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Outcome of Trabeculectomy with Mitomycin C in Patients with Advanced Glaucoma

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Abstract

Background/Aims

To determine the medium term intraocular pressure control and visual outcomes for patients with advanced glaucoma undergoing trabeculectomy with mitomycin C.

Methods

All patients with advanced glaucoma (MD ≥ -20 dB or above) undergoing trabeculectomy with mitomycin C between 2000 and 2008 under the care of a single glaucoma surgeon were included. Intraocular pressure, visual acuity and visual field outcomes were assessed from data prospectively collected into a surgical outcome database.

Results

One hundred and three patients were eligible for inclusion. The post-trabeculectomy group mean IOP varied between 11.3 and 13.3mmHg between 1 and 7 years. At year 5, 85.2% had an IOP < 16 mmHg and 96.3% had an IOP < 21 mmHg. The number completing a reliable visual field exam decreased significantly year on year, however the change in mean MD for the group as a whole and for individual patients remained stable. 28 patients experienced a significant reduction in acuity defined as 2 or more lines of Snellen, although this was not due to glaucoma surgery in the majority. The only pre-operative determinant for a significant reduction in VA was the pre-operative MD (-27.00 dB (n=21) compared with -24.79 dB (n=63; p=0.029).

Conclusion

Trabeculectomy is a successful method of controlling intraocular pressure in the short to medium term in patients with advanced glaucoma.

Introduction

Currently intraocular pressure (IOP) is the only modifiable risk factor in patients with glaucoma and several studies have demonstrated reduced visual field progression when IOP has been lowered.[1-3] Glaucoma patients with advanced visual field loss represent a difficult group to manage as presentation with advanced visual field loss is a risk factor for further progression and blindness and therefore a very low IOP may be required to avoid further visual field loss.[1-5]

The use of Mitomycin C (MMC) in trabeculectomy surgery has been shown to reduce the risk of failure in certain groups.[6] In addition the success of modern glaucoma surgery has been further enhanced by the use of postoperative bleb manipulation.[7-9] The safety of modern glaucoma surgery using intraoperative techniques such as tight closure of the scleral flap and the anterior chamber maintainer to reduce the risk of hypotony have been encapsulated in the concept of the safe trabeculectomy.[10,11]

In this study we assess outcome of trabeculectomy surgery combined with MMC in patients with advanced glaucoma to document success in terms of IOP and visual outcomes. In addition we quantify the post-operative interventions undertaken to achieve these outcomes.

Methods

All trabeculectomies and phaco-trabeculectomies carried out by a single surgical team between October 2000 and July 2008 were reviewed. Data on all trabeculectomies was entered into a surgical database at the time of surgery and updated at each follow-up visit. Patients who had severe pre-operative glaucomatous visual field defects, defined as an MD greater than 20dB and patients who had poor acuity secondary to glaucoma which precluded formal visual field assessment were identified. Demographic and clinical information including any post-operative interventions was available from the database. All identified cases were included with no specific exclusion criteria. Data on all patients were included until the last recorded appointment which was considered the end of their follow-up.

An intervention was defined as any procedure or process undertaken after trabeculectomy surgery aimed at enhancing the success of the surgical outcome. These were bleb massage, suture removal, 5-fluorouracil (5-FU) injection and needling in combination with 5-FU injection. Bleb massage was performed by applying digital pressure to the globe through the upper eyelid behind the posterior lip of the scleral flap.

Statistical analysis was undertaken using SPSS V.14.0. The tests for statistically significant differences between variables were performed using the χ^2 test or Fisher exact test for discrete variables, Student's t-test for parametric data and

the Mann–Whitney U test for non-parametric data. Two-tailed p values <0.05 were taken to indicate significance.

The success of surgical outcome was defined as unqualified when no additional medication was required or qualified when additional medication was required to achieve the specific IOP definition. Success was also defined at two IOP cut-off points (IOP <21 mm Hg and IOP <16 mm Hg). Furthermore sustained hypotony <6mmHg for greater than 6 months was considered a failure. Visual acuity was measured on a Snellen chart and a reduction of 2 or more lines was considered significant.

The safe trabeculectomy approach was used.[11] The dosage and exposure time of MMC was varied for patients according to the various preoperative and peroperative risk factors for surgical failure. The final dosage decision was taken once scleral exposure had been achieved. The dosage of MMC was defined as the product of the MMC concentration and the application time.

Results

In total 103 eyes were identified for the study (Table 1), second eyes that were eligible were not included. Twenty one patients were unable to complete a satisfactory pre-operative visual field test, the majority of whom (17) had poor existing visual acuities. All patients were on topical drops pre-operatively. The presenting IOP is not known in 17 patients as these were referred from other units and this information was not provided. Twelve patients in the cohort had previously undergone trabeculectomy surgery.

	N (%)	Mean	SD	Median	Range
Male gender	55 (54%)				
Age (yrs)	103 (100%)	72.8	15.85	76.0	16-96
Presenting IOP (mmHg)	87 (84%)	31.5	11.5	30.0	14-60
Pre-operative IOP (mmHg)	103 (100%)	25.81	8.05	24.00	13-55
Pre-operative VA	103 (100%)			6/12	6/6-HM
Pre-operative drops	103 (100%)	2.8	1.03	3.0	0-5
Pre-operative MD (dB)	85 (82%)*	-25.34	3.49	-24.74	-20.03/-34.62
Follow-up (days)	103	1136	698	1087	85-2757
Previous procedures					
	Trabeculectomy	12			
	ECCE	10			
	Goniotomy	1			
	Vitreotomy	3			
	Cyclodiode	2			
	YAG PI	7			
Type of glaucoma					
	Inflammatory	9			
	POAG	52			
	PXS	4			
	PDS	6			
	NTG	13			
	CACG	11			
	Other**	8			

Table 1. Patient demographics

* 21 Patients unable to complete a reliable VF test

POAG-primary open angle glaucoma, PXS-pseudoexfoliation syndrome, PDS-pigment dispersion syndrome, NTG-normal tension glaucoma, CACG-chronic angle closure glaucoma, ** Other (Congenital 1, postpenetrating keratoplasty 3, traumatic 1, rubeotic 3).

IOP reduction

Intra-ocular pressure reduction achieved at 1 year was significantly below pre-operative IOP (12.4mmHg from 25.7mmHg, $p<0.0005$) and was maintained throughout the duration of follow-up.

IOP (mmHg)(number)	Mean	SD	Median	Range
Presenting (87)	31.5	11.5	30.0	14-60
Pre-operative (103)	25.8	8.0	24.0	13-55
Day1 (102)	14.3 *	8.1	13.5	1-40
Month 3 (102)	11.3 *	4.8	10.0	2-28
Year 1 (87)	12.3 *	5.2	12.0	2-30
Year 2 (73)	13.1 *	5.6	12.0	5-40
Year 3 (59)	12.9 *	4.3	13.0	2-22
Year 4 (38)	12.3 *	3.8	12.0	6-22
Year 5 (26)	12.5 *	5.0	12.0	6-30
Year 6 (14)	11.5 *	3.6	11.0	4-18
Year 7 (3)	13.3 ^	3.5	13.0	10-17

Table 2. Change in IOP (* $p<0.0005$, ^ $p=0.02$ compared with pre-op IOP)

The majority of patients achieved a successful outcome, although 35 (33.7%) required drops at the end of their follow-up to achieve the target IOP (mean number of drops 2.2, SD 1.08, range 1-4). This represented a significant reduction in the number of drops required. When viewing the group as a whole a mean number of 0.74 drops per-patient were required compared to an average of 2.8 pre-operatively (figure 1).

There was a reduction in the number of patients achieving an unqualified success year on year, declining from 82% and 88% (<16mmHg and <21mmHg respectively) at year 1 (n=88) to 52% and 56% at year 5 (n=27). However, there was no real reduction in qualified success numbers which remained relatively

static at roughly 85% and 95% for the duration (for IOPs <16mmHg and <21mmHg respectively). Figure 2 (a-d). Only one patient developed sustained hypotony (<6mmHg for greater than 6 months).

Subgroup survival analysis demonstrated a significantly better survival of those with primary open angle glaucoma for both IOP outcomes ≤ 21 mmHg (log rank = 0.002) and ≤ 16 mmHg (log rank <0.0005). Figure 2 (e,f). Further subgroup analysis of survival revealed no difference in outcome for patients having their surgery performed by either a consultant or glaucoma fellow trainee, for combined procedures compared to trabeculectomy or for patients who had their cataract surgery following their trabeculectomy compared to those that did not.

Visual field changes

Numbers completing a reliable visual field exam decreased significantly year on year. Some attrition was due to the fact that a number of patients had 24-2 Humphrey visual fields pre-operation but only 10-2 fields post-operation. Post-operation there was no statistically significant deterioration in MD. Both the change in mean MD of the group as a whole and the change in individual patients' MDs for each of the time periods (years 1 (n=58), 3 (n=29) and 5 (n=14)) remained stable with no statistically significant decline evident.

Visual acuity changes

Pre-operative acuities ranged from 6/6 to perception of light, with a median acuity of 6/12. Post-operative median acuity remained unchanged with a range of 6/6 to no perception of light. 28 patients experienced a significant reduction in acuity defined as 2 or more lines of Snellen. However, it should be noted only a minority of these were due to the surgery itself (table 3).

No form of intervention was found to be associated with a significant reduction in acuity. The only pre-operative determinant for a significant reduction in VA was the pre-operative MD (-27.00dB (n=21) compared with -24.79dB (n=63)) indicating those patients with more advanced field defects were more likely to experience a reduction in VA post-operatively (p=0.029). No association with VA loss was demonstrated between sex, surgeon, surgical approach, dose of MMC, number of pre-operative drops, any post-operative bleb manipulation or age at the time of surgery.

Pathology	Number
Progressive glaucoma	7
No specific cause (presumed fluctuation in VA)	5
Cataract-declined surgery	4
CRVO	2
Corneal decompensation	2
Dry AMD	2
Progressive glaucoma plus cataract	2
Macroaneurysm (leaking)	1
Uncontrolled IOP followed by pthisis	1
Extinction	1
Dry AMD and progressive glaucoma	1

Table 3. Reasons for decline in VA.

Cataract Surgery

The development or removal of clinically significant cataract may affect both VA and visual field parameters. At the time of their final follow-up a total of 63% of patients were pseudophakic. 24 (23%) were pseudophakes pre-trabeculectomy, 12 (12%) underwent phaco-trabeculectomy surgery, 28 (27%) had cataract surgery after their drainage procedure and 39 (37%) remained phakic (in 4 cases surgery was declined despite being indicated). There was no statistically significant difference in post-trabeculectomy MD between those that had cataract surgery after their drainage procedure (MD -25.55 (SD 3.091, n=20) and those that did not (MD -25.25 (SD 4.629, n=39) $p=0.943$ (Mann Whitney)). Furthermore similar proportions (20-30%) of each group (cataract surgery or no cataract surgery) experienced a decline in VA with little difference between the two.

Bleb Manipulations

In total 83 (79.8%) patients had some form of bleb manipulation, the majority of which had an episode of bleb massage (64%), Table 4. The first intervention occurred a median of 6.0 days post-op (mean 58.2, SD 178).

	N (%)	Mean (days)	SD	Median (days)	Inter-quartile range (days)	Range (days)
All	82 (79.6%)	58.2	177.7	6.0	1.0-15.0	1-1080
Massage	66 (63.5%)	32.4	114.5	5.0	1.0-20.3	1-864
Suture removal	38 (36.5%)	52.4	149.9	15.0	7.0-39.8	1-868
5-FU injection	35 (34.0%)	71.0	187.2	19.0	7.0-35.0	2-1025
Needling and 5-FU injection	32 (30.5%)	179.4	280.3	46.0	28.0-202.0	15-1080

Table 4. Frequency and timing (in days) for different types of postoperative bleb manipulations.

There was no statistically significant correlation between intervention and final MD or final VA. Looking at the group as a whole, any intervention was more likely if the operating surgeon was a trainee (p 0.006). Interventions were not associated with the concentration of MMC used although bleb manipulation was more likely with a lower dose (product of concentration with exposure time) of MMC (0.374 mg/ml/min vs 0.645 mg/ml/min, p 0.002). Patients receiving a 5-FU injection were significantly younger than those not doing so and also had significantly more advanced VF defects pre-op (MD -27.14dB vs -24.14dB, p<0.005). Indeed this was the only intervention associated with more advanced disease defined by the visual field defect.

Patients achieving an unqualified success (<16mmHg and <21mmHg) were statistically less likely to have had any intervention, a 5-FU injection or a needling episode (p 0.005, 0.006, <0.0005 and p 0.005, 0.014, <0.0005 respectively). Final IOP success was otherwise not related to any form of intervention.

Discussion

For patients with advanced glaucoma target IOP is likely to be very low, introducing an additional challenge in this group of patients. Surgery has several potential advantages over medical management, including the magnitude of mean diurnal IOP lowering and the extent of any diurnal spiking of IOP.[12] Currently there are no reports of medium to long-term outcomes following MMC trabeculectomy in patients with advanced glaucoma. In this group of patients most likely to go blind from progressive disease such information would greatly inform management.

Intra-ocular pressure control

In our cohort IOP reduction was maintained significantly below pre-operation levels up to 6 years after surgery. Two previous studies have demonstrated adequate short-term IOP control between 3-12 months post-trabeculectomy with MMC in patients with advanced disease (MD -24.8 +/- 4.1dB and -27.94 +/- 2.7 respectively).[13,14] However this is the first report to demonstrate sufficient IOP lowering in the medium to long-term in patients with advanced disease and are consistent with those of Beckers et al for trabeculectomy with MMC in a non-advanced disease cohort.[15] At 5 years he demonstrated a 60% success rate, defined as a final IOP <15mmHg. In our study 51.9% achieved a final IOP of ≤16mmHg, rising to 85.2% when those also on topical medication were included. There is a significant decrease in the number of patients able to maintain their

IOP <16mmHg without the use of additional topical medication and we found a third of patients required drops to maintain target pressure. One may have expected this to be higher in this cohort with advanced disease as their target IOP would be as low as possible. It is therefore likely that medications were re-introduced earlier and at lower IOPs than would have been the case if the patients had had less advanced disease. Subset analysis of the outcomes revealed that patients undergoing surgery for primary open angle glaucoma were more likely to have a successful outcome, this is not surprising as many of the patients in the other group will have had risk factors for failure such as previous conjunctival incisional surgery, uvetis etc.. Furthermore, no difference was found in outcomes between consultants and trainees for this surgery, although more interventions were required to achieve this in the fellow group. This may reflect that although glaucoma fellows undergo extensive surgical exposure they are still surgeons in training and therefore require some additional interventions to achieve similar results.

The influence of cataract surgery on the outcomes of glaucoma surgery remains unresolved.[16-18] In our cohort, sub-group analysis indicated that cataract surgery following trabeculectomy had no effect on survival.

Change in visual field

Our study failed to demonstrate a decline in visual field over a time period of 5 years in those completing visual field assessment. This should be viewed with some caution. Although the median MD remained constant at roughly -25.0dB the numbers completing the field test declined year on year. This loss of follow up may be expected with time. However it may also represent the fact that some of the patients previously able to reliably complete a visual field examination were subsequently unable, possibly as a result of disease progression or poorer acuity. Additionally a number of patients had only 10:2 Humphrey visual fields performed post-operatively making direct comparison to the pre-operative field test impossible. A similar attrition rate was demonstrated by Law et al where only 39% of patients with advanced glaucoma were able to complete a reliable field test 1 year post-trabeculectomy.[19]

Bleb manipulations

A high proportion of our patients (79.6%) had some form of manipulation post-operatively. In our attempt to minimise the potential risks associated with high dose MMC we tended to err on the side of caution when applying MMC. As a consequence some patients on the lower MMC doses required additional intervention (bleb manipulation) to manage post-operative bleb scarring. Another contributory factor could be the need to achieve low target IOPs and consequent intensive bleb manipulation to achieve this. However, our intervention rates were similar to a previous study of mixed visual field loss subjects suggesting patients

with more advanced disease are no more likely to have any intervention post-operatively compared to those with less advanced disease.[8]

Topouzis' prospective study on eyes with advanced glaucoma undergoing trabeculectomy augmented with MMC had similarly high intervention rates with 9/21 patients (43%) undergoing a 5 FU injection and 10/21 (48%) requiring argon suturelysis during a 3 month follow-up period.[13]

Loss of vision

Worries exist as to the possibility of severe loss of central vision or “extinction” described as the sudden reduction of visual acuity after filtration surgery in end-stage glaucoma, with no apparent ocular pathology to account for this decline.[20]

In total 27% (28/104) experienced a significant reduction in VA defined by a loss of 2 or more lines of Snellen acuity. Cataract formation was in the order of 63% which is comparable to that of the AGIS study (78% risk) and could not, by itself explain the drop in acuity.[21] The only pre-operative factor found to be predictive for VA loss was more advanced visual field loss. Additionally we were unable to demonstrate any association between post-op intervention and VA loss. This is significant as this is one of the first studies specifically assessing the impact of post-operative bleb manipulation on final VA. Importantly all but one had ocular pathology which explained this loss of acuity with a minority associated with the surgery. In the case where acuity was lost inexplicably (presumed wipeout) the VA dropped from 6/18 to HM post-operation. Estimates of the risk of severe loss of central vision range from rare to 15.4% in patients with advanced pre-operative field defects.[13,14,20,22,23] Only two have concentrated specifically on trabeculectomy augmented with MMC.[13,14] The larger of these studies suggests severe loss of central vision following surgery to be in the order of 6%, however none of these were attributed to extinction and of the 7 eyes (out of a total of 117) experiencing loss of central vision, the decline was attributed to hypotony maculopathy (3), uncontrolled elevated IOP (2), posterior subcapsular

lens opacities (1) and inflammatory reaction (1).[14] Similarly Topouzis' study of 21 consecutive patients with end-stage glaucoma undergoing MMC augmented trabeculectomy found no unexplained loss of vision although follow-up was for only 3 months.[13]

Five patients had no identifiable cause for visual acuity loss. It is presumed that fluctuation in Snellen acuity accounted for their loss although this assumption cannot be proven. The extent of the loss in all these cases were 2 Snellen lines only.

The information in this study may be extrapolated to managing patients initially presenting with advanced disease. A relatively large number of patients continue to present with advanced glaucoma, which tends to be associated with social deprivation in the UK.[24,25] A recent systematic review suggested that evidence from several studies supported the use of primary surgery over primary medical treatment in patients presenting with advanced glaucoma.[26] This is further supported from the results of CIGTS which indicated that patients with severe disease at presentation had slower visual field loss when randomised to the surgery group.[27] Furthermore primary surgery would avoid the effects of long term antiglaucoma therapy which may affect the outcomes of glaucoma surgery.[28,29]

Limitations of this study include the loss of numbers, particularly those able to complete a reliable visual field test during the follow-up period and refraction at

each clinic visit to overcome the possible error associated with visual acuity fluctuation. However, this study adds to the existing literature on the effectiveness of trabeculectomy with MMC in a cohort of patients with advanced glaucoma. IOP remained controlled over a period of up to 6 years albeit with the requirement of increasing medications with time. The visual acuity underwent further decline post-operation although unexplained loss of vision was rare.

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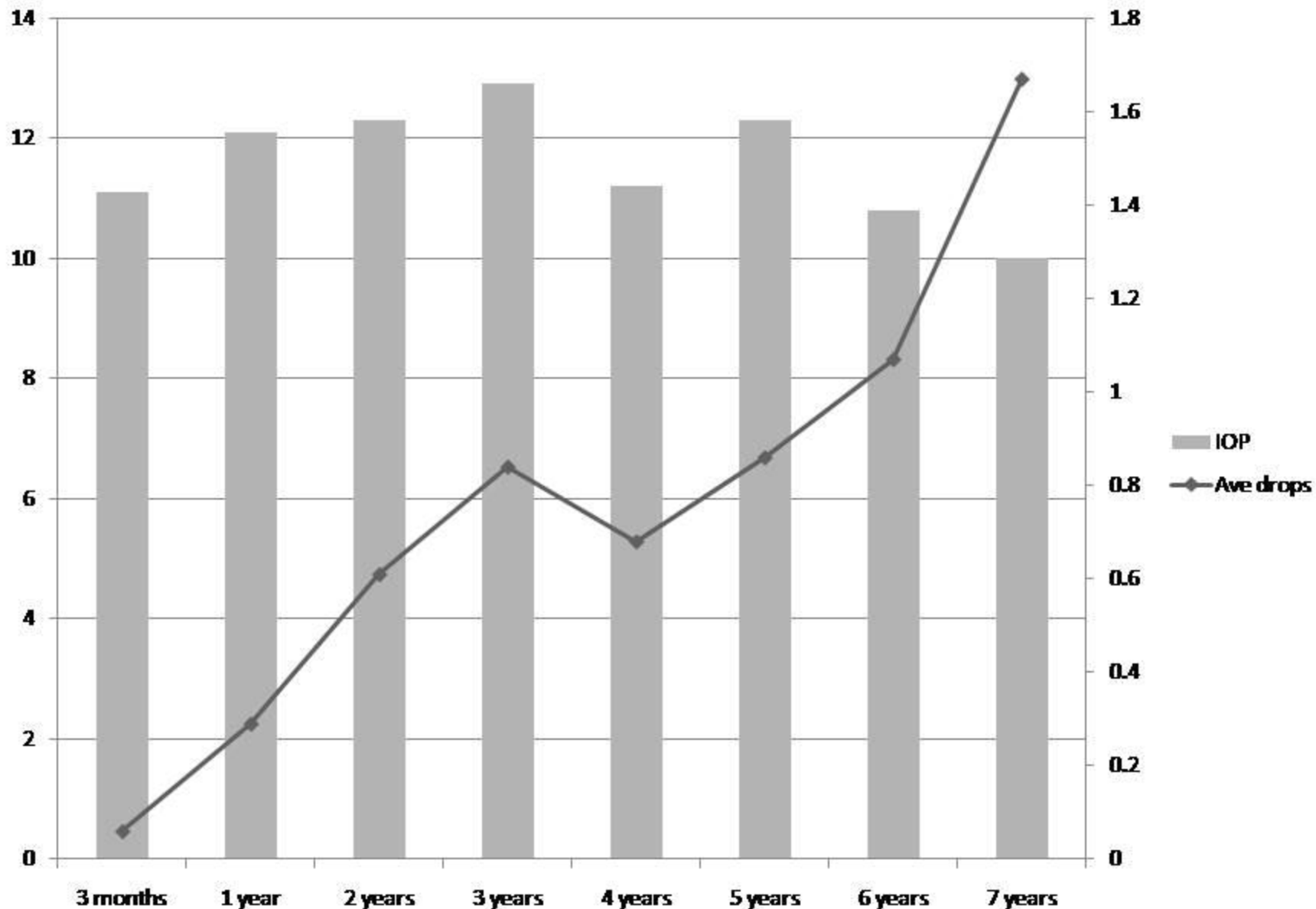
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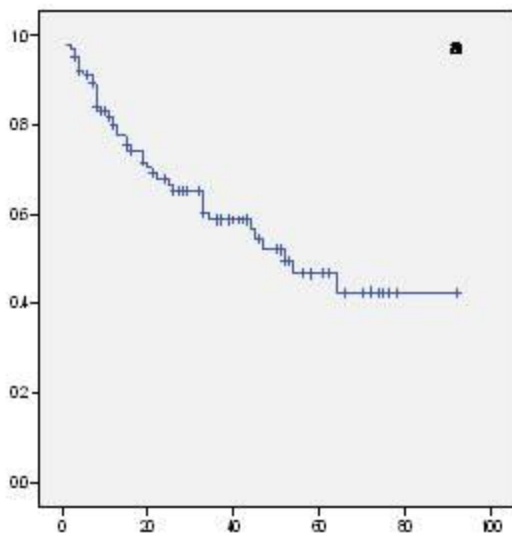
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Figure Legends

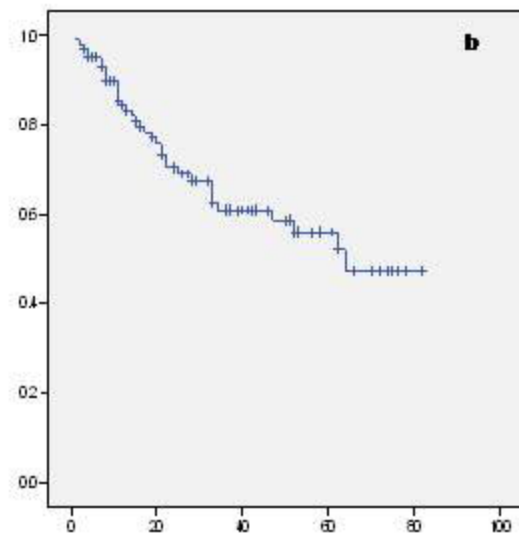
Figure 1: Plot demonstrating mean IOP and mean number of drops used for each year of follow up.

Figure 2: Kaplan-Meier survival curves demonstrating qualified and unqualified survival outcomes for defined success IOPs of 21mmHg and 16mmHg (a-d). Survival outcomes between primary open angle glaucoma and secondary glaucoma for IOP >21mmHg (e,f).

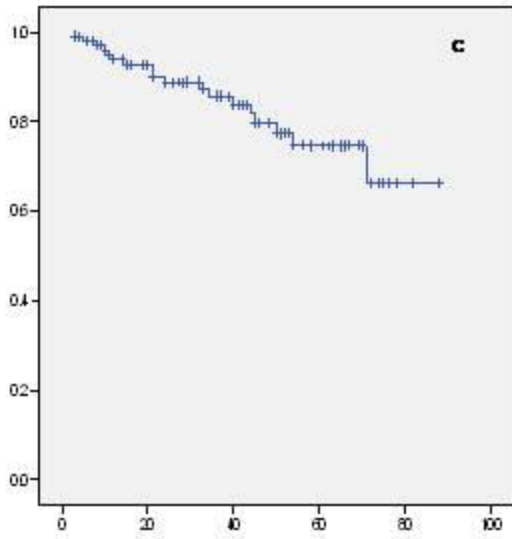




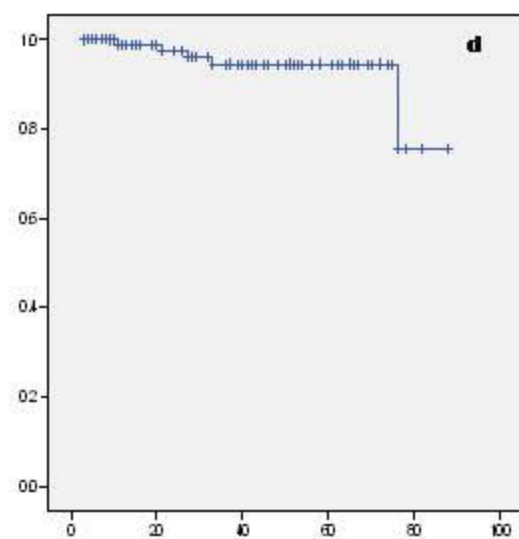
Time (months) to unqualified failure (IOP > 16)



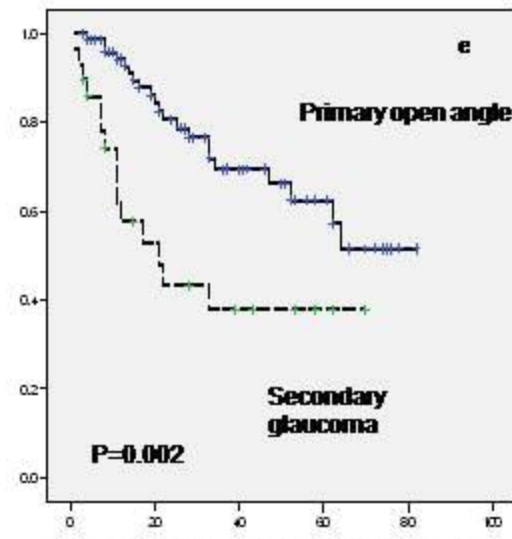
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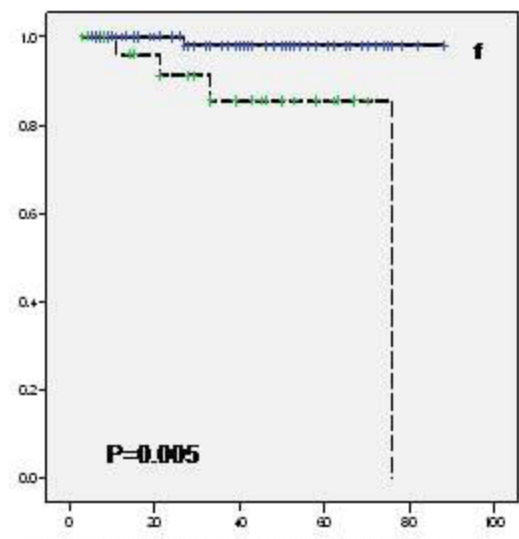
Time (months) to qualified failure (IOP > 16)



Time (months) to qualified failure (IOP > 21)



Time (months) to unqualified failure (IOP > 21)



Time (months) to qualified failure (IOP > 21)