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Outcomes of viscocanalostomy in patients with advanced glaucoma.

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Abstract

Purpose

To determine the medium-term outcomes for patients with advanced glaucoma undergoing viscocanalostomy.

Methods

All patients with advanced glaucoma (Mean Deviation -12.00 dB or above) and patients with poor visual acuity secondary to advanced glaucoma which precluded formal visual-field assessment undergoing viscocanalostomy (VC) and phaco-viscocanalostomy between 2010 and 2014 under the care of a single surgical team were

included. Intraocular pressure (IOP), visual acuity and visual field outcomes were assessed from data prospectively collected into a surgical outcome database. Success was defined at two IOP cut-off points: IOP \leq 21mmHg and \leq 16 mmHg with (qualified) or without (complete) medications.

Results

135 patients were included. Mean IOP changed from 23.6 ± 6.4 mmHg pre-operatively to 15.3, 15.8 and 14.8 mmHg between 1 and 3 years, a change of 35%, 33.5% and 39% respectively. Qualified success for an IOP \leq 21mmHg was achieved in 95.66% at year 1, 90.6% at year 2 and 80% at year 3. Qualified success for an IOP \leq 16 mmHg was achieved in 66.6% at year 1, 66.05% at year 2 and 60% at year 3. The cumulative probability for achieving an IOP \leq 21mmHg with or without drops was 86.1, 81.4 and 81.4% at 12, 24 and 36 months. During the follow up period 11 patients (8%) failed to achieve adequate IOP control and needed further surgical intervention. Eleven (8.1%) patients needed an intervention (Yag goniopuncture) following viscocanalostomy. Four patients (2.9%) had some post-operative complication, which resolved within two weeks following surgery. Nine patients (6.7%) lost more than 2 Snellen lines. There was no significant change in the MD across time points.

Conclusion

Viscocanalostomy is a safe and effective method of controlling IOP in the medium-term in patients with advanced glaucoma.

Key words: Viscocanalostomy, advanced glaucoma, non-penetrating glaucoma surgery, glaucoma

Introduction

Patients most at risk of blindness during their lifetime, due to glaucoma, are those who present with advanced disease. Saunders *et al* [1] reported that almost 60% of patients progressing to statutory blindness had one eye with an MD worse than -14 dB at baseline. 10% to 39% of glaucoma patients present with advanced disease in at least one eye in the UK [2-4]. In a questionnaire to all the UK consultant ophthalmologists the consensus opinion for both glaucoma specialists and non-glaucoma specialists was to start with primary medical therapy, most commonly citing surgical risk as the primary reason (23% and 22% respectively) [5].

National Institute for Health and Clinical Excellence (NICE) guidelines suggested different management approaches for patients presenting with early and advanced disease where the latter should be offered primary surgery [6]. However, there is limited evidence supporting this recommendation and the type of surgery to be offered.

Stead and King [7] have reported medium-term results for trabeculectomy combined with Mitomycin-C (MMC) in patients with advanced glaucoma ($MD \leq 20$ dB). Although trabeculectomy was successful at controlling IOP in this group, a quarter of patients experienced a significant reduction in acuity. The only pre-operative determinant for a significant reduction in VA was the pre-operative MD.

The treatment for advanced glaucoma study (TAGS) will report the outcomes of

primary trabeculectomy compared with medical management for advanced glaucoma [8]. Non-penetrating glaucoma surgery (NPGS) has been shown to provide comparable long-term success rates to trabeculectomy, with reduced postoperative complications [9-11] but there is limited information on its success in patients with advanced glaucoma.

In this study, we assessed the outcomes of viscocanalostomy in patients with advanced glaucoma to document success in terms of IOP and visual acuity. In addition, we quantified the postoperative interventions undertaken to achieve these outcomes.

Methods

Advanced glaucoma was classified as MD between -12.00 to -20.00 dB and severe glaucoma MD -20.01dB or worse [12].

All patients with advanced glaucoma and patients with poor visual acuity secondary to advanced glaucoma which precluded formal visual-field assessment undergoing viscocanalostomy (VC) and phaco-viscocanalostomy between 2010 and 2014 under the care of a single surgical team were included.

The technique involved superior corneal traction with 7-0 vicryl. The conjunctiva and Tenon's capsule were then opened in the upper fornix to expose the sclera. Careful haemostasis using wet field cautery was performed. A two-third scleral thickness limbus based scleral flap measuring 5x5 mm was dissected and advanced 1 mm into clear cornea. A 4x4 mm deep scleral flap was then dissected reaching Schlemm's canal, which was de-roofed and extended into corneal stroma to the level of Descemet's membrane to create the trabeculo-Descemet's membrane (TDM). High viscosity

hyaluronic acid (Viscoat TM) was injected into the two surgically created ostia of Schlemm's canal, aiming at dilating both the ostia and the canal and was also placed in the scleral bed. The deep flap was excised close to the TDW. The superficial scleral flap and conjunctiva were closed with 10-0 vicryl sutures. No antimetabolite was used.

There were no specific exclusion criteria. Data on all patients were included until the last recorded appointment, which was considered the end of their follow-up. Post-operatively patients were followed up day 1, week 1, month 3, month 6, and then every 6 months. Minimum follow up was 1 year. An intervention was defined as any procedure or process undertaken after viscocanalostomy aimed at enhancing the success of the surgical outcome. This was Nd:YAG laser goniopuncture.

Primary outcomes were changes in IOP and visual field (MD). These were assessed from data prospectively collected into a surgical outcome database. Secondary outcomes were change in visual acuity, post-operative complications and interventions and number of glaucoma drops used.

Subgroup analysis was performed to look at confounding factors such as age, race, combined cataract surgery and previous glaucoma surgery or laser. Differences in outcomes between primary open angle glaucoma (POAG) and secondary glaucoma were also examined.

With regards to statistical analysis normality of intraocular pressure (IOP), number of drops (Drops) and visual field mean deviation (MD) data was examined using the Kolmogorov-Smirnov test. Further, pre-operative MD scores were divided into two groups; MD between -12 and -20 dB, and MD -20.01 dB and worse, and normality was also examined. Consequently, a linear mixed model was used to examine for

differences in IOP and MD between pre-operative (pre-op) and year one (Y1), year two (Y2), year three (Y3) post-operatively and to compare the two MD groups at these time points. Drops were examined with Friedman's test and if a difference was found, pairwise comparisons were conducted using Wilcoxon test. Associations between presenting IOP, cataract surgery post-viscocanalostomy and combined surgery were examined with point biserial correlation. For all statistical analysis, IBM SPSS v22 (SPSS, Chicago, Illinois) was used.

Success definition:

Complete surgical success was defined as $IOP \leq 21$ mmHg with no additional medication and qualified surgical success, an $IOP \leq 21$ mmHg with additional glaucoma medication. Failure was defined as $IOP > 21$ mmHg on 2 consecutive visits, $IOP \leq 5$ mmHg on 2 consecutive study visits after 3 months, reoperation for glaucoma or loss of light perception. Success was also defined at two IOP cut-off points ($IOP \leq 21$ mm Hg and $IOP \leq 16$ mm Hg). Visual acuity was measured on a Snellen chart, and a reduction of two or more lines was considered clinically significant.

Results

In total 135 eyes of 133 patients were identified for the study. The patients' demographics for all variables over time can be seen in Table 1. Sixty three (46.7%) patients had combined viscocanalostomy with cataract surgery. The vast majority of eyes (132) were on topical drops preoperatively. IOP at diagnosis was not known in 55 patients, as these were referred from other units, and this information was not provided. Twenty-five patients had previous intervention for glaucoma including trabeculectomy,

cyclodiode, Argon laser trabeculoplasty (ALT) and Selective laser trabeculoplasty (SLT) (Table 1).

IOP outcome

IOP was significantly lower at all examined time points (Y1: by 35.0%; Y2: by 33.5%; Y3: by 39.2% $p < 0.001$ at all time points) compared to the pre-op value. Glaucoma drops were significantly different across time points ($p = 0.001$) with a significantly lower median at all examined time points compared to pre-op drops. Visual field MD was not significantly different across time points ($p = 0.289$). When comparing IOP, drops and MD scores between the two MD groups, no significant interaction was seen between groups and time points for IOP ($p = 0.999$), Drops ($p = 0.384$) or MD ($p = 0.061$). Descriptive statistics of all of the above can be seen in Table 2, while Figure 1 displays IOP and Drops data plotted over the time points.

With regards to qualified and complete success (Table 3), at year 1 qualified success was noted in 95.66% patients (for $IOP \leq 21$ mmHg) and 66.6% patients (for $IOP \leq 16$). Complete success was noted in 52.5% and 44.8% respectively. At year 2, qualified success was noted in 90.6% patients (for $IOP \leq 21$ mmHg) and 66.05% patients (for $IOP \leq 16$). Complete success was noted in 48.6% and 37.6% respectively. At year 3, qualified success was noted in 80% patients (for $IOP \leq 21$ mmHg) and 60% patients (for $IOP \leq 16$). Complete success was noted in 30.6% patients in both groups.

During the follow up period 11 patients (8%) failed to reach any of the above success criteria and needed further surgical intervention. Four patients failed in year 1, another four patients in year 2 and another three patients in year 3 (Table 4). Of these, 4 had

uveitic glaucoma, 2 were pseudoexfoliative glaucoma (PXFG) and five were Primary Open Angle Glaucoma (POAG).

Kaplan-Meier survival curves were significantly different between complete and qualified success with $IOP \leq 21$ ($p = 0.001$, Figure 2) but not between different glaucoma types for either complete ($p = 0.912$) or qualified success ($p = 0.541$). Kaplan-Meier survival curves were not significantly different between MD groups for complete ($p = 0.512$) and qualified ($p = 0.079$) success.

Visual Acuity outcome

Visual acuity was stable for the vast majority of patients (126 patients, 93.3%). Nine patients lost more than 2 Snellen Lines. The reason for reduced vision in 7 patients was glaucoma and high myopia and proliferative diabetic retinopathy in the other 2 patients. Majority of these patients (8 out of 9) had MD worse than -20dB. In 2 patients with $MD < -20$ dB visual acuity dropped significantly from 6/36 at pre-op to hand movement and perception of light in the early post-operative period (presumed wipe out).

Visual field changes

Prior to surgery 20 patients were unable to perform a reliable visual field test (24-2 Humphrey visual field). During the follow up period the number of patients that were able to perform a reliable visual field test gradually decreased. A total number of 52 patients completed a reliable field test from 115 at pre-op. In those patients mean deviation (MD) was not significantly different across time points ($p = 0.105$) compared to pre-op.

Confounding factors

Twenty-five patients had previous surgery. Presenting IOP, age, glaucoma type, glaucoma duration and having previous surgery did not comprise a sufficiently good model that could predict the intervention (Yag GP, $p = 0.128$) or intra- and post-operative complications following surgery ($p = 0.175$). The patient group that had combined surgery and the patient group that did not, were not significantly different in outcome ($p = 0.313$). All descriptive statistics of the above variables can be found in Table 1.

Cataract surgery

Of the 59 patients who underwent viscocanalostomy alone and were phakic at the time of surgery, 3 patients (5%) underwent cataract surgery following viscocanalostomy by their final follow-up. Twenty-three (17%) were pseudophakes pre-viscocanalostomy.

Complications

Four patients (2.9%) had some post-operative complication during the follow up period, which resolved within two weeks following viscocanalostomy and did not cause any visual loss (Table 5).

Post-operative intervention

Eleven (8.1%) patients needed an intervention (Yag GP) following their operation. The time frame for the intervention varied between 2 months to 18 months.

Discussion

We report our results with un-augmented VC in a cohort of patients with advanced glaucoma. VC was able to achieve an IOP ≤ 21 mmHg in 80 to 95% patients with a 35-39% drop in IOP from baseline with a good safety profile. To our knowledge, our study provides the largest number of eyes with the longest follow up yet reported for VC in patients with advanced glaucoma.

There is limited evidence for the outcomes of glaucoma surgery for advanced glaucoma and no recent studies reporting the outcomes of NPGS for this cohort of patients. Ates *et al* [13] reported their experience of deep sclerectomy in 54 eyes with advanced glaucoma in 1999. 2 eyes out of 54 (3.8%) had IOP greater than 18 mmHg following non-penetrating deep sclerectomy and collagen implant. In our cohort, IOP reduction was maintained significantly below pre-operation levels up to 3 years after surgery. We have previously reported qualified (87.5-90.2%) and complete success (78– 90%) rates in a cohort of patients with POAG [10]. Shaarawy *et al* [11] have previously reported a 90% qualified and 60% complete success rate at 5 years with VC. It is likely that Schlemm's canal sclerosis and collapse with advanced disease is the most likely explanation for the lower complete success rates for VC in the present study. We have previously augmented VC with MMC in high-risk eyes [9] but did not find a difference in outcome when compared to un-augmented VC [9, 10], which suggests a possible bleb-independent mechanism for the success of VC.

Trabeculectomy is still considered the gold standard and achieves better control of IOP than viscocanalostomy [14]. The benefits of NPGS however, are potential gains for the patient in terms of their quality of life and reduced likelihood for post-operative interventions and sight-threatening complications [14]. Kirwan *et al* [15] in a recent

multicenter analysis of current trabeculectomy practice reported the requirement for frequent post-operative interventions in the majority of patients. They concluded that intensive proactive post-operative care is required after trabeculectomy and completion of trabeculectomy surgery is just the beginning of a process that takes several months to complete.

There are no like for like trials and limited published data to compare our results to those for trabeculectomy or NPGS in a similar patient cohort. Stead and King's [7] results for trabeculectomy augmented with MMC in advanced glaucoma fare better in terms of IOP control compared to our group. However, with regards to post-operative interventions, 79.8% patients had some form of bleb manipulation [7] compared to only 8.1% in our study that had Yag goniopuncture.

Reduced visual acuity is well recognised complication of glaucoma surgery and might be due to glaucoma progression, comorbidity or the procedure itself. Kirwan *et al* [15] reported the outcomes of 428 trabeculectomies. 15% had lost > 1 Snellen line at 1 year and 6% had lost >2 Snellen lines by 2 years post trabeculectomy (13% with advanced visual field loss). 27% of patients in Stead and King's study experienced a loss of two or more lines of Snellen acuity [7]. 9 patients (6.7%) in our study experienced a loss of >2 Snellen lines. Eight out of these 9 patients had a MD worse than 20 dB. The drop in vision was attributed to glaucomatous progression in 7 eyes (5.2%); 2 (1.5%) of which were presumed to be a wipeout. The risk of loss of central vision in patients with advanced visual field loss ranges from rare to as high as 14% [16, 17]. This may be attributable to readily identifiable complications including cataract, cystoid macular edema, suprachoroidal and vitreous haemorrhage, endophthalmitis and uveitis or be unexplained (wipe-out). The exact mechanism of the "wipe-out" phenomenon remains

elusive, but it has been suggested that it may be associated with the occurrence of sudden intra-operative hypotony resulting in optic nerve hemorrhage and decreased perfusion pressure to an already compromised nerve blood supply [18]. The lower rates of drop in vision in the present study reflect the benefit of avoiding sudden decompression of the eye in patients with end-stage glaucoma with viscocanalostomy.

Cataract formation is a reported complication after trabeculectomy and can be in the order of 78% [19]. More recent data suggest this to be in the order of 30% [15]. King *et al* [7] reported a 63% incidence of cataract formation post trabeculectomy requiring cataract surgery in 27% cases. Only 3 patients (5%) in our group required cataract surgery in the study period. Cataract surgery can decrease the success of a trabeculectomy with an increased likelihood of post-operative interventions and requirement for glaucoma medication in 30-39% cases [20, 21]. These risks are avoided with VC due to its bleb-independent mechanism of action.

NICE recommends primary surgery should be offered to patients presenting with advanced loss [6]. Stead and King recommend this to be trabeculectomy augmented with MMC [7]. The use of antimetabolites is a recognized risk factor for bleb-related infection and endophthalmitis [22] which is more pronounced in this group of patients and reflects the opinion of UK Consultants' for not advocating primary surgery for this group [2]. Avoidance of antimetabolite use and bleb-related complications with viscocanalostomy is an important consideration in this group of patients and even more so in patients with thin conjunctiva, childbearing age and pregnant patients. A major advantage of VC compared with trabeculectomy is retention of the TDW which appears to serve as a barrier to infection [22] and allows titrated aqueous flow, thus avoiding

hypotony and its complications such as shallow and flat anterior chamber, choroidal detachments and suprachoroidal haemorrhages.

Non-penetrating filtering surgical techniques have greater safety with a lower risk of complications when compared to trabeculectomy [22-25]. The UK national trabeculectomy surgery survey [26], which reported outcomes of more than 1200 trabeculectomies, reported early complications in 578 cases (46.6%) and late complications in 512 cases (42.3%). Kirwan et al reported an incidence of 14% bleb leaks, 7.2% late onset hypotony and 0.75% endophthalmitis with trabeculectomy [15]. A Cochrane review [14] reported relatively fewer complications with non-penetrating glaucoma surgery (17%) compared to trabeculectomy (65%). In our study only 4 patients (2.9%) had some post-operative complication, which resolved within two weeks following viscocanalostomy and did not result in any long-term complications.

Our study showed that mean deviation was not significantly different across time points ($p = 0.105$) compared to pre-op. It remained stable around 19dB. However, the number of patients completing the field test declined slightly year on year which may be expected with time [1], with 45.2% of patients finally having a reliable field test. Our results are comparable to previous reports where only 39% of patients with advanced glaucoma were able to complete a reliable field test 1-year post-trabeculectomy [7, 27].

Eleven eyes failed and required further surgery. Of these 4 had uveitic glaucoma (3 Fuchs' heterochromic cyclitis (FHC)) and 2 pseudoexfoliative glaucoma (PXFG) both known to have an aggressive course and a poor surgical outcome [28]. We have previously reported good outcomes for NPGS in uveitic glaucoma [10]. In this study 8 pts had uveitic glaucoma of which 3 had FHC. All patients with FHC failed. The failure of VC in FHC could be related to the increased likelihood of subclinical

neovascularisation and Schlemm's canal sclerosis in these patients [29].

Limitations of this study include the loss of numbers, particularly those able to complete a reliable visual-field test during the follow-up period. However, to our knowledge this is the first study to report the effectiveness of un-augmented viscocanalostomy in a cohort of patients with advanced glaucoma. IOP remained controlled over a period of up to 3 years, albeit with the requirement of increasing medications with time and visual acuity remained stable in the majority of patients. Viscocanalostomy had similar qualified success rate to MMC trabeculectomy with a good safety profile, avoidance of MMC and its attendant complications and minimal post-operative interventions. The benefits also transpose to the wider context of economic and quality of life benefits to be achieved with non-penetrating glaucoma surgery [30]. NICE recommends primary surgery in this group of patients [6]. TAGS will address the outcomes of primary trabeculectomy for advanced glaucoma [8]. Our study supports the extension of the trial to include the use of primary viscocanalostomy for advanced glaucoma.

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TABLES

Table 1. Patients' demographics. Patient numbers (and as percentage of whole sample), mean \pm SD or median and range (minimum to maximum values), as appropriate, are presented for each variable.

	N (%)	Mean	SD	Median	Range
Age (years)	135 (100)	69.8	13.9	73	25 to 92
Duration of glaucoma (years)	101 (74.8)	10.8	7.1	10	1 to 30
Presenting intraocular pressure (mm Hg)	78 (57.8)	32.7	12.0	29	17 to 64
Preoperative intraocular pressure (mm Hg)	134 (100)	23.5	6.0	22	14 to 44
Preoperative visual acuity	111 (82.2)			6/6-6/9	6/6-6/9 to hand movement
Preoperative drops (number)	135 (100)	3.1	1.1	3	0 to 5
Preoperative MD (dB)	115 (85.2)	-19.6	5.5	-19.4	-12 to -32.7
Previous procedures					
None	110 (81.4)				
Trabeculectomy	11 (8.1)				
Retinal detachment surgery	7 (5.2)				
SLT, ALT	4 (3.0)				
Cyclodiode	3 (2.2)				
Glaucoma type					
Primary open-angle glaucoma	92 (68.1)				
Chronic angle closure glaucoma	11 (8.1)				
Pseudoexfoliation	10 (7.4)				
Uveitic	8 (5.9)				
Pigment dispersion syndrome	6 (4.4)				
Normal tension glaucoma	5 (3.7)				
Fuch's heterochromic cyclitis	3 (2.2)				

Table 2. Descriptive statistics of IOP, Drops and MD at all time points including number of patients per year. IOP and MD data is presented as mean \pm SD, while Drops data as median and range. *denotes significant difference with Pre-op.

	Pre-op (135)	Y1 (135)	Y2 (109)	Y3 (75)
IOP (mm Hg)	23.6 \pm 6.4	15.3 \pm 3.2*	15.8 \pm 4.1*	14.8 \pm 3.4*
for MD between -12.01 and -20.00 dB	22.1 \pm 5.2	15.3 \pm 3.1	15.9 \pm 3.3	15.0 \pm 2.7
for MD -20.01 dB and worse	23.9 \pm 6.5	15.5 \pm 3.6	15.2 \pm 3.1	14.8 \pm 3.8
Drops (number of)	3, 0 – 5	0, 0 – 3*	1, 0 – 4*	1, 0 - 4*
Mean Deviation (dB)	-19.6 \pm 5.5	-18.8 \pm 5.6	-18.0 \pm 10.5	-19.8 \pm 4.4

IOP, intraocular pressure; Drops, number of medications; MD, mean deviation; M6, month six post-operation; Y1, year one post-operation; Y2, year two post-operation; Y3, year three post-operation;

Table 3. Number and percentage of patients achieving IOP \leq 16 mmHg with no medication, IOP \leq 16 mmHg with additional medication, IOP \leq 21 mmHg with no medication, and IOP \leq 21 mmHg with additional medication for all time points.

	Y1	Y2	Y3
IOP \leq 16 mmHg with no medication	60/135 (44.8%)	41/109 (37.6%)	23/75 (30.6%)
IOP \leq 16 mmHg with additional medication	90/135(66.6%)	72/109 (66.05%)	45/75 (60.0%)
IOP \leq 21 mmHg with no medication	71/135 (52.5%)	53/109 48.6%	23/75 (30.6%)
IOP \leq 21 mmHg with additional medication	129/135(95.66%)	96/109 (90.6%)	60/75 (80%)

IOP, intraocular pressure; Y1, year one post-operation; Y2, year two post-operation 1; Y3, year three post-operation.

Table 4. Descriptives of failures.

No	Type of glaucoma	Previous surgery/ laser	Pre-op IOP(mmHg)	Pre-op MD(dB)	Pre-op BCVA	Pre-op drops (No)	BCVA at final follow up	MD (dB) at final follow up	Time of failure post-op (months)
1	FHC*	nil	20	U/C*	6/60	3	6/60	U/C*	24
2	FHC*	nil	32	-18.59	6/12	3	6/18	-21.54	36
3	POAG*	nil	28	-25.7	6/6	1	6/9	-29.23	36
4	PXF*	nil	39	-27.48	6/36	5	6/36	U/C*	24
5	POAG	Previous VS*	30	-12.87	6/6	4	6/9	-14.85	24
6	FHC*	nil	28	-23.92	6/12	4	6/18	-25.48	24
7	POAG	nil	24	-21.73	6/6	4	6/9	-22.68	12
8	POAG	nil	24	U/C*	6/60	4	6/60	U/C*	24
9	Uveitic glaucoma	cyclodiode	28	-14.73	6/24	4	6/36	-16.73	24
10	POAG	nil	25	-16.73	6/6	4	6/6	-17.75	12
11	PXF	trabeculectomy	16	-21.07	6/12	4	6/12	-22.78	24

*U/C: Unable to perform reliable fields

Table 5. Intra- and post-operative complications.

Complication type	No of patients
Intra-op TDW* perforation	17/135
Wound conjunctival leak treated with bandage contact lens	2/135
Scleral flap leak repaired with tutoplast	1/135
Wound leak repaired with suturing	1/135

*Trabeculo-Descemet's Window

FIGURES

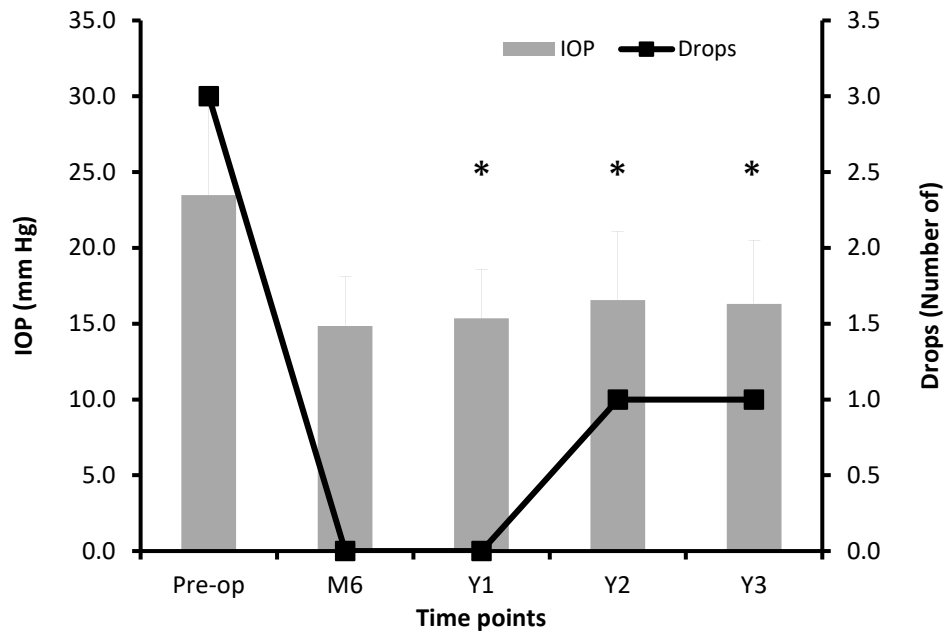


Figure 1. Mean intraocular pressure (IOP) and median number of drops (Drops) plotted against the time points. Error bars have been excluded for clarity. *denotes significant difference with pre-operative values. Pre-op, pre-operative; M6, month six post-operative (not considered in statistical analysis); Y1, year one post-operation; Y2, year two post-operation; Y3, year three post-operation.

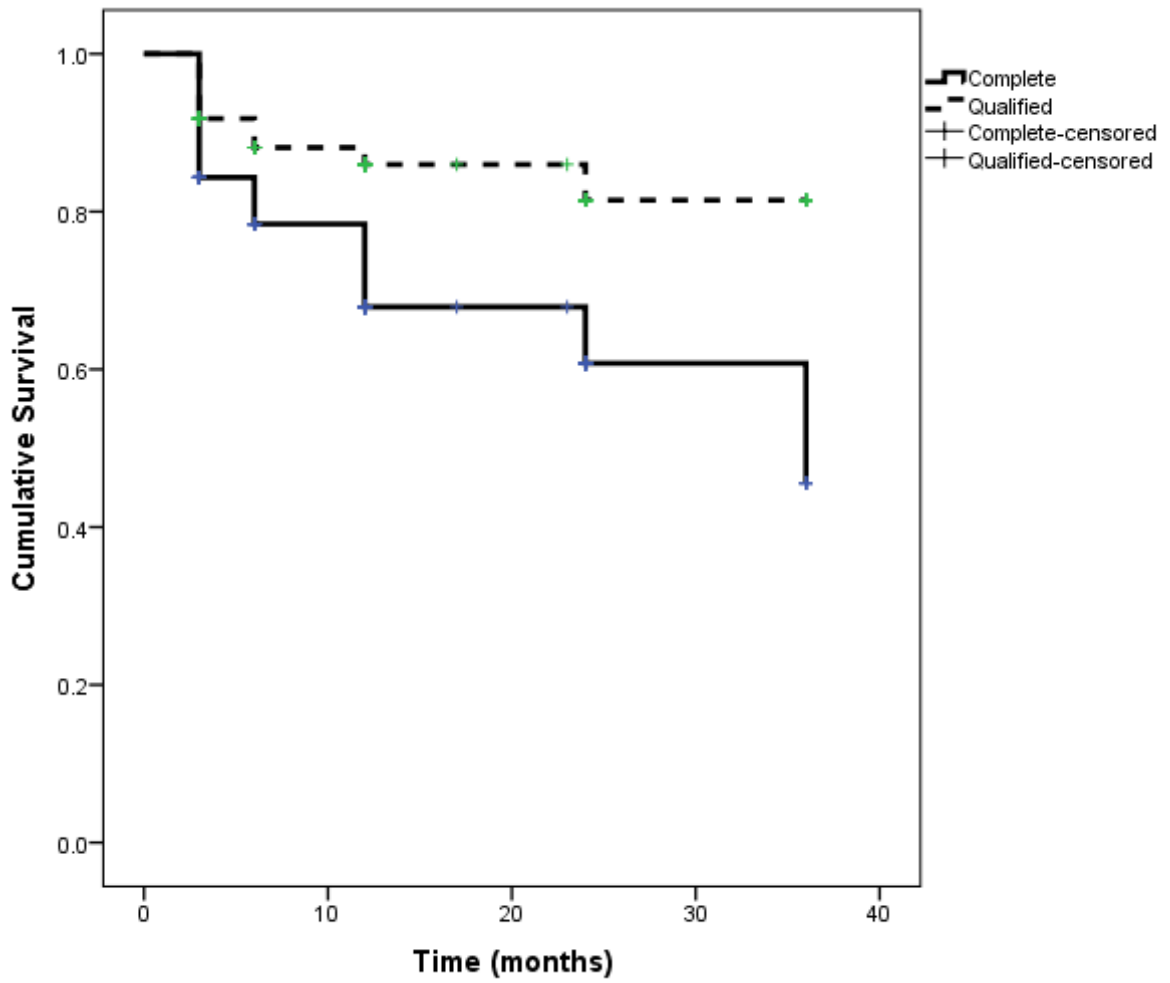
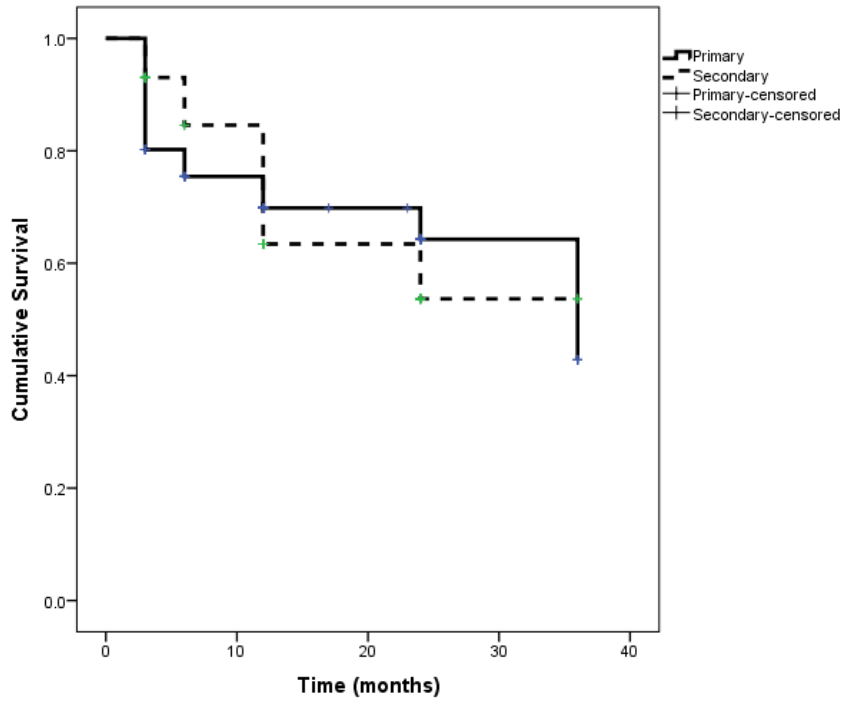


Figure 2. Kaplan-Meier survival plot for complete (defined as IOP \leq 21 mmHg with no medication) and qualified (defined as IOP \leq 21 mmHg with additional glaucoma medications) success.

Complete success



Qualified success

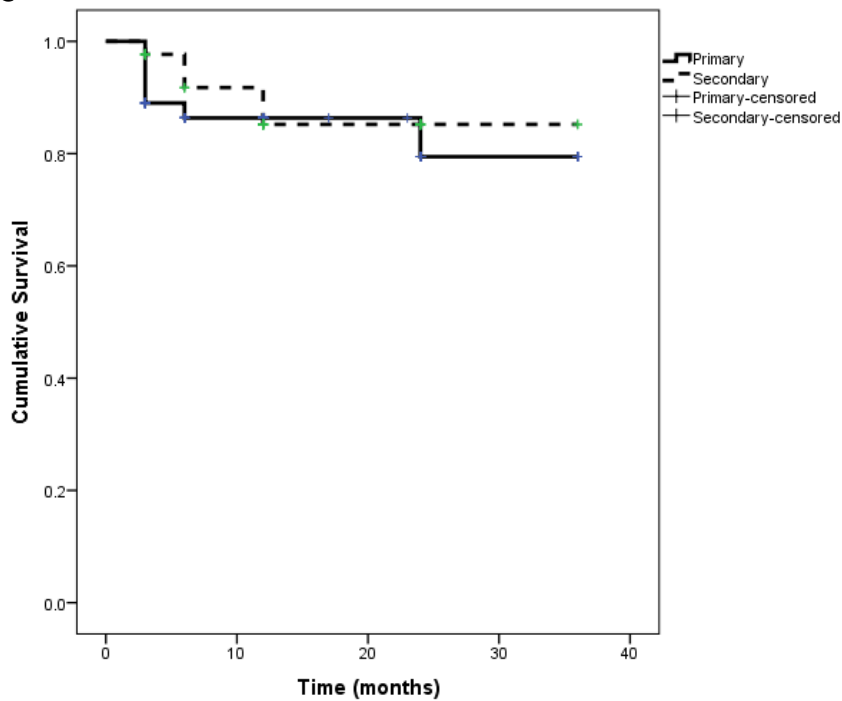


Figure 3. Kaplan-Meier survival plot for primary and secondary glaucoma type for complete success (defined as $IOP \leq 21$ mmHg with no medication, top panel) and qualified success (defined as $IOP \leq 21$ mmHg with additional glaucoma medications, bottom panel).