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Article

Difference in Nycthemeral IOP Variation and Outflow Facility after Filtering Microshunt versus Canal-Based Ab Interno Glaucoma Surgery

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Abstract

Purpose: We hypothesized that a recently introduced epibulbar micro-shunt (PRESERFLO, P) produces nycthemeral (24h) intraocular pressure (IOP) profiles different from ab-interno trabeculectomy (Trabectome, T). P is a flow restrictor that drains fluid into the sub-tenon space. In contrast, T increases conventional outflow, which is limited by episcleral venous pressure.

Methods: In this prospective cohort, we analyzed 68 patients (34 P and 34 T) who presented for 24-h IOP monitoring 6 to 12 months after surgery. IOP and tonographic outflow facility were measured in the habitual position using a pneumatonometer. The IOP variation was considered the primary outcome measure. Glaucoma medications were also compared.

Results: P had a higher baseline IOP than T (24.8±10.0 vs. 17.3±7.9 mmHg, p=0.001). Postoperatively, P and T had similar nycthemeral IOP profiles, but IOP in P was significantly lower than in T, except at 4 pm. P had a lower absolute IOP variation than T (5.8±2.6 vs. 7.1±2.7 mmHg, p=0.049). The relative IOP variation was similar in both (34.8±13.2 vs. 37.2±13.1, p=0.45) as was the tonographic outflow facility (0.35±0.23 vs. 0.26±0.18 µl/min/mmHg, p=0.097).

Conclusion: Nycthemeral IOP profiles of P and T were similar, but P had lower IOPs and less variation than T. This could reflect how T, unlike P, is more impacted by habitual, positional factors, especially at night.

Keywords: glaucoma; PRESERFLO; Trabectome; nycthemeral IOP measurement; tonographic outflow facility

Introduction

About 50% of patients with glaucoma eventually require invasive surgery, although they are initially treated with laser and medications [1]. The primary resistance to outflow resides in the proximal part of the conventional outflow system. Trabeculectomy, a traditional filtering glaucoma surgery, circumvents this resistance by shunting aqueous humor to a sub-tenon reservoir called the bleb. It does so effectively but with a relatively high chance of complications [2]. Aqueous humor in the bleb is absorbed primarily by ocular lymphatics, while some also slowly passes through the bleb's pliable, elastic wall. The mechanism is independent of the episcleral venous pressure (EVP). Surgeons attempt to regulate flow in trabeculectomy by suturing a scleral flap, with variable tension levels, over the ostium that opens into the anterior chamber to adjust flow to match the physiological rate of 2.2 to 3.1 µl/min [3]. The PRESERFLO (P; Santen, Osaka, Japan) is a newer iteration of a class of biocompatible, flow-restricting microshunts that standardize this procedure and make it safer [4–6]. Several studies have demonstrated P's efficacy in reducing IOP and medication count [5–9].

In contrast, ab interno trabeculectomy with the Trabectome (T; MicroSurgical Technology, Redmond, Washington) removes the trabecular meshwork via plasma ablation to enhance outflow along its physiological, conventional route through Schlemm's canal, collector channels, and into the episcleral veins [10]. T can be used to treat mild, moderate, and advanced glaucoma [11, 12], but it typically achieves an IOP closer to 15 mmHg, higher than the EVP of 7 mmHg [13]. It is safer than filtering surgery because the long-term complications of blebs are avoided [14], and the IOP can theoretically never be lower than EVP.

An IOP too high for the affected eye is the principal cause of glaucoma [15, 16], but several studies have also linked an increased variation of diurnal or nycthemeral IOP to glaucoma progression [17–20]. Both trabeculectomy [21] and trabectome surgery [22] reduce the IOP as well as its variation. The dependence on EVP in T is commonly seen as an advantage because it prevents hypotony, but EVP is higher at night in the supine position [23]. This could subject patients with T to more IOP variation and a higher risk of progression than in P.

In this study, we hypothesized that P produces nycthemeral (24h) IOP profiles with less variation than T due to its different mode of action and independence from EVP. We obtained nycthemeral, inpatient IOP profiles of 68 participants to answer this question.

Methods

Study Design

This was a prospective study carried out at the ophthalmology department of the University of Würzburg and approved by the Institutional Review Board (#114/21). Informed consent was acquired from all participants. The study abode by the principles stated in the Declaration of Helsinki and its amendments. Data from 68 patients with glaucoma who underwent either a PRESERFLO implantation (P) or plasma-mediated ab-interno trabeculectomy with the trabectome (T) between October 2020 and July 2021 were analyzed. The surgical indication was the need to lower the IOP because of glaucoma progression or the inability to adhere to glaucoma medications. Exclusion criteria were prior glaucoma surgery, surgical failure leading to an indication for additional surgery, angle-closure glaucoma, or secondary open angle glaucoma. Additionally, patients younger than 18 and those who underwent P or T less than six months ago or over 1 year were excluded. Only the right eye was included when a patient had two eyes that qualified.

We assessed age, gender, preoperative/baseline IOP, visual field function, and the number of glaucoma medications. The visual field function was evaluated using an Octopus 900 perimeter (Haag-Streit, Köniz, Switzerland). When patients presented for their six-month follow-up visit, patients were admitted for 24 hours for pneumatonometer (Reichert, Buffalo, New York, United States) measurements at 5 AM, 11 AM, 4 PM, 8 PM, and midnight. In addition to the pre-operative value, one Goldmann postoperative IOP measurement was also obtained (recorded as the post-operative value in the table). Inpatient IOP measurements and medication counts were compared to the preoperative baseline.

Outflow Facility Measurement

The outflow facility was measured for all recruited patients at 11 AM using a pneumatonometer. In order to do this, the patients had their baseline IOPs recorded in both sitting and supine positions. This was followed by placing a 10 g weight on the pneumatonometer probe and continuous measurement of the IOP for 2 minutes. The IOP curves were used to calculate the outflow facilities.

PRESERFLO Micro-shunt Implantation Technique

A superior corneal traction suture was placed approximately 1 mm anterior to the limbus. A 3 mm wide peritomy with a direct opening of Tenon’s layer 2 mm posterior to the limbus was fashioned using Westcott scissors. The sub-tenon space of the bleb was opened and dissected with an iris spatula. Three sponges soaked with mitomycin C (0.5 mg/ml) were inserted for three minutes, followed by irrigation with buffered saline solution (BSS). Three millimeters posterior to the limbus, a 2 mm long and 1 mm wide pocket oriented towards the limbus was created with the paracentesis blade included in the kit. A 25 gauge needle was inserted into the pocket with the bevel up and advanced into the anterior chamber to enter halfway between the cornea and the iris. The microshunt was moved into the tunnel, with the bevel pointing up until the wings were secured within the sclera pocket. The microshunt’s function was confirmed by visualizing aqueous exiting at the tail. Tenon’s capsule and the conjunctiva were pulled over the shunt and secured at the limbus with two wing sutures using 10-0 nylon. The knots were rotated. The bleb that formed was checked for leakage. The postoperative regimen consisted of dexamethasone drops four times a day for a month, then tapered by one drop per week, and ofloxacin drops four times a day for a week. Subconjunctival 5-fluorouracil (50 mg/ml, 0.2 ml) was given on day one, week one, and week 2 after surgery.

Trabectome Surgical Technique

A peripheral iris-planar incision was made in the right-hand position, approximately 2 mm anterior to the limbus. Lidocaine was injected intracamerally through it. Pressure on the posterior lip of the incision released a small amount of aqueous humor to produce hypotension and reflux of venous blood into Schlemm's canal, which highlighted the ablation target. The patient's head was rotated 45° away from the surgeon while the microscope was tilted in the opposite direction toward the surgeon. The trabecular meshwork along the nasal angle was visualized with a modified Schwan-Jakob lens, irrigation of the trabectome was activated, and the tip of the trabectome was inserted through the incision. The tip of the footplate of the trabectome was inserted into Schlemm's canal, ablation was activated, and continued to the left for up to 90 degrees. The trabectome was rotated 180 degrees, reinserted into Schlemm's canal where the ablation had started, and continued up to 90 degrees towards the right. After removing the trabectome from the anterior chamber, venous blood was observed to flow from the collector channels into Schlemm's canal, confirming a successful connection to the peripheral aqueous drainage system. The patient's head was rotated back to the normal position, and the microscope was centered. The normal anterior chamber depth was restored with BSS. The corneal incision was hydrated with BSS and checked for water tightness. The intraocular pressure was normal on palpation. The postoperative regimen consisted of dexamethasone drops four times a day for a week, then tapered by one drop per week, and ofloxacin drops four times a day for a week.

Data Analysis

We used SPSS (Version 26, IBM, New York, USA) for statistical analysis. Variables were classified as either dichotomous or continuous. A sample size calculation showed that 68 patients were needed to achieve a power of 80%. The continuous variables were reported as means and standard deviations, while the dichotomous variables were reported as percentages. We checked for a normal distribution with the Kolmogorov-Smirnov test. Independent means of normally distributed variables were compared using an unpaired t-test, while the Mann-Whitney-U test was used for non-normally distributed parameters. A paired t-test or Wilcoxon signed rank test was deployed to compare dependent means. The Chi-squared test was used for categorical variables. Absolute IOP variation was calculated as the difference between the peak and trough of measured nycthemeral IOP values. In addition, we calculated relative IOP variations in 2 ways. IOP variation 1 was defined as follows:

$$IOP\ Variation\ 1 = \frac{Absolute\ IOP\ variation\ (mmHg)}{IOPmean\ (mmHg)}$$

where

$$IOPmean\ (mmHg) = \frac{IOPmaximum\ (mmHg) + IOPminimum\ (mmHg)}{2}$$

IOP variation 2, in contrast, was calculated as the ratio of the absolute IOP variation divided by the area under the curve acquired for each patient using the five measured IOP values using properly scaled time points. A p-value of 0.05 or less was considered statistically significant for all analyses.

Results

No patient discontinued the 24-hour IOP monitoring session. Table 1 shows the patients' demographics, preoperative IOP, visual field defects, and medication count. The groups had highly similar age, gender ratio, preoperative medication count, visual acuity and mean visual field defects ($p > 0.05$ for all parameters). P had a mean IOP that was 7.5 mmHg higher than in T ($p = 0.001$).

The 24-hour IOP measurements were obtained 7.9±2.1 months after the surgery. Both P and T achieved a significantly lower IOP level than their baseline values (Table 2, $p < 0.05$ for both). Both groups had a remarkably low IOP, with P at only 10.9±2.9 mmHg and T at only 12.6±3.3 mmHg.

P experienced a significant IOP decline by 13.9 mmHg (56%). In contrast, T reduced the IOP by only 4.7 mmHg or 27%. P also had a medication reduction by 2.2 drops (88%) compared to 0.5 drops (20%) in T. Although both IOP changes were significant, only P had a significant change in medication count ($p < 0.001$).

At the last follow-up, P had a significantly lower IOP value than T (10.9±2.9 mmHg in P vs. 12.6±3.3 mmHg in T, $p = 0.05$). P patients also took fewer medications (0.3±0.6 drops vs. 1.9±1.5 drops, in P and T, respectively, $p < 0.001$).

Figure 1 shows the IOP measurements throughout the 24-hour observation period at five different time points. Except for the measurement at 4 PM ($p = 0.13$), all P IOP values were significantly lower in P than in T ($p \leq 0.01$). Both groups had their peaks at 5 AM (18.6±4.7 mmHg in P and 21.3±3.3 mmHg in T) and their troughs at 8 PM (14.7±3.2 mmHg in P and 17.3±3.9 mmHg in T). T patients had an additional trough at 11 AM (17.3±3.2 mmHg).

Patients in P had a smaller absolute nycthemeral IOP variation than patients in T (5.8±2.6 mmHg in P vs. 7.1±2.7 mmHg in T, $p = 0.049$). However, when the relative variation was considered, the difference was not significant despite a numerically larger variation percentage in T. When we compared the IOP variation as a fraction of the time under tension (area under the curve, AUC), there was also no significant difference (p values = 0.40).

Moreover, we investigated the outflow function in P and T by performing facility measurements to study this parameter as a potential cause for the differences. Although P appeared to have a larger average facility than T, statistical significance was not reached (p = 0.097).

Discussion

In this study, we followed 68 patients prospectively to discover differences in 24-hour nycthemeral IOP patterns produced by the PRESERFLO (P), a filtering micro-shunt draining into the sub-tenon space (P) and the Trabectome (T), a device that ablates the trabecular meshwork using plasma. We only included eyes that did not require any revision or additional surgery during the observation time to obtain the specific characteristics of a functioning P and T, respectively. We used a pneumatonometer to accurately record the IOP in the habitual position (sitting and supine) and determine the outflow facility.

With exception to the IOP, P and T had remarkably similar baseline characteristics, including the visual field loss. This reflects our practice pattern and past experience to offer T as the first line of surgery in mild to advanced glaucoma when bleb avoidance and risk reduction are requested. We found that an IOP reduction can be more pronounced in eyes with more severe outflow resistance than in mild glaucoma [11, 12, 24].

In this study, we found that P had a larger IOP reduction than studies that used a mitomycin C concentration lower than our 0.5 mg/ml [25]. Our P had an IOP that was lower than, for instance, the trabeculectomy group in the study by Baker et al., who used 0.2 mg/ml for 2 minutes and achieved an IOP of 14.3±4.3 mmHg. Beckers et al. compared 0.2 to 0.4 mg/ml for 2-3 minutes and found an average IOP of 14.5±4.6 mmHg, with a higher success rate in the 0.4 mg/ml group, still slightly less than what we used [26]. This could suggest that a reduction of fibrosis and better bleb function might be achieved in blebs created by mircroshunts when a higher concentration of mitomycin C is used.

We found that patients in T also experienced a relatively large IOP drop, although their preoperative IOP was comparatively low. This is somewhat unexpected and contradicts the common assumption that subjecting individuals to ab interno trabeculectomy who do not have a preoperative IOP well above 20 mmHg may be of limited use.

The glaucoma medications were significantly lowered only in P, but not in T. This is unsurprising, as filtering surgeries have a higher chance of reducing the medication count than Schlemm’s canal-based ab interno glaucoma surgeries [27, 28]. The downside is that they also carry a higher surgical risk, including hypotony. The fact that we could achieve a relatively low IOP of 12.6±3.3 mmHg in T while continuing some drops shows how important it is to consider T in patients who prefer a low-risk, bleb-free procedure. This low IOP is normally more than appropriate for advanced glaucomas [29].

The nycthemeral IOP patterns were similar in both groups, with a peak at 5 AM and a trough at 8 PM. These time points are aligned with other nycthemeral IOP studies. Investigators found an early morning IOP peak at 5:30 AM [30, 31]. IOP is higher in the supine position, presumably due to increased venous pressure, particularly EVP, as one mechanism [32–35]. Our trough value at 8 PM was similar to that published in another study, which reported an IOP trough at 9:30 PM [36].

As expected, the IOP variation was smaller in P than in T. The differences were not as large as we anticipated based on the assumption that the variation in T is driven by the IOP's dependence on the EVP, which is higher at night when in the supine position [23]. Interestingly, our IOP variation in P (5.8±2.6 mmHg) was similar to that in post-trabeculectomy eyes (5.78±2.48 mmHg) [21]. But in healthy eyes, large differences in normal, physiological IOP variation far exceed these values: a shorter axial length in hyperopia is associated with a higher IOP variation of 12.8±3.4 mmHg than longer, myopic eyes with only 8.3±2.8 mmHg variation [37]. In contrast to the differences in absolute variation, however, we found that the relative IOP variation and variation per "time under tension" (area under the curve) were similar in P and T. The relevance of IOP variation in glaucoma progression or pathogenesis is debated. Some studies found no correlation [38, 39], but more recent ones do [17–20]. Beyond an observed correlation, causation has not been demonstrated.Regardless, a smaller IOP variation could certainly be advantageous in advanced glaucoma.

We examined how P and T respond to a higher outflow demand caused by increased pressure during facility measurements to investigate factors contributing to a larger variation. Although P had a numerically higher facility than T, our study was underpowered to answer whether P allows displacing fluid from the anterior chamber more readily than an unroofed Schlemm's canal in T. Even if it did so temporarily, as can be seen after trabeculectomy due to a distensible bleb [40, 41], it is likely that an equilibrium will be reached beyond the relatively short facility measurement.

The strengths of this study lie in the fact that it is a prospective study, all patients were operated on by the same surgeon (NAL), and the same researcher carried out all measurements (MB). The limitations of our study were that although low IOPs were achieved by P and T in advanced glaucoma, this study was not designed to comprehensively analyze P and T surgeries and their failure rate. This study also had a low power of discovery for facility differences. We measured IOP only five times per night instead of every two hours, which prevented us from applying more advanced acrophase detection and curve fitting [37, 42].

In conclusion, we found that both P and T achieved low IOPs and that P produces an IOP curve similar to T, but with lower IOPs and less IOP variation.

Declarations

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Code Availability: Not applicable.

Ethics Approval: Approval was obtained from the Institutional Review Board (IRB) of the University of Würzburg.

Consent for Participation: Informed consent was acquired from all participants.

Consent for Publication: All listed authors consent to the publication of this manuscript.

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Tables

Table 1: Demographic parameters of recruited patients.

	PRESERFLO (n = 34)	Trabectome (n = 34)	p-value
age (years) (mean±SD)	68.5±9.1	68.4±9.7	0.95
gender ratio (M:F)	0.42	0.36	0.79
preoperative IOP (mmHg) (mean±SD)	24.8±10.0	17.3±7.9	0.001
preoperative medications (drops) (mean±SD)	2.5±1.2	2.4±1.6	0.72
baseline visual Acuity (mean±SD)	0.6±0.26	0.7±0.30	0.26
visual field defect (dB) (mean±SD)	12.2±6.7	12.5±8.3	0.87

Table 2: Follow-Up parameters

	PRESERFLO (n = 34)	Trabectome (n = 34)	p-value
postoperative IOP (mmHg) (mean±SD)	10.9±2.9	12.6±3.3	0.05
absolute IOP variation (mmHg) (mean±SD)	5.8±2.6	7.1±2.7	0.049
absolute $IOP_{variation}$ / IOP_{mean} (%) (mean±SD)	34.8±13.2	37.2±13.1	0.45
absolute $IOP_{variation}$ / AUC (1/hour)	0.019±0.008	0.021±0.008	0.40
outflow facility (µl/min/mmHg) (mean±SD)	0.35±0.23	0.26±0.18	0.097
postoperative medications (drops) (mean±SD)	0.3±0.6	1.9±1.5	< 0.001

$IOP_{mean} = (IOP_{maximum} + IOP_{minimum}) / 2$.

AUC = time under tension = area under the curve of the 5 acquired IOP measurements.

Figures:

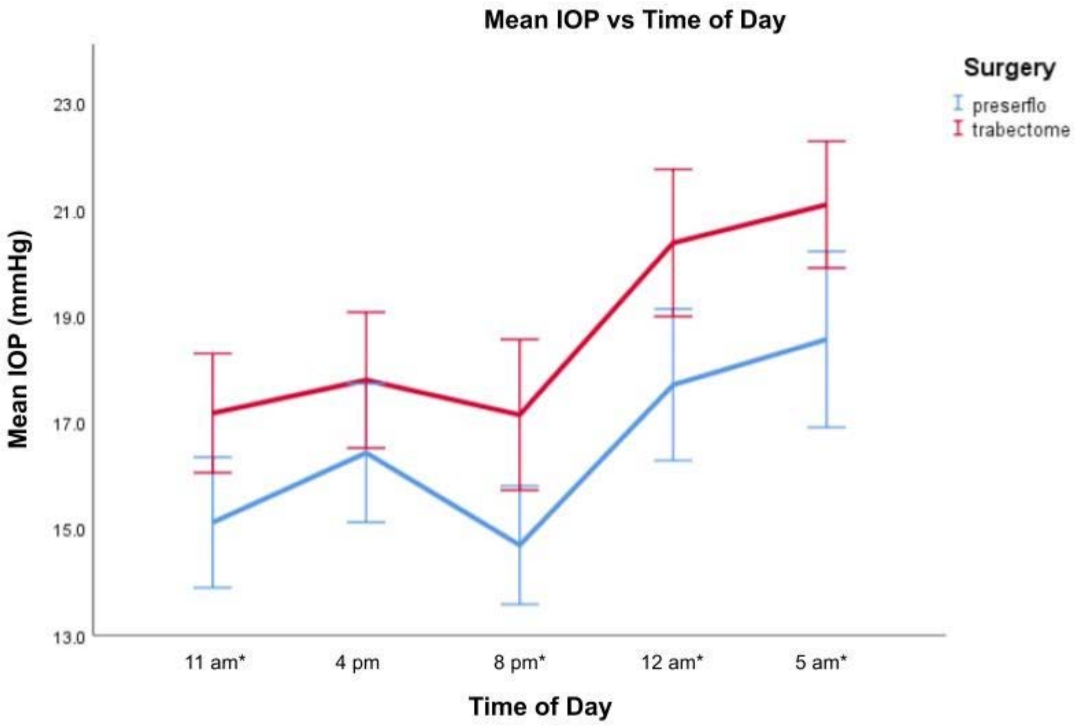

Figure 1: Mean IOP vs. Time. P patients had lower IOP values than T patients at all times. This difference was always significant except at 4 pm. Both curves mirror each other, with P and T having IOP peaks and troughs at 5 AM and 8 pm, respectively.

* $p < 0.05$. Values were plotted as mean ± SEM.