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Bilateral Non-Penetrating Deep Sclerectomy: Difference in Outcomes between First-Operated and Second-Operated Eyes at 24 Months

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Abstract

Background/Aims

The purpose of this study was to assess the difference in outcome between the first-operated eye and the second-operated eye following non-penetrating deep sclerectomy (DS), and to identify potential success predictors for the second eye.

Methods

This single-surgeon, retrospective study analyzed the outcomes of all bilateral non-simultaneous DS with at least 24 months of follow-up. Its main outcome measure was surgical success, defined as unmedicated intraocular pressure (IOP) ≤ 15 mmHg associated with a relative reduction ≥20%.

Results

In all, 104 eyes of 52 patients who underwent bilateral (standalone or combined) DS, within a mean of 344.3 ± 526.3 days of each other, were analysed. Post-operatively, mean medicated IOP decreased from 20.7 ± 7.9 (first-operated) and 19.3 ± 6.6 mmHg (second) at baseline ($p = 0.107$) to 13.8 ± 4.8 ([-33.3%; $p < 0.001$] first-operated eyes) and 12.7 ± 3.8 mmHg ([-34.2%; $p < 0.001$] second eyes) after 2 years ($p = 0.619$). Post-operative IOP and treatments reduction respectively showed fair ($r = 0.53$) and good ($r = 0.71$) levels of correlation between fellow eyes. Rates of complete success were comparable between first-operated and second-operated eyes (32.7% and 40.4%, respectively; $p = 0.364$). At 2 years, among patients whose first-operated eyes were considered a success, 82.4% of surgeries in second eyes were successful ($p=0.001$). The odd ratio of a second-operated eye experiencing complete success were 6.32 ($p = 0.011$) if the first operated eye experienced complete success.

Conclusion

The present study demonstrated a strong association between first-operated eyes and second-operated eyes following DS, in terms of surgical outcomes and IOP reduction. In effect, surgical success in the first-operated eye increases the odds of success in the second eye by 6 folds.

Keywords: Glaucoma; Filtering; Filtration; Surgery; Contralateral; Risk; Complications; IOP; Symmetry; Association

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Introduction

Ophthalmology literature abounds with cases where both eyes of a same person do not behave completely independently. Yet, in most cases, the physiological mechanisms connecting both eyes and their clinical significance remain unknown. In some instances sympathetic innervation was clearly identified as a vector of contralateral inflammation,[1,2] in others, like macular holes or retinal detachments, a shared structural defect is responsible for an increased incidence of the pathology,[3,4,5,6] while in some, inflammatory mediators were suspected to play a role.[7] However, in a number of instances, the correlation remains purely speculative.[8,9] In the field of glaucoma, studies on trabeculectomies have shown that while early post-operative intraocular pressures (IOP) were on average significantly lower in the first-operated eyes,[7] failure in these eyes was correlated with higher failure rates in second eyes,[10] and longer intervals between bilateral surgeries were associated with higher rates of failure in second-operated eyes.[11] Furthermore, eye-specific confounders such as glaucoma severity, cumulative exposure to topical medications, lens status or intraocular inflammation were all suggested as potential factors influencing the outcomes of the procedure.[7,10,11,12] No study, however, has yet investigated whether these observations applied to non-penetrating deep sclerectomy (DS).

Multiple studies have demonstrated that DS had a superior safety profile than trabeculectomy, with a comparable IOP lowering potential.[13,14,15,16] These benefits stem from the non-penetrating nature of the technique, in which the anterior chamber is not entered and aqueous initially percolates into the sclerectomy through an intact trabeculo-Descemet's membrane.[17] The purpose of this study was to assess the differences in outcome between first-operated eyes and second-operated eyes following (standalone or combined) bilateral DS, and to identify any success predictor for the second eye.

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Methods

Study Design

This was retrospective study, conducted at a single tertiary glaucoma centre. The study was reviewed and approved by the local ethical committee (IRB) and written informed consent for data collection was obtained from all patients. The study was conducted in full compliance with the Declaration of Helsinki and registered at ClinicalTrials.gov (identifier, NCT04381611).

Study Population

Patients with primary or secondary open-angle glaucoma (OAG) who underwent bilateral DS at the investigators' specialist glaucoma centre between January 2010 and June 2018 were retrospectively enrolled if at least 24 months of postoperative follow-up were available in their medical notes. Patients with angle-closure glaucoma or neovascular glaucoma, and patients under the age of 18 years at the time of surgery were excluded from this study. Open-angle glaucoma was defined as the association of repeatable visual fields defects (persistent scotoma on at least two consecutive standard automated perimetry tests [Octopus, Haag Streit, Koeniz, Switzerland] with a test reliability index ≥ 15%), with an abnormal optic disc appearance (presence of neuroretinal rim thinning or localized or diffuse retinal nerve fiber layer [RNFL] defects indicative of glaucoma) indicative of glaucoma as observed under slit-lamp examination or on SD-OCT imaging (Spectralis OCT, Heidelberg Engineering AG, Germany), and a gonioscopically open iridocorneal angle.

Data Collection

For all patients, the following data were collected: age, sex, glaucoma diagnosis, best-corrected visual acuity (BCVA), IOP (Goldmann applanation tonometry), central corneal thickness (CCT), mean RNFL thickness, visual field mean deviation (MD), and square of loss

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variance (sLV), number of anti-glaucoma medications (defined as the number of active ingredients for combined treatments), any adverse event (AE) or additional procedure.

The last pre-operative visit was used as baseline for all values except for IOP. To minimize systematic bias that could be caused by incidental spikes of IOP, baseline IOP was defined as the mean of the last two clinical visits prior to surgery. Post-operative data from the closest visit were reported for each timepoint, when the time difference was no more than 15%. The following post-operative timepoints were used: day 1, day 7, and months 1, 3, 6, 12 and 24. No data was collected beyond 24 months.

Surgical Technique

All surgeries were performed by a single experienced surgeon (AM) following the same standard protocol, as described by the World Glaucoma Association.[11] The main steps are summarized below.

Following topical and parabulbar anaesthesia, the conjunctiva was opened at the limbus and dissected with Tenon's capsule to expose a scleral area adjacent to the superior limbus. The surface of the exposed sclera was scraped with a Hockey blade (Feather®, Osaka, Japan) to remove loose epithelial tissue. Three surgical sponges soaked with 0.2 mg/ml MMC were then inserted under the conjunctiva for 2 to 3 minutes depending on patients' ethnicities. No washout was performed. A superficial scleral flap of 5 x 5 mm was created, extending at least 1 mm into the clear cornea. A deep scleral flap, measuring approximately 4 x 4 mm, was then dissected using a crescent blade and leaving a thin layer of deep sclera covering the choroid on the posterior plane. While proceeding anteriorly with the deep scleral dissection, the roof of Schlemm's canal was removed and the dissection is carefully extended further into the corneal stroma. The TDM was then exposed and the deep scleral flap was excised at the level of Descemet's membrane. The inner wall of Schlemm's canal and the juxta-canalicular trabeculum were peeled off using toothed forceps. A porous collagen space maintainer

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(Ologen, Aeon Astron Europe, Leiden, Netherlands) was subsequently inserted in the scleral bed to prevent collapse of the superficial flap and secured with a single nylon 10-0 suture to the thin remaining deep scleral layer. The superficial scleral flap was repositioned over the collagen implant and secured with 2, or more, nylon 10-0 sutures, depending on the outflow. The conjunctiva and Tenon's layer were closed vicryl 8-0 resorbable sutures. When phacoemulsification was indicated, it was performed in a standard manner prior to the DS. Postoperatively, all patients were treated with a topical combined therapy of tobramycin and dexamethasone (Tobradex®, Alcon, TX, USA), initially 4 times a day, then in reducing doses, tapered down by one drop a week over 4 weeks. All anti-glaucoma medications were stopped on the day of surgery.

Cases where significant variations from this standard protocol were reported, such as those where perforation of the trabeculo-Descemet's membrane led to a conversion into trabeculectomy, were excluded from this study.

Post-operative Procedures

When needling revisions were required, they were systematically performed following the same protocol: after topical anaesthesia was instilled, the eye was prepared with 2 drops of povidone-iodine 5%, and a sterile lid retractor was positioned. Superior corneal bridle sutures were used to expose the filtration bleb and facilitate eye orientation and manipulation. A 27-gauge needle was inserted in the subconjunctival space and used to relieve episcleral adhesions above and below the scleral flap, in a sweeping motion. Once all the adhesions were released, MMC with a concentration of 0.01% was injected subconjunctivally in the superonasal quadrant, 6-8 mm posterior to limbus.

Outcome Measures

Primary outcome measure was surgical success probability. Surgical outcomes were calculated separately for first-operated and second-operated eyes in order to provide an inter-

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eye comparison criterion. Success was either defined as “complete" if the unmedicated IOP at the 24-month visit was ≤15 mmHg with a relative reduction of the IOP of 20% or more from baseline ; or “qualified” if IOP met the same criteria with fewer medications than at baseline. Criteria for complete failure were the requirement of additional glaucoma surgery or loss of light perception. Additional glaucoma surgeries were defined as any incisional procedure carried out in operating theatre, including open bleb revision, but excluding needling revisions and sutures of early post-operative bleb leaks. Secondary efficacy outcome measures included IOP and anti-glaucoma medication relative reductions, and the number of needling procedures performed. Safety end points were intraoperative complications, the observed rate of intraocular adverse events (AEs), and loss of visual acuity over the follow-up period.

Statistical Analysis

For demographics and clinical data, the mean and the standard deviation were calculated when distribution followed a normal curve, and median and interquartile range were used for non-normally distributed values, to obtain a clear statistical representation of the samples. Visual acuities measured on a decimal scale were converted into LogMAR using the formula -log10 (acuity) for the purpose of statistical analysis.[18] Paired t-tests were used to compare baseline and post-operative values between first-operated and second-operated eyes. Pearson correlation coefficients were calculated for absolute IOP and treatment changes between fellow (paired) eyes. The cumulative probability of success was assessed for first-operated and second-operated eyes using Kaplan–Meier survival analysis, based on the aforementioned definitions of success and failure. Chi-square test was used to assess the relationship between the surgical outcomes of fellow eyes, and logistic regressions were used to calculate the odds ratio for potential associations. The tests were two-tailed and P-values < 0.05 were considered statistically significant. All calculations were performed with a commercially available software (Stata version 14.2; StataCorp, College Station, TX).

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Results

A total of 52 patients (104 eyes) met the inclusion criteria and were retrospectively enrolled.

Baseline Characteristics

Mean age was 68.7 ± 13.5 years, with 48.1% of female patients (n = 25). The most common diagnoses were primary open-angle glaucoma (POAG; 44.2%) and pseudoexfoliative glaucoma (PEXG; 36.5%). First-operated eyes presented a mean baseline IOP of 20.7 ± 7.9 mmHg on an average of 2.63 ± 1.19 medications. Second-operated eyes had a mean baseline IOP of 19.3 ± 6.6 mmHg (p = 0.107) on an average of 2.71 ± 1.23 medications (p = 0.322). Mean BCVA in first-operated eyes was 0.71 ± 0.33 (decimal) compared to 0.80 ± 0.32 in second-operated eyes (p = 0.045), and baseline visual field MD were -10.5 ± 6.7 dBs and -7.5 ± 6.2 dBs, respectively (p = 0.147). Other preoperative clinical characteristics were similar across both eyes. **Table 1** compares clinical characteristics between first-operated and second-operated eye at the time of surgery.

Intraocular Pressure

Eyes that underwent additional glaucoma surgery (n = 9; 8.7%) were considered failed surgeries and were excluded from analyses from the day of the re-operation. Over the 24-month follow-up, mean medicated IOP decreased in both eyes from an average of 20.7 ± 7.9 (first-operated eyes) and 19.3 ± 6.6 mmHg (second-operated eyes) at baseline to 13.8 ± 4.8 ([-33.3%] first-operated eyes) and 12.7 ± 3.8 mmHg ([-34.2%] second-operated eyes) after 2 years (p = 0.619). The mean IOP reduction was significant (p < 0.001) with no statistically significant difference between fellow eyes. The greatest difference between eyes was observed at the 7-day timepoint, when the mean intraocular pressure amongst second-operated eyes was 2.2 mmHg higher than that of first-operated eyes at the same timepoint (p = 0.270). No significant difference was observed at any timepoint. **Figure 1** shows the mean IOP and treatments of first-operated eyes and second-operated eyes at each timepoint.

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The Pearson correlation coefficient between IOP changes in fellow eyes was fair (r = 0.53).

Medical Therapy

Concomitant reduction in topical medication use was observed in both eyes. The mean number of glaucoma medications decreased from 2.63 ± 1.19 (first-operated eyes) and 2.71 ± 1.23 (second-operated eyes) at baseline to 0.46 ± 0.92 and 0.27 ± 0.79 respectively after 24 months (p = 0.873). At two years, 80.8% of both first-operated and second-operated eyes required no medications to control their IOP (p = 1.000). Amongst patients who did not require any medications to control IOP in their first-operated eye, 81.0% required no medications in their second eye either. Conversely, 60.0% of patients who required post-operative anti-glaucoma medications in their first-operated eyes required post-operative reinstatement of some anti-glaucoma medications in their second eye. The Pearson correlation coefficient between treatment changes in fellow eyes was good (r = 0.71). **Figure 2** compares the changes in IOP and treatments at 24-month between paired first-operated and second-operated eyes.

Goniopunctures and Needling Revision

In all, 73 eyes (70.2%) underwent laser goniopuncture. At 1-month post-operatively, 44.3% of them had undergone laser goniopuncture, while at 3-month, the figure rose to 84.3%.

In this cohort, 19.7% of eyes underwent at least one needling procedure (first-operated eyes 23.1%; second-operated eyes 17.3%). Fourteen eyes required more than one needling revision, with a mean of 2.6 procedures (2.7 for first-operated eyes and 2.5 for second-operated eyes). Of them, 42.9% were in first-operated eyes, and 57.1% were in second-operated eyes, with only two patients requiring several needling revisions on both eyes. In all, only 3 patients underwent bilateral needling revisions (5.8%), and undergoing a needling revision in the first-operated eye did not significantly increase the risk of requiring a similar procedure in the second eye (odds ratio [OR] = 1.77; p = 0.492). The number of needling

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revisions performed in the first-operated eye was not significantly associated with the surgical outcomes of the second eye (OR = 1.53; p = 0.11).

Surgical Outcomes

In this sample, complete surgical success at 24 months, defined as an unmedicated IOP ≤ 15 mmHg with a 20% IOP reduction from baseline, was achieved in 36.6% of eyes (32.7% of first-operated eyes, 40.4% of second-operated eyes; p = 0.364). Amongst patients whose first-operated eyes were a complete surgical success, 82.4% of surgeries on the second eye were successful. Conversely, amongst patients whose first-operated eyes were considered a surgical failure, 77.1% of surgeries performed on the second eye failed (p = 0.001). **Figure 3** shows the Kaplan Meier survival curves of first-operated and second-operated eyes for complete success and compares the survival curves of second-operated eyes for whom first-operated eyes were successful and a failure. **Table 2** presents the rates of complete success depending on the outcomes of fellow eyes.

Qualified surgical success was achieved in 43.3% of eyes (44.2% of first-operated eyes, 42.3% of second-operated eyes).

Of all the studied factors, including baseline clinical parameters, time interval between the two surgeries (OR = 1.00; p = 0.152) and the number of needling revisions performed in the first-operated eye (OR = 1.17; p = 0.591), the surgical outcome of the first-operated eye was the only factor that had a statistically significant effect on the surgical outcomes of the second eye. The odds of a second-operated eye experiencing complete success were 6.32 (p = 0.011) if the first operated eye experienced complete success. **Table 3** presents the odds ratios for complete success of the second-operated eye, for all analysed clinical parameters.

Surgical Complications

Overall, a total of 60 ocular AEs were recorded in 51 eyes during the follow-up period. The most frequent AE reported after surgery was hypotony (29.8%), only one case of which was

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associated with choroidal effusion (1.9%). Complication rates were similar across first-operated and second-operated eyes (83.8%). **Table 4** presents all reported AEs.

Discussion

The present study is the first study comparing the outcomes of non-penetrating deep sclerectomy between fellow eyes. It demonstrates the existence of a significant correlation in IOP lowering and surgical outcomes between the two eyes of a same patient. Similarly, the rates of complications across both eye groups were similar.

This study represents a retrospective analysis of 104 eyes that underwent bilateral DS. The relative reductions in IOP and treatments observed in the present study are similar to that reported in prospective studies of DS.[19,20,21]

In this study, the only significant difference between first-operated eyes and second-operated eyes was the mean baseline BCVA (p = 0. 045). Such a difference had already been described in several studies comparing the outcomes of trabeculectomies in fellow eyes,[10,11] and can be accounted for by the fact that eyes with more advanced glaucoma are usually operated on first, thus leading to poorer central vision in this group. Two years post-operatively, however, no significant clinical difference remained between the two groups. Other clinical factors were similar across first-operated and second-operated eyes: types of glaucoma were identical, severities were comparable (p = 0.147), and only one second-operated eye underwent a different type of surgery to the first-operated eye (p = 0.847). Additionally, it is worth noting that, in the present analysis, neither the diagnosis or the type of surgery (whether DS was combined or standalone) had an impact on the surgical outcome.

In terms of complications, Mietz et al. observed an increased rate of needling revision in second eyes, following bilateral trabeculectomies.[10] This observation led to speculations over a potential immune reaction caused by intraocular antigen coming in contact with the subconjunctival space of the first-operated eye. This theory was further supported by Iwasaki

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et al. who observed that longer intervals between a first successful trabeculectomy and the operation of a fellow eye were associated with increased failure rates, whereas the length of the interval had no effect when the first operation failed and only limited amount of aqueous drained into the subconjunctival space.[11] In the present study, no significant difference in the rates of needling revisions between fellow eyes and no significant associations between the length of the inter-operation interval and the surgical outcomes were observed. Several hypotheses could explain such a difference. Firstly, while bilateral operations in the present study were performed within a similar interval to that of Iwasaki et al's study (344.3 days on average vs. 297.5 days),[11] it could be theorized that, if subconjunctival aqueous flow carrying inflammatory mediators is responsible, as speculated, for the worse surgical outcomes observed in second eyes following bilateral trabeculectomies, the reduced aqueous flow resulting from the preservation of the trabeculo-Descemet's membrane in DS may have a protective effect in this regard, thus preserving the full potential of the stent in the fellow eye. Yet, most patients had undergone laser goniopuncture in their first-operated eye by the time they had surgery in their second eye, but it may be supposed that the partial opening of a trabeculo-Descemet's window still produces a limited outflow compared to trabeculectomy.[22] Finally, Zhu et al. has observed the presence of pain-associated chemokines in the aqueous humor of eyes following contralateral phacoemulsification.[23] It could be theorized that the use of parabulbar anesthesia in all studied procedures might be associated with less significant chemokines-induced contralateral effects. Based on the present observations, it appears that, contrary to trabeculectomy, DS does not impair the outcomes of subsequent surgeries in the fellow eye. However, the outcomes of DS in the second-operated eye are strongly associated with that of the first-operated eye, with odds ratios of 6.32 ($p = 0.011$). This may suggest that the outcomes of DS are dependent on systemic factors that may be associated with variations in connective tissue structures and scarring processes, but remain widely unidentified.

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One of the limitations of the present study was the fact that the outcome of the first surgery was unmasked to the treating ophthalmologist, which may have affected the choice of the procedure used in the second-operated eye. Then, the reported success rates refer to a relatively small cohort encompassing both standalone and combined procedures. Their analysis was used in the context of an inter-eye comparison, and while the type of surgery was not found to affect the outcomes, caution should be taken before interpreting them out of context, as they may be subject to size bias and to the effect of phacoemulsification.

Conclusion

The present study demonstrated a strong association between first-operated eyes and second-operated eyes following DS, both in terms of surgical outcomes and IOP reduction. Indeed, second eyes are over 6 times more likely to fail when the first-operated eye was a failure. It also suggested that DS does not impair the outcomes of subsequent contralateral surgeries, regardless of the length of time between the procedures. Clinically, this suggests that surgical outcomes of a first-operated eye should be considered when deciding on the indication and type of surgical procedure for the second eye, and from a research point of view, this association should be considered in studies evaluating the outcomes of glaucoma surgeries that include both eyes of subjects for analysis

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Legends

Figure 1 – Progression of mean intraocular pressure (graph) and number of anti-glaucoma medications (vertical bars) compared between first-operated eyes (dark green) and second-operated eyes (light blue). Vertical bars represent standard deviations. (BL: Baseline; D: Day; M: Month).

Figure 2 – Paired comparison of the changes in intraocular pressure (A) and treatments (B) at 24-month between first-operated and second-operated eyes of each patient. Dot diameters express the number of overlapping data. When additional glaucoma surgery was performed to one eye, both eyes of the same patient were excluded from this graph. Dashed lines represent x = y, where identical changes were observed in both eyes of a same patient.

Figure 3 - Kaplan Meier survival curves comparing (A) the rates of complete surgical success of first-operated and second-operated eyes, and (B) the rates of complete surgical success of second-operated eyes based on first-operated eyes' outcomes.

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Clinical data	First-operated eyes n = 52	Second-operated eyes n = 52	*P*
Diagnosis			1.000
POAG	23 (44.2%)	23 (44.2%)	
PEXG	19 (36.5%)	19 (36.5%)	
NTG	8 (15.4%)	8 (15.4%)	
Uveitic	2 (3.8%)	2 (3.8%)	
Baseline BCVA (decimal)	0.71 ± 0.33	0.80 ± 0.32	0.045
Baseline IOP (mmHg)	20.7 ± 7.9	19.3 ± 6.6	0.107
Baseline MD (mean)	-10.5 ± 6.7	-7.5 ± 6.2	0.147
Baseline CCT (µm)	535.2 ± 45.5	537.0 ± 54.2	0.593
Baseline Medications	2.63 ± 1.19	2.71 ± 1.23	0.322
Combined procedures	18 (34.6%)	19 (36.5%)	0.847
Interval between surgeries (days)	344.3 ± 526.3		

Table. 1 *- Pre-operative clinical characteristics in both eye groups (POAG: primary open-angle glaucoma, PEXG: pseudo-exfoliative glaucoma, NTG: normal tension glaucoma, BCVA: best corrected visual acuity, IOP: intraocular pressure, MD: mean deviation, CCT: central corneal thickness).*

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		Outcomes for second-operated eyes	
		Success *(n = 22)*	**Failure** *(n = 30)*
Outcomes for first-operated eyes	**Success** *(n = 17)*	82.4% *(n = 14)*	17.7% *(n = 3)*
	Failure *(n = 35)*	22.9% *(n = 8)*	77.1% *(n = 27)*

Table 2. Row percentage table showing the rates of complete surgical success depending on the outcomes of the second-operated eyes, as per definition: IOP ≤ 15 mmHg associated with a reduction from baseline ≥ 20%.

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Clinical factors	**Complete success of second-operated eyes** *(IOP ≤15 mmHg & ≥ 20% reduction)*		
	Odds ratio	95% CI	p-value
Complete success of the first-operated eye	**6.32**	**(1.54, 25.99)**	**0.011**
Age	0.96	(0.91, 1.01)	0.149
Sex	1.76	(0.41, 7.53)	0.448
Diagnosis	0.93	(0.22,4.00)	0.928
Type of surgery (combined vs. standalone)	0.58	(0.16, 2.13)	0.411
Baseline IOP	1.01	(0.91, 1.12)	0.825
Baseline treatments	1.01	(0.57, 1.80)	0.964
Interval between surgeries	1.00	(1.00, 1.00)	0.152
Total needling revisions in the first operated eye	1.17	(0.65, 2.10)	0.591
Day-1 IOP	0.95	(0.90, 1.04)	0.261

Table 3 - *Table presenting the odds ratios for complete success of the second-operated eye for all analysed parameters. Statistically significant values are shown in bold (p < 0.05); CI: Confidence internal.*

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Adverse Events	First-operated eyes n = 52	Second-operated eyes n = 52	All eyes n = 104
Complications-free eyes	29 (55.8%)	24 (46.2%)	53 (51.0%)
Complications			
Hypotony (IOP < 6 mmHg)	13 (25.0%)	18 (34.6%)	31 (29.8%)
Hyphema	4 (7.7%)	4 (7.7%)	8 (7.7%)
Seidel	5 (9.6%)	3 (5.8%)	8 (7.7%)
Iris incarceration	2 (3.8%)	3 (5.8%)	5 (4.8%)
Corneal oedema	1 (1.9%)	3 (5.8%)	4 (3.8%)
Anterior chamber cells	1 (1.9%)	1 (1.9%)	2 (1.9%)
Choroidal effusion	0	1 (1.9%)	1 (1.0%)
Bleb dysesthesia	0	1 (1.9%)	1 (1.0%))
Needling revisions	12 (23.1%)	9 (17.3%)	21 (19.7%)
Additional glaucoma surgery	6 (11.5%)	3 (5.8%)	9 (8.7%)

Table 4 - *Table presenting the rates and details of all adverse events recorded during the 24-month follow-up.*

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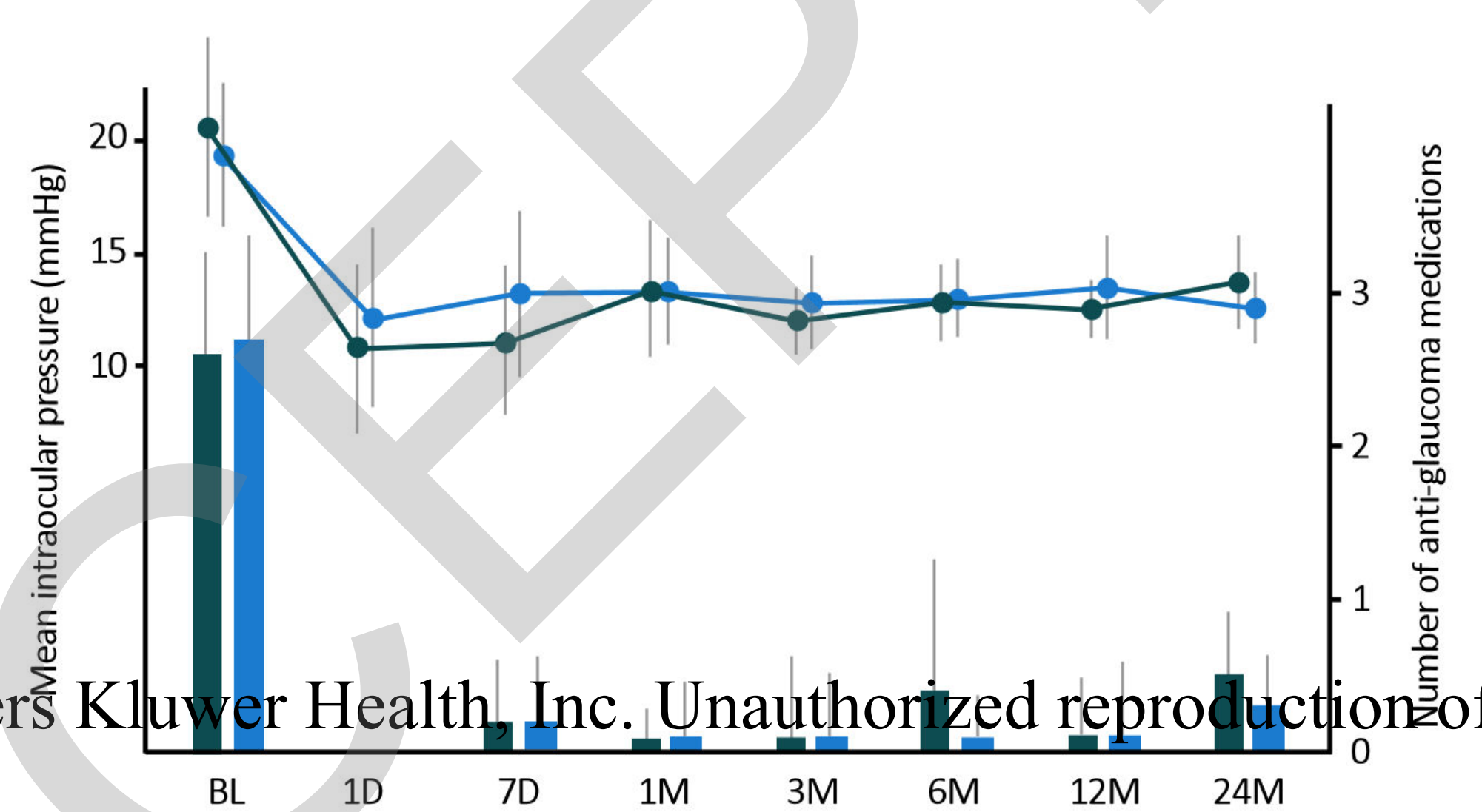

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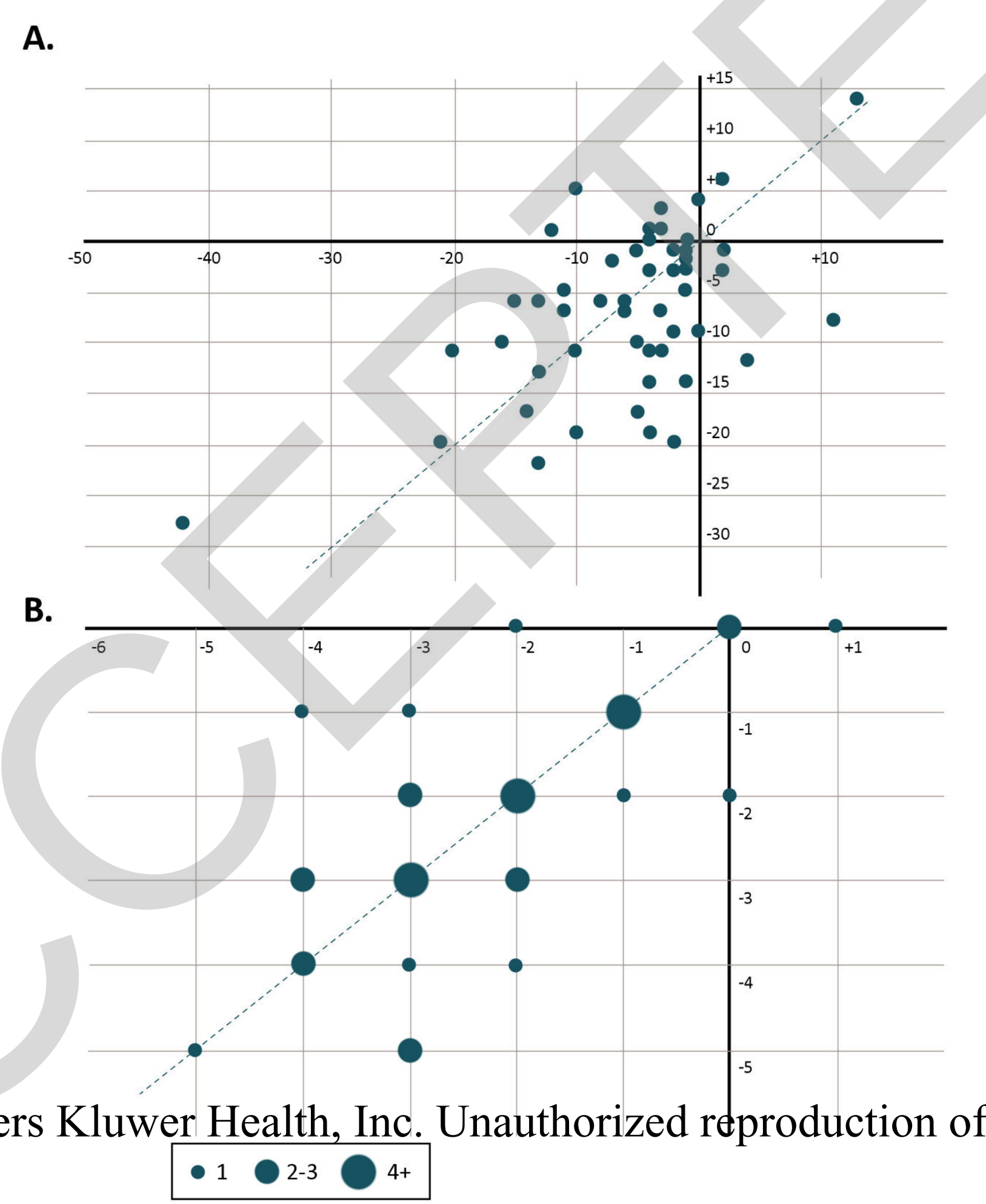

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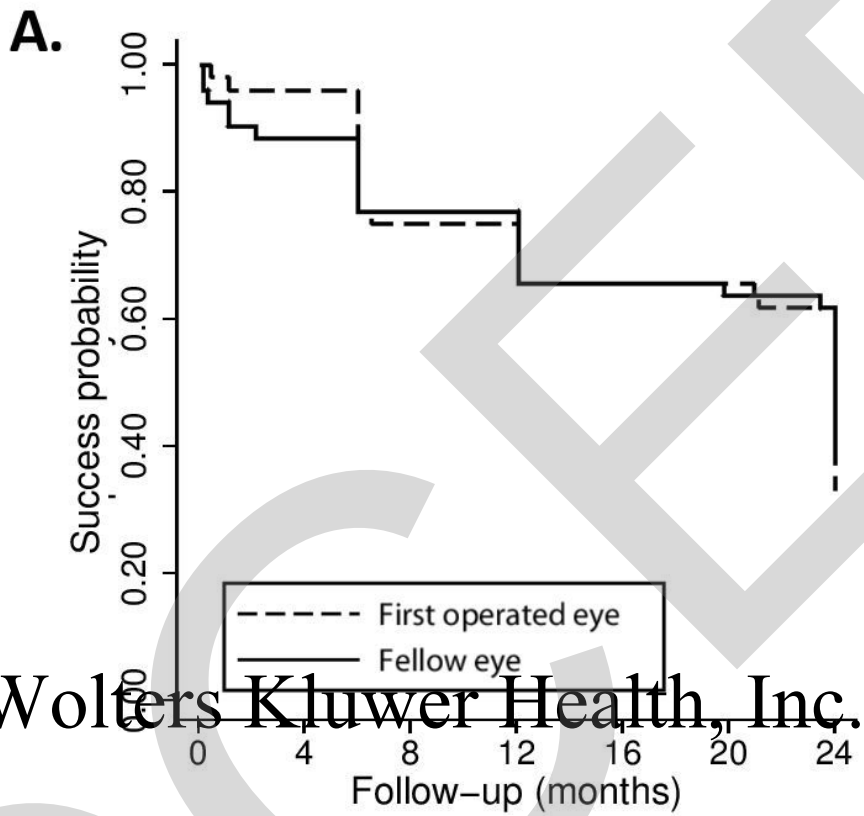

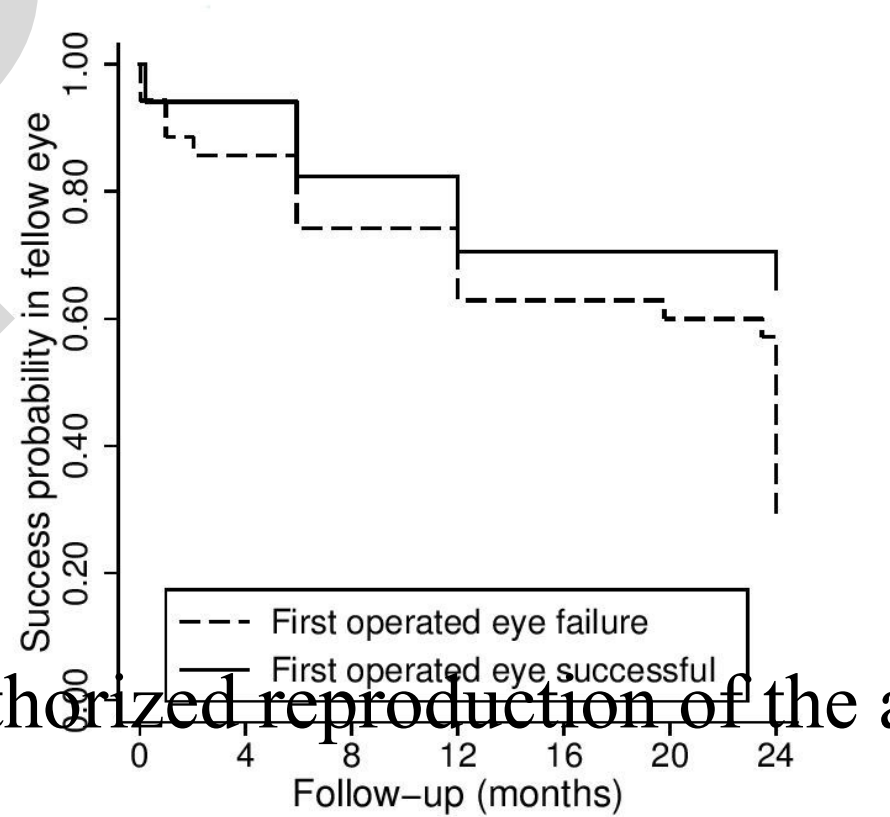

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