not be considered progression.

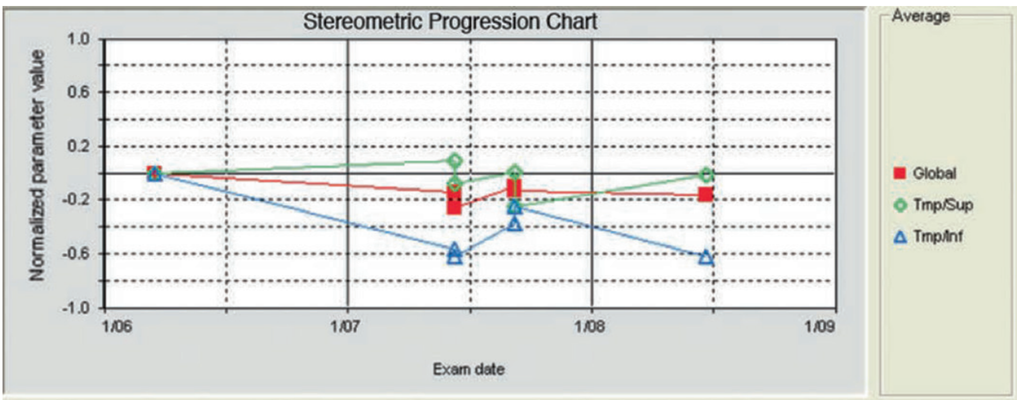


Fig. 14: Stereometric parameter analysis of the same patient after 2 years showing progressive inferotemporal rim thinning but stable supratemporal rim in the left eye.

margin that is reproducible in follow-up exams. A high probability value indicates that the likelihood of a change is low. On the other hand, when the error probability of the height change is less than 5%, the likelihood that the difference was due to chance is low and the change is likely to be real. Areas in red are those that show a decrease and areas in green are those that show an increase. The exact values for area, volume, and the change can be obtained each location of change (Fig. 13). Red areas located along the blood vessels or alternating clusters of red and green areas are typically artifacts and should not be considered progression [7].

In a study comparing the detection of glaucomatous progression by expert examination of stereo photographs to HRT-2 TCA, there was agreement in only 65% of cases on progression status while 30% of patients showed progression by TCA alone and only 6% showed progression by stereo photographic assessment alone. One reason for the discrepancy is that stereo photographic examination assesses certain features of the optic disc, such as rim narrowing, blood vessel deviation and appearance of splinter hemorrhages, whereas TCA identifies areas of surface height change that are less easily appreciated on photographs [8].

Stereometric Parameter Analysis

Glaucoma progression can also be detected by trend analysis of stereometric parameters over time. Each value is normalized using the ratio of the difference between the measured value and baseline measurements and the difference between average values in a normal eye and an eye with advanced glaucoma. Thus, the change in different parameters of the optic disc over time can be easily displayed on the same scale (Fig. 14). Like many other algorithms, definite progression requires confirmation in at least two out of three consecutive tests. This strategy accounts for isolated events that misleadingly suggest progression but reverse with subsequent testing [9].

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Source: Moghimi S., SafiZadeh M., Do J., Weinreb R.N. (2021) Confocal Scanning Laser Ophthalmoscopy and Glaucoma. In: Mohammadpour M. (eds) Diagnostics in Ocular Imaging. Springer, Cham. https://doi.org/10.1007/978-3-030-54863-6_28.

Notes:

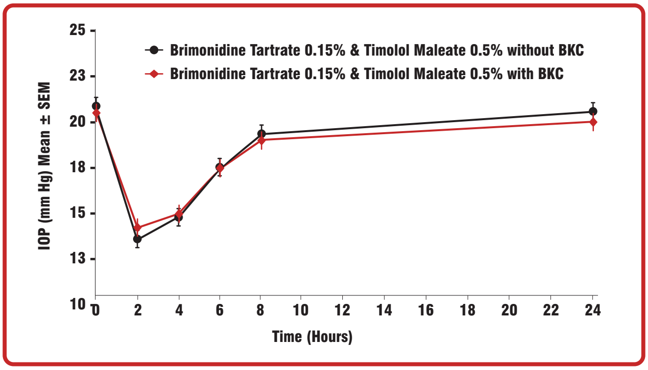
In Primary Open Angle Glaucoma & Ocular Hypertension

Rx BRIMOLOL

Brimonidine Tartrate 0.15% + Timolol Maleate 0.5%

Combined power, Greater benefits

BKC free BTFC offers comparable IOP lowering to BKC preserved BTFC[1*]



- Single ocular instillation of BTFC without BKC showed statistically significant IOP reduction at 6 hrs. compared with baseline mean IOP value
- Maximum reduction in IOP observed at 2 hrs. following single instillation:
  - BTFC without BKC was 35.8%
  - BTFC with BKC was 32%

"The efficacy of Brimonidine Tartrate 0.15% & Timolol Maleate 0.5% preserved with PHMB was comparable to reference item Brimolol® (BKC preserved)[1]"

1. Thavkar A et al. Int J Basic Clin Pharmacol. 2020 Jul;9(7):1050-1054

• BTFC - Brimonidine Timolol Fixed Combination *Efficacy study in NZW rabbits
• BKC - Benzalkonium Chloride • PHMB - Polyhexamethylene biguanide • IOP - Intraocular Pressure • SEM: Standard Error of Mean

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