• Clinical Research •

Intraocular pressure profiles between ipsilateral surgically and contralateral medically-controlled in primary open angle glaucoma patients

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Received: 2025-04-24 Accepted: 2026-05-20

Abstract

● **AIM:** To compare the fluctuating characteristics, mean value and peak value of intraocular pressure (IOP) between medically and surgically controlled eyes in patients with primary open angle glaucoma (POAG) based on a 12-hour daytime diurnal curve (12-DDC) and water drinking test (WDT). Additionally, this study evaluated the consistency of 12-DDC outcomes measured on two separate days.

● **METHODS:** This was a cross-sectional observational study. Eligible POAG patients with unilateral medically and contralateral surgically controlled IOP *via* functional augmented trabeculectomy bleb were enrolled. Diurnal IOP was detected every 3h from 8:00 *a.m.* to 8:00 *p.m.* over two consecutive days to establish the 12-DDC. The WDT was performed subsequent to the completion of diurnal IOP measurement.

● **RESULTS:** A total of 21 POAG patients were included, with a mean age of 65.5±7.3y, predominantly male (*n*=17, 81.0%), and of Malay ethnicity (*n*=13, 61.9%). The medically controlled eyes exhibited significantly greater diurnal IOP fluctuation (4.6±1.7 mm Hg) compared with surgically controlled eyes (3.0±1.5 mm Hg, *P*=0.005). Similarly, the peak IOP derived from WDT was significantly higher in medically controlled eyes (19.6±4.1 mm Hg) than in surgical counterparts (11.2±3.4 mm Hg, *P*<0.001). A strong and significant positive correlation was identified between peak IOP values of 12-DDC and WDT. For surgically controlled eyes, 12-DDC measurements obtained on two different days showed excellent consistency at all corresponding time points, with Kappa values ranging from 0.88 to 0.95.

● **CONCLUSION:** Under the condition of consistent physiological background affecting IOP circadian variation in the same individual, surgically controlled eyes demonstrate a superior IOP profile with lower fluctuation and peak IOP compared with medically controlled eyes in POAG patients.

KEYWORDS: diurnal curve; water drinking test; intraocular pressure fluctuation; primary open angle glaucoma

DOI:10.18240/ijo.2026.09.07

Citation: Chow TS, Jaafar F, Nasaruddin RA, Lam CS, Din NM. Intraocular pressure profiles between ipsilateral surgically and contralateral medically-controlled in primary open angle glaucoma patients. *Int J Ophthalmol* 2026;19(9):1720-1730

INTRODUCTION

Primary open angle glaucoma (POAG) is defined as a chronic, progressive optic neuropathy with characteristic glaucomatous disc changes due to loss of retinal ganglion cells; alongside corresponding visual field defects and normal appearing open angles on gonioscopy in the absence of other secondary causes[1]. The prevalence of POAG worldwide and in Asia are 2.4% and 1.31%, respectively[2-3]. While various risk factors including raised intraocular pressure (IOP), advancing age, family history of glaucoma, myopia and thin central corneal thickness contribute to POAG, IOP is the only modifiable risk factor for glaucoma progression[1]. Both raised IOP and IOP fluctuation increase the risk of glaucoma progression[4].

IOP is not a fixed value, rather, it fluctuates throughout the day, following the diurnal and nocturnal rhythms related to physiological secretion of cortisol hormone, aqueous production, bodily posture and other daily activities[5]. Cheng *et al*[6] found that IOP reaches a maximum value in the early morning, decreases progressively in the day, and increases again throughout the night in POAG patients. Approximately three quarter of POAG patients have peak IOP in the early morning from 2 *a.m.* to 10 *a.m.*, and most remarkably at 6 *a.m.*[6], and this fluctuation is notably greater compared to normal eyes[7].

While the mean IOP taken during office-hour and over 24-hour were not statistically different[8], higher peak and wider IOP fluctuation were demonstrated in a 24-hour curve compared to a typical office-hour IOP curve[9]. Ideally a 24-hour IOP curve is better in providing information on the true IOP curve in patients who shows glaucoma progression despite an apparently acceptable IOP reading in the clinic[10]. However, a complete 24-hour IOP measurement is cumbersome for the majority of patients. Hence comparisons between daytime diurnal versus 24-hour IOP measurements has been evaluated.

Lat-Luna *et al*[11] found that the probability of peak IOP occurring during office hours (08:00–17:00) ranged between 64% and 80%. Ruparelia *et al*[12] evaluated the IOP value of daytime (08:00–18:00) versus 24-hour phasing in patients treated for glaucoma progression despite apparent adequate IOP control. They found that daytime diurnal curve was as effective as 24-hour IOP measurements with no statistically significant differences in mean peak IOP between clinic and both daytime and night-time readings, although mean peak IOP was significantly higher in daytime than night-time[12]. Mosaed *et al*[13] found strong correlation between supine daytime and nocturnal mean and peak IOP in glaucoma patients compared to normal. In addition, Ford *et al*[14] reported that a four-hour IOP phasing during office-hour refined the diagnosis in a third of POAG patients and led to treatment initiation in 43.8% of patients, suggesting that short protocol office hour IOP phasing (09:00–16:00) was useful in diagnosis and management of glaucoma patients.

IOP reduction is the mainstay of glaucoma treatment, either by medical, laser or surgical therapy. Medical treatment is usually the initial treatment of choice. Surgery is indicated when IOP is uncontrolled despite maximum tolerated medical therapy[3]. While medical and surgical treatment are able to reduce the mean and diurnal IOP fluctuation[15-17], diurnal mean, peak, and fluctuations in IOP were greater in medically treated patients than those who have undergone trabeculectomy[18-21].

Approximately two-third of glaucoma patients have their peak IOP outside of office hours[22-24]. However, taking 24-hour IOP measurement is inconvenient and the water drinking test (WDT) has been used to predict the diurnal peak IOP instead[18]. Kadambi *et al*[19] reported a strong correlation between diurnal peak IOP with WDT (r=0.73, P<0.001). Those with uncontrolled glaucoma showed significantly higher mean peak IOP and IOP fluctuation assessed with the WDT[25], so does medically *vs* surgically-treated advanced glaucoma patients[18,26].

Most individuals show identical IOP patterns from day to day, although approximately 10% to 20% of patients have different diurnal IOP curves over time[7]. Bozgül *et al*[27] found fair to good agreement of IOP values in two diurnal curves performed one week apart in treated POAG patients. Hatanaka *et al*[28] evaluated the repeatability of diurnal IOP curve in glaucoma patients and found strong agreement in IOP repeatability at each time point in two consecutive days.

Studies evaluating IOP fluctuations in medically and surgically controlled POAG patients recruited independent groups of patients in which interpatient variability like endogenous cortisol hormone production, might be a confounding factor[18-20]. While previous studies evaluated the office-hour IOP (08:00–17:00) and WDT between medically and surgically controlled patients in two different groups, the repeatability of IOP measured with these two methods on different days have not been studied[18,26]. Hence, this study was designed to compare the IOP profile as assessed by a two-day 12-hour daytime diurnal curve (12-DDC) and WDT between medically and surgically controlled eyes of the same POAG patient. We also assessed the repeatability of 12-DDC at each time point between the first and second day.

PARTICIPANTS AND METHODS

Ethical Approval The conduct of this study adhered to the Tenets of the Declaration of Helsinki and Malaysian Guidelines for Good Clinical Practice and was approved by the UKM Research and Ethics Committee (FF-2020-100) and National Medical Research Register (NMRR-20-1474-52751). Written informed consent was obtained from all participants.

Study Population This was a cross-sectional observational study conducted at the Ophthalmology ward in Hospital Sultanah Bahiyah from January 2020 to December 2021. Study population were adults with bilateral POAG in which one eye's IOP was medically controlled and the fellow eye has a functioning filtering bleb after trabeculectomy with good IOP control for at least three months prior to study entry. Convenience sampling was used by screening through the augmented trabeculectomy operation log from 1st January 2010 to 31st December 2019.

Medically-controlled eyes were those with IOP reading of ≤21 mm Hg with topical anti-glaucoma medications alone at study entry. Surgically-controlled POAG eyes were those with the same level of cut-off point and was controlled by a functioning augmented trabeculectomy bleb without topical anti-glaucoma medications at study entry. Inclusion criteria included patients aged 19y and above fulfilling the definitions above, and able to ambulate and be examined at the slit lamp. Exclusion criteria included adult POAG patient with IOP of >21 mm Hg in either eye, pregnancy, any corneal abnormality, patients who have undergone glaucoma laser treatment (*e.g.* laser trabeculoplasty or trans-scleral cyclophotocoagulation), patients who required topical antiglaucoma therapy after trabeculectomy, and patients with medical conditions making them unfit for WDT (*e.g.* end-stage renal failure, congestive

cardiac failure, liver failure, swallowing difficulty, malignancy and psychiatric disorder).

All subjects recruited had completed follow-up for at least for 1y prior to study entry and the adherence to medication was self-declared. Additionally, the IOP control in the previous visits had been optimal (IOP less than 21 mm Hg) and consistent. However, we still could not completely exclude the possibility of "white-coat syndrome" where adherence is increased shortly before the ophthalmologists' visit.

Each patient contributed one eye to the medically controlled and another eye to the surgically controlled group. Sample size estimation was calculated using two population means formula. Prior data indicate that the mean diurnal IOP fluctuation of medically controlled eyes was 8.6±4.2 mm Hg and in surgically-controlled eyes was 4.9±2.5 mm Hg[17]. Thus, a minimum sample size of 14 eyes per group was required to reject the null hypothesis with a probability (power) of 0.8. The Type I error associated with this test for this null hypothesis was 0.05. With an additional 30% dropout rate, the sample size was calculated to be 20 samples per group.

Patients who fulfilled the inclusion and exclusion criteria were identified and assessed in the eye clinic before recruited in the study. After written informed consent was obtained, socio-demographic profile, patient's comorbidities and ocular histories including IOP and types of antiglaucoma medications were recorded. Best corrected visual acuity (BCVA) was taken using a Snellen visual acuity and converted into logMAR values for analysis. IOP was measured with the same Goldmann applanation tonometer (Haag-Streit International, Koeniz, Switzerland), indirect gonioscopy with the Volk G-3 gonioscopy lens (Volk Optical Inc. OH, USA) and a dilated stereoscopic fundus examination with the Volk Super Field lens (Volk Optical Inc. OH, USA) and a slit lamp (Haag Streit BM 900, Koeniz, Switzerland) on the same day. The Goldmann applanation tonometer was calibrated daily according to the manufacturer's recommendations. The patients were then warded for two days for diurnal IOP measurements. Patients were told to continue their usual topical medications throughout the study.

Systemic co-morbidities in our patients range between no known medical illness to having one or a combination of diabetes, hypertension and dyslipidemia. While some systemic medications may influence IOP control, none of our patients were on any systemic medications that has significant IOP lowering effect such as carbonic anhydrase inhibitors (*e.g.* acetazolamide) and hyperosmotic agents (*e.g.* mannitol, glycerol).

Photos and grading of all the augmented trabeculectomy blebs were not collected as that success of trabeculectomy is not a function of a "filtering bleb", and that IOP maybe controlled without the presence of a clinically visible bleb. However, all patients had sufficient IOP control of less than 21 mm Hg without topical antiglaucoma drops. All the surgically treated eyes had trabeculectomy done ranging from 3mo up to 8y before study entry.

The 12-DDC consists of five IOP measurements taken at three-hour intervals from 8 *a.m.* to 8 *p.m.*[18,20]. This represents the daytime IOP profile and excluding potential nocturnal and early-morning peaks. The primary investigator (Chow TS) observed the prism mires and turned the tonometer knob, while another investigator (SBM) reads the knob and records the IOP before resetting the tonometer back to 0. This measurement was repeated three times and the average of the three readings was used in the analysis[10].

The WDT was done following previous reported protocol[29]. Patients were liquid-fasted for two hours (6 *p.m.* to 8 *p.m.*) before instructed to drink 800 mL of plain water in five minutes. IOP was measured prior to water ingestion and three times after water ingestion at 15min interval.

Data Analysis Data were recorded in Microsoft Excel Worksheet (version 2018) and data analysis was done using Statistical Package for Social Sciences (SPSS, version 26.0; IBM Corp., Armonk, NY, USA). Graphical plots were generated using SPSS version 25.0 and R software version 4.5.0. Normality was tested using Shapiro Wilk test and histogram. Continuous variables were deemed to be normally distributed if the histogram were approximately bell-shaped with skewness and kurtosis of less than 2. A *P* value greater than 0.05 in Shapiro Wilk test was considered as normal distribution. Results were expressed as mean and standard deviation (SD) for continuous variables.

IOP profiles from the 12-DDC was analysed as one-day and two-days readings. The IOP profiles consist of mean, peak (highest IOP recorded) trough (lowest IOP recorded) and fluctuation (peak minus trough IOP), analysed from one-day or two-days readings. Similar IOP profiles were also calculated after the WDT, recorded as one-day and two-days readings.

We specified a three-level hierarchical structure: repeated IOP measurements over time (Level 1) nested within eye-level groups (medical vs surgical, Level 2), which were in turn nested within patients (Level 3). IOP from 12-DDC and WDT at different time points in two days, in both groups, were analysed using a linear mixed-effects model with restricted maximum likelihood estimation. Fixed effects included the intervention (medical *vs* surgical), time (ten IOP readings from 12-DDC and six WDT readings over two days), interaction between intervention, and time; adjusting for the baseline IOP. A random intercept for each patient was specified to account for clustering of eyes within patients (within-subject correlation), and a compound symmetry or autoregressive

covariance structure was applied to the repeated measures within each eye. Estimated marginal means were compared using Bonferroni adjustment. Results were expressed with the corresponding 95% confidence intervals (95%CI). *P*-value of <0.05 was considered as statistical significance.

Agreement of IOP measured between day one and day two was assessed using intraclass correlation coefficient (ICC). ICC more than 0.75 indicate excellent agreement beyond chance, 0.40 to 0.75 indicate fair to good agreement beyond chance, and less than 0.4 indicate poor agreement beyond chance. Pearson correlation was used to examine the strength of correlation between peak IOP in 12-DDC and WDT in both groups. Correlation coefficient of 0.00–0.19 was considered as very weak, 0.20–0.39 as weak, 0.40–0.59 as moderate, 0.60–0.79 as strong and 0.80–1.00 as very strong. Agreement between peak IOP in 12-DDC and peak IOP in WDT were accessed using Bland-Altman plot.

RESULTS

A total of 21 patients were recruited in this study. The mean age was 65.5±7.3 years old and predominantly of male gender (*n*=17, 81.0%) and Malay ethnicity (*n*=13, 61.9%). In the medically controlled eyes, seven (33.3%) patients were on two (latanoprost and timolol), six (28.6%) patients on three (latanoprost, timolol and dorzolamide/brimonidine) while eight (38.1%) patients were on four glaucoma medications (latanoprost, timolol, dorzolamide and brimonidine). Approximately three quarter (76.2%) of the surgically controlled eyes had advanced or severe glaucoma compared to only about half (47.6%) of the medically controlled eyes (Table 1).

Table 1 Demographic and baseline clinical data *n* (%)

Parameters	*n*=21
Age (y), mean±SD	65.5±7.3 (range 51–76)
Gender	
Male	17 (81.0)
Female	4 (19.0)
Ethnicity	
Malay	13 (61.9)
Chinese	6 (28.6)
Indian	2 (9.5)
Number of anti-glaucoma used in medically controlled eyes	
2	7 (33.3)
3	6 (28.6)
4	8 (38.1)
Staging of glaucoma	
Medically controlled eyes	
Mild (MD>-6.00 dB)	6 (28.6)
Moderate (MD≤-6.00 to -12.00 dB)	5 (23.8)
Advanced (MD≤-12.01 to -20.00 dB)	6 (28.6)
Severe (MD≤-20.00 dB)	4 (19.0)
Surgically controlled eyes	
Mild (MD>-6.00 dB)	1 (4.8)
Moderate (MD≤ -6.00 to -12.00 dB)	4 (19.0)
Advanced (MD≤-12.01 to -20.00 dB)	11 (52.4)
Severe (MD≤-20.00 dB)	5 (23.8)

MD: Mean deviation; dB: Decibel; SD: Standard deviation.

Table 2 shows the diurnal IOP readings at different time points in two days in both medically and surgically controlled eyes. There were no significant differences in diurnal IOP profiles between the two days in medically controlled eyes, *P*>0.05. However, in surgically controlled eyes, the diurnal mean IOP between day one (9.1±2.8 mm Hg) and day two (9.5±3.1 mm Hg) showed a small but statistically significant difference (*P*=0.007). IOP profile from the WDT on both days were not significantly different in both medically and surgically controlled eyes (*P*>0.05).

Table 3 shows the IOP profiles in two days from 12-DDC measurements and WDT in medically and surgically-controlled eyes. Medically-controlled eyes showed significantly higher diurnal peak IOP in two days than surgically-controlled eyes (16.7±3.2 *vs* 10.8±3.2 mm Hg, *P*<0.001), higher mean diurnal IOP (14.7±2.2 *vs* 9.3±3.0 mm Hg, *P*=0.039) and greater diurnal IOP fluctuation (4.6±1.7 *vs* 3.0±1.5 mm Hg, *P*=0.005). Likewise, the IOP profiles from WDT showed higher mean IOP (14.7±2.2 *vs* 9.3±3.0 mm Hg, *P*<0.001), higher peak IOP (19.6±4.1 *vs* 11.2±3.4 mm Hg, *P*<0.001) and greater IOP fluctuation (8.0±5.0 *vs* 2.1±1.7 mm Hg, *P*<0.001 in medically than surgically-controlled eyes. The mean peak IOP recorded from WDT were consistently higher than 12-DDC measurements, both in medically (19.6±4.1 *vs* 16.7±3.2 mm Hg, *P*<0.001) and surgically controlled eyes (11.2±3.4 *vs* 10.8±3.2 mm Hg, *P*=0.012). The IOP from 12-DDC and WDT profiles are demonstrated in Figures 1 and 2, respectively.

The linear mixed-effects model demonstrated that higher baseline IOP was significantly associated with higher IOPs from 12-DDC [$F_{(1,35.92)}$=20.25, *P*<0.001]. An overall treatment effect was also observed, with surgically treated eyes showing significantly lower IOP reading compared to medically treated eyes (mean difference=3.58, 95%CI 2.13, 5.03) over two days [$F_{(1,25.01)}$=25.75, *P*<0.001]. In contrast, there was no significant main effect of time [$F_{(9,360)}$=0.89, *P*=0.538], indicating that mean IOP did not change substantially across the ten IOP readings from 12-DDC over two days when averaged across treatment groups. Similarly, the intervention×time interaction was not significant [$F_{(9,360)}$=0.97, *P*=0.461], suggesting that the trajectory of IOP changes over time did not differ significantly between medical and surgical treatment modalities.

Two medically treated patients (subjects 4 and 8) had IOP

Table 2 Diurnal IOP profile at different time points and IOP profile from WDT of medically and surgically controlled eyes mean±SD

Parameter	Medically controlled eyes (*n*=21)			Surgically controlled eyes (*n*=21)			*P*[a]	
	Day 1	Day 2	Δ (Day 2–Day 1)	Day 1	Day 2	Δ (Day 2–Day 1)	Medically	Surgically
08:00	15.0±3.0	15.1±2.5	0.2	8.8±3.0	9.0±2.9	0.2	0.587	0.586
11:00	14.7±3.1	15.1±2.5	0.5	9.1±2.8	9.5±3.2	0.4	0.158	0.202
14:00	14.3±2.8	14.7±2.4	0.5	9.1±2.9	9.7±3.3	0.6	0.156	0.097
17:00	14.7±2.7	14.4±2.5	-0.3	9.0±2.8	9.7±3.3	0.5	0.695	0.212
20:00	14.5±2.6	14.9±3.0	0.4	9.3±2.7	9.8±3.2	0.5	0.183	0.171
Mean IOP	14.7±2.9	14.9±3.0	0.2	9.1±2.8	9.5±3.1	0.4	0.542	0.007
Peak IOP	16.4±2.4	16.7±2.5	0.3	10.1±3.0	10.6±3.4	0.5	0.411	0.095
IOP fluctuation	2.6±1.5	3.7±1.7	+0.1	2.4±2.1	2.1±1.5	-0.3	0.800	0.531
WDT								
Baseline	14.5±2.6	14.9±3.0	0.4	9.3±2.7	9.8±3.2	0.5	0.183	0.171
15min	16.3±2.9	17.0±4.0	0.7	10.2±3.0	10.2±3.5	0.0	0.397	0.883
30min	17.2±4.0	17.0±4.0	0.8	10.0±2.9	10.4±3.2	0.4	0.129	0.248
45min	17.3±3.7	17.8±3.9	0.5	10.0±2.6	10.5±3.2	0.5	0.316	0.363
Peak IOP	17.9±3.8	18.9±4.0	1.0	10.7±2.9	10.5±3.2	0.3	0.246	0.355
IOP fluctuation	2.1±1.4	2.7±1.6	0.6	1.2±0.8	1.2±1.0	0.0	0.158	1.000

[a]*P*-value calculated using paired *t*-test for intra-eye comparison across two days. Δ: Difference between Day 2 and Day 1 values. IOP: Intraocular pressure; SD: Standard deviation; WDT: Water drinking test.

Table 3 Two days IOP profile from diurnal and WDT measurements in medically and surgically controlled eyes *n*=21, mm Hg (SD)

12-DDC for two days	Medically controlled eyes	Surgically controlled eyes	*P*[a]
Mean IOP	14.7±2.2	9.3±3.0	0.039
Peak IOP	16.7±3.2	10.8±3.2	<0.001
Trough IOP	12.6±2.1	7.8±2.5	<0.001
IOP fluctuation	4.6±1.7	3.0±1.5	0.005
WDT for two days			
Baseline IOP	14.7±2.7	9.5±2.9	<0.001
15min	16.6±3.5	10.2±3.3	<0.001
30min	17.6±3.8	10.2±3.0	<0.001
45min	17.6±3.8	10.3±2.9	<0.001
Peak IOP	19.6±4.1	11.2±3.4	<0.001
IOP fluctuation	8.0±5.0	2.1±1.7	<0.001

[a]Independent *t*-test. 12-DDC: 12-hour daytime diurnal curve; WDT: Water drinking test; IOP: Intraocular pressure.

elevation more than 30% from baseline at the third reading of WDT (from 15 to 25 mm Hg and from 16 to 24 mm Hg). Both patients were on two antiglaucoma drops, and a further two antiglaucoma drop were added and continued upon discharge and reviewed in the clinic. After removing the two subjects, the linear mixed-effects model consistently demonstrated that higher baseline IOP was significantly associated with higher IOPs from 12-DDC [$F_{(1,29.66)}$=21.38, P<0.001]. An overall treatment effect remains the same, with surgically treated eyes showing significantly lower IOP reading compared to medically treated eyes (mean difference=3.23, 95%CI 1.81, 4.65) over two days [$F_{(1,21.34)}$=22.40, P<0.001]. The main effect of time [$F_{(9,360)}$=0.89, P=0.538] and the intervention×time interaction remains not statistically significant [$F_{(9,324)}$=0.88, P=0.548; Table 4)].

Table 5 shows linear mixed-effects models examining the effects of intervention, time, the intervention × time interaction, and baseline IOP, accounting for variability within subjects in WDT. The results show that higher baseline IOP lead to higher WDT [$F_{(1,46.39)}$=12.54, P=0.001]. A significant effect of intervention was also found [$F_{(1,32.28)}$=33.06, P<0.001], indicating that the patients who received surgical intervention had significantly lower WDT compared to those receiving medical intervention (mean difference=5.20, 95%CI 3.36, 7.05). However, time [$F_{(5,176.72)}$=1.23, P=0.349] and the intervention x time interaction [$F_{(5,176.72)}$=1.19, P=0.313] did not have significant effects.

After removing Subjects 4 and 8, the model consistently demonstrated that higher baseline IOP results in higher WDT [$F_{(1,42.83)}$=24.81, P<0.001]. An overall treatment effect remains the same, with significantly lower WDT were observed in surgically treated eyes compared to medically treated eyes (mean difference=4.11, 95%CI 2.69, 5.53) over two days [$F_{(1,31.30)}$=34.65, P<0.001]. The main effect of time [$F_{(5,148.10)}$=0.62, P=0.685] and the intervention×time interaction remains not statistically significant [$F_{(5,148.10)}$=0.91, P=0.479].

Figure 3 shows correlation graphs of peak IOP obtained from the 12-DDC and WDT in medically and surgically treated eyes (Figure 3A–3B). Both graphs show strong correlation between the two IOP profiles, more seen in surgically treated eyes (correlation coefficient, r=0.731 *vs* 0.948 in medically and surgically treated eyes, respectively). When subject 4 and 8 were excluded (Figure 3C–3D), we found that the correlations were stronger in both groups (r=0.761 and 0.953 in medically and surgically treated eyes, respectively).

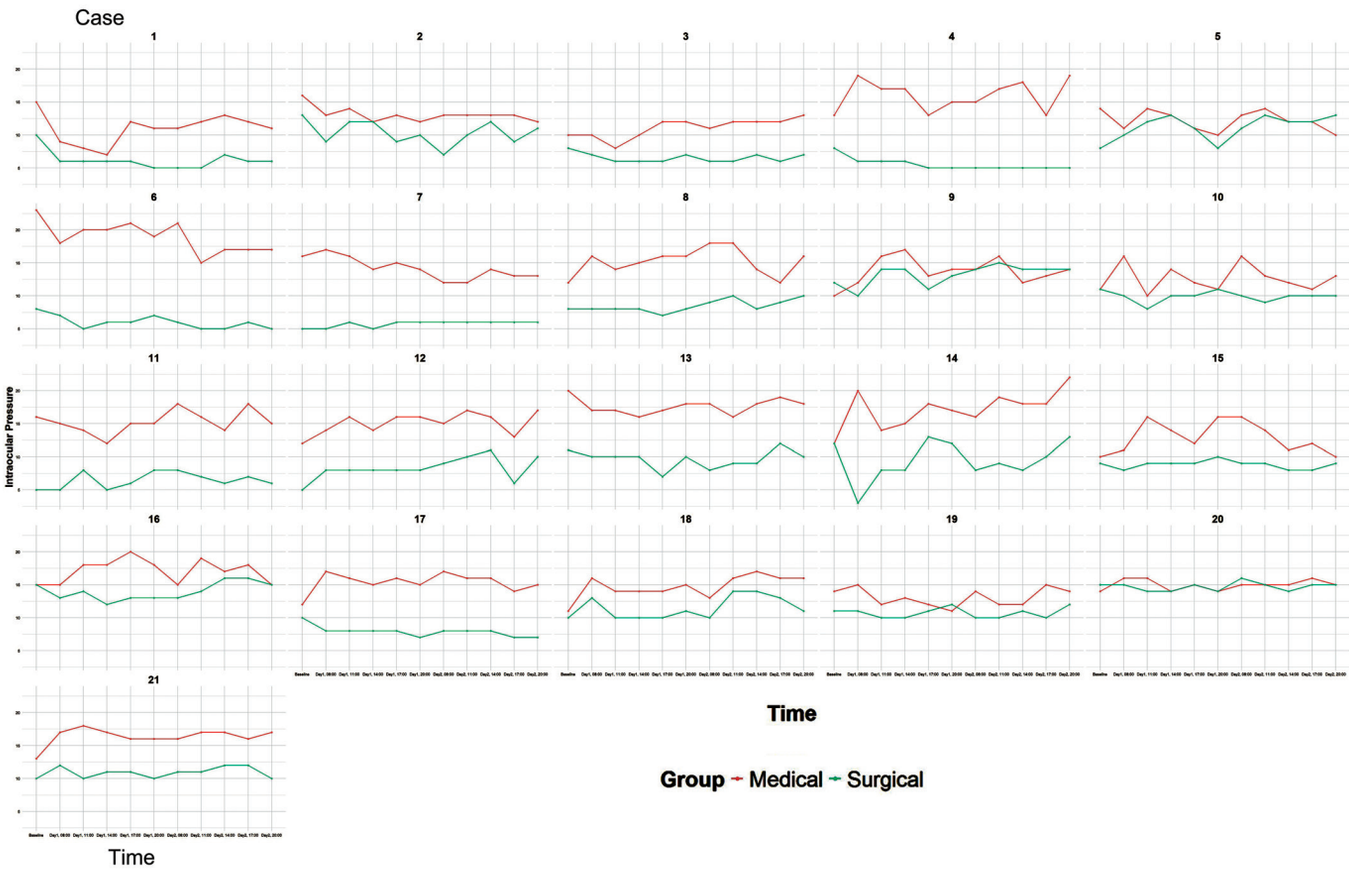

Figure 1 Intraocular pressure over time by treatment group.

Table 4 Estimates of fixed effects on diurnal intraocular pressure profile

Parameter	Model 1					Model 2				
	Estimate	Std. Error	*df*	*t*	*P*	Estimate	Std. Error	*df*	*t*	*P*
Intercept	5.21 (2.88, 7.53)	1.15	43.15	4.52	<0.001	5.37 (3.02, 7.71)	1.16	37.86	4.64	<0.001
Baseline	0.47 (0.26, 0.68)	0.10	35.92	4.50	<0.001	0.47 (0.26, 0.68)	0.11	29.66	4.62	<0.001
Medical Intervention	3.20 (1.54, 4.86)	0.82	46.25	3.88	<0.001	2.71 (1.06, 4.35)	0.82	43.07	3.31	0.002
Day 1, 08:00	-1.00 (-1.88, -0.12)	0.45	360.00	-2.22	0.027	-1.05 (-1.98, -0.12)	0.47	324.00	-2.23	0.026
Day 1, 11:00	-0.62 (-1.50, 0.27)	0.45	360.00	-1.38	0.170	-0.63 (-1.56, 0.30)	0.47	324.00	-1.34	0.181
Day 1, 14:00	-0.67 (-1.55, 0.22)	0.45	360.00	-1.48	0.139	-0.68 (-1.61, 0.24)	0.47	324.00	-1.45	0.148
Day 1, 17:00	-0.81 (-1.69, 0.08)	0.45	360.00	-1.80	0.073	-0.74 (-1.66, 0.19)	0.47	324.00	-1.56	0.119
Day 1, 20:00	-0.48 (-1.36, 0.41)	0.45	360.00	-1.06	0.290	-0.42 (-1.35, 0.51)	0.47	324.00	-0.89	0.373
Day 1, 08:00	-0.76 (1.65, 0.12)	0.45	360.00	-1.69	0.091	-0.79 (-1.72, 0.14)	0.47	324.00	-1.68	0.095
Day 1, 11:00	-0.24 (-1.12, 0.65)	0.45	360.00	-0.53	0.597	-0.26 (-1.20, 0.66)	0.47	324.00	-0.56	0.577
Day 1, 14:00	-0.10 (-0.98, 0.79)	0.45	360.00	-0.21	0.832	0.00 (-0.93, 0.93)	0.47	324.00	0.00	1.000
Day 1, 17:00	-0.29 (-1.17, 0.60)	0.45	360.00	-0.64	0.526	-0.26 (-1.19, 0.66)	0.47	324.00	-0.56	0.577
Day 1, 20:00	0	0	-	-	-	0	0	-	-	-

Model 1 consists of all subjects [-2 Restricted log Likelihood=1619.300, Akaike's Information Criterion (AIC)=1625.300, Schwarz's Bayesian Criterion (BIC)=1637.266]; Model 2 excludes Subjects 4 and 8 (-2 Restricted log Likelihood=1458.638, AIC=1464.638, BIC=1476.288).

ICC was calculated to assess the agreement of 12-DDC IOP readings measured in two days. Daytime diurnal curve values at each time point had good agreement between day one and two in medically controlled eyes (ICC range: 0.70 to 0.83) and excellent agreement in surgically controlled eyes (ICC range: 0.88 to 0.95), indicating more repeatable readings in surgically controlled eyes (Table 6).

Figure 4 shows a Bland-Altman analysis illustrating that three of 42 data points (7.14%) exceed the lower limit of agreement, indicating that the two tests may not give good agreement for some observations. In the three observations, peak IOP in WDT overestimates the peak IOP in diurnal curve by 8 mm Hg in the medically treated eyes in the Subjects 3, 4 and 8. Therefore, 95% limits of agreement (-6.17, 3.17) contain

Figure 2 Water drinking test over time by treatment group.

Table 5 Estimates of fixed effects on water drinking test

Parameter	Model 1					Model 2				
	Estimate	Std. Error	*df*	*t*	*P*	Estimate	Std. Error	*df*	*t*	*P*
Intercept	6.07 (3.22, 8.92)	1.42	53.27	4.27	<0.001	5.59 (3.19, 7.99)	1.20	53.76	4.67	<0.001
Baseline	0.45 (0.20, 0.71)	0.13	46.39	3.54	0.001	0.51 (0.30, 0.72)	0.10	42.83	4.98	<0.001
Medical Intervention	5.50 (3.37, 7.63)	1.06	52.94	5.18	<0.001	4.43 (2.65, 6.22)	0.89	62.37	4.97	<0.001
Day 1, 15min	-0.29 (-1.85, 1.28)	0.79	153.67	-0.36	0.719	-0.21 (-1.69, 1.27)	0.75	121.37	-0.28	0.778
Day 1, 30min	-0.52 (-2.00, 0.95)	0.75	182.55	-0.70	0.485	-0.53 (-1.95, 0.90)	0.72	147.09	-0.73	0.466
Day 1, 45min	-0.43 (-1.78, 0.92)	0.69	209.05	-0.63	0.532	-0.47 (-1.81, 0.86)	0.68	178.41	-0.70	0.485
Day 2, 15min	-0.24 (-1.41, 0.93)	0.59	217.82	-0.40	0.688	-0.11 (-1.30, 1.09)	0.60	196.78	-0.17	0.862
Day 2, 30min	-0.05 (-0.93, 0.83)	0.45	196.18	-0.11	0.915	-0.05 (-0.98, 0.88)	0.47	171.15	-0.11	0.911
Day 2, 45min	0	0	-	-	-	0	0	-	-	-

Model 1 consists of all subjects [-2 Restricted log Likelihood=1074.097, Akaike's Information Criterion (AIC)= 1080.097, Schwarz's Bayesian Criterion (BIC)=1090.526]; Model 2 excludes Subjects 4 and 8 (-2 Restricted log Likelihood=952.605, AIC=958.605, BIC=968.716).

only 92.86% (*n*=39/17) of the discrepancies in the peak IOP readings.

DISCUSSION

This study assessed the variations in IOP measured with 12-

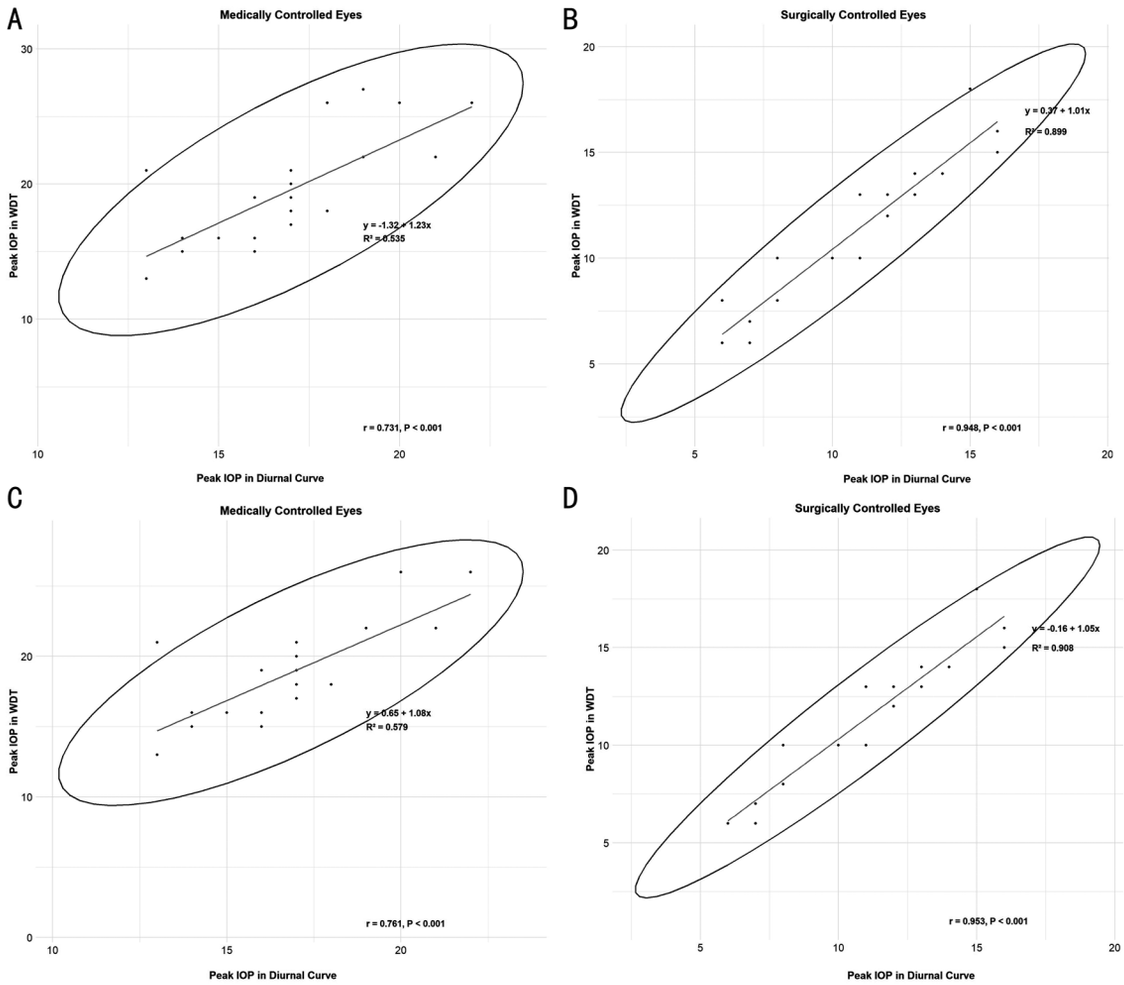

Figure 3 Correlation graphs between peak IOP in diurnal curve and peak IOP in WDT in medically controlled (A) and surgically controlled eyes (B). The correlation graphs appear similar when subject 4 & 8 were excluded in medically controlled (C) and surgically controlled eyes (D).

Table 6 Intraclass correlation coefficient for agreement of intraocular pressure at each time point between two days in 12h daytime diurnal curve

Time	Medically controlled eyes	Surgically controlled eyes
08:00	0.73	0.88
11:00	0.70	0.95
14:00	0.71	0.94
17:00	0.83	0.90
20:00	0.79	0.93

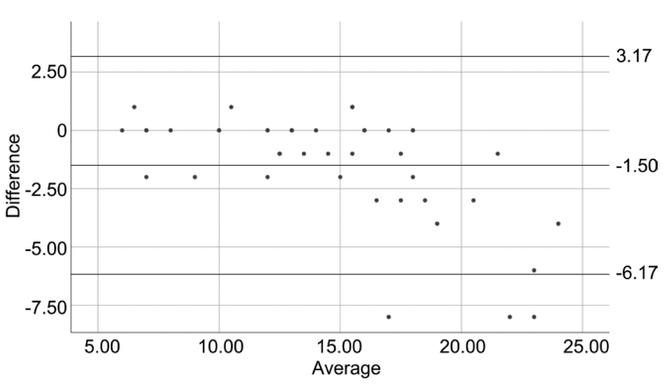

Figure 4 Bland-Altman plot of peak intraocular pressure in diurnal curve and peak intraocular pressure in water drinking test.

DDC and WDT in the same patient to investigate whether medical or surgical control of IOP can maintain a steady IOP reading, while considering the effect of intrinsic physiological factors in a glaucoma patient. This is unlike previous studies which looked at eyes from independent individuals[18-19,26]. Comparing two different eyes of the same patient will minimize the inter-patient variability which could influence the IOP measurements. Various inter-patient lifestyle factors such as exercise, resistance training, diet, cigarette smoking, alcohol or coffee intake and emotional stress may influence the IOP[30-31]. Daily physiological IOP fluctuations ranged between 3.2 to 5.0 mm Hg in normal individuals[28]. However, glaucoma patients have higher diurnal IOP fluctuations ranging from 5 to 18 mm Hg[22]. Brubaker found that aqueous production can rise during systemic challenges, but normal eyes counterbalance this with adequate outflow facility[32]. Sit's hemodynamic studies showed that during WDT, the IOP rise is mainly due to increased EVP and impaired ability of glaucomatous eyes to increase trabecular outflow facility[33]. Thus, the WDT is essentially a physiologic stress test of outflow facility, with normal showing modest changes and glaucoma eyes showing

exaggerated IOP spikes due to rigid outflow pathways. Gaboriau *et al*[34] believed that diurnal IOP fluctuation and peak IOP were risk factors for glaucoma progression. The advanced glaucoma intervention study (AGIS) found positive correlations between IOP fluctuation and glaucoma progression[4]. Medeiros *et al*[18] found that medically treated eyes have higher IOP fluctuation (3.2±1.5 mm Hg) than trabeculectomy eyes (2.2±1.7 mm Hg). This agrees with our study which showed diurnal IOP fluctuation measure in two days was higher in medically than surgically controlled eyes of the same patient. Other studies also showed that trabeculectomy results in lesser IOP fluctuation than medically treated patients[18-20].

In any case, we found that IOP fluctuations in both groups of eyes were lower than 5 mm Hg, similar to that seen in non-glaucomatous eyes[34]. Rabiolo *et al*[35] found that IOP fluctuation of 5.5 mm Hg or higher has six times greater risk of glaucoma progression at five years compared to those with IOP fluctuation of 3 mm Hg. They suggested that IOP fluctuation should be less than 5 mm Hg for patients with mild glaucoma, less than 4 mm Hg for patients with moderate glaucoma and less than 3 mm Hg for patients with advanced glaucoma[35]. Hence, in patients with higher IOP fluctuation, surgical intervention is warranted to blunt the IOP fluctuation to slow down glaucoma progression[10].

We found that daily diurnal means IOP between day one and day two in the surgically controlled eye was statistically significant, albeit small, with a difference of 0.4 mm Hg. This clinically small difference in IOP which was lesser than 1 mm Hg does not carry clinical significance in daily practice as suggested by Medeiros *et al*[18] who found out that a 1 mm Hg increment in mean IOP was associated with a 20% increased risk of glaucoma progression. The early manifest glaucoma trial (EMGT) concluded that a 1 mm Hg reduction in IOP would decrease the risk of glaucoma progression by 10%[36-37]. Likewise, a 1 mm Hg increase in IOP fluctuation would increase the odds of visual field progression by 30%[4].

WDT has been proposed to be able to predict the peak IOP in POAG patients[25]. The raised IOP seen after WDT in a glaucoma patient is due to compromised outflow facility. A challenge with 1000 mL water ingestion could not be offset by IOP-lowering treatment, unlike a functioning trabeculectomy that provide a steady pathway for aqueous drainage[26]. We found consistent IOP profiles on WDT in the two days in both groups (P>0.05) suggesting that the WDT is a reliable and consistent tool. Peak IOP was significantly higher in medically than surgically controlled eyes at each time point of the WDT, agreeing with Danesh-Meyer *et al*[26]. The IOP rise after WDT reflects the aqueous humor dynamics and outflow resistance. Previous studies have shown that surgically treated eye enhances outflow facility, thereby blunting WDT-induced IOP rise[38]. In contrast, eyes treated with medication alone may retain limited reserve in outflow capacity, explaining the higher WDT peaks in our medically controlled eyes. Our study also agrees with Medeiros *et al*[18] who found that the peak IOP from WDT was significantly higher than from 12-DDC[18]. Peak IOP was not only significantly correlated between a 24-hour diurnal curve and WDT[25], but also between modified diurnal curve and WDT[27,39]. This agrees with our finding of significant, strong positive correlation of peak IOP between 12-DDC and WDT in both medically (correlation coefficient: 0.715; P<0.001) and surgically controlled eyes (correlation coefficient: 0.943; P<0.001). We therefore conclude that the WDT is a convenient tool to predict the peak IOP from diurnal IOP phasing which requires hospital admission.

We found excellent agreement of IOP readings at each time point of 12-DDC between the two days, more so in the surgically-controlled than medically-controlled eyes. This is similar to the study by Hatanaka *et al*[28] who found reproducible diurnal IOP readings with excellent agreement measured in two days in POAG patients. Even when the diurnal curves were taken one week apart, fair to good agreement was found at each time point in treated POAG patients[28]. Our findings suggest that a single 12-DDC may adequately represent the IOP profile in postoperative patients who are stable for at least three months following trabeculectomy. However, for patients whose IOP is not controlled with medication, or in those with unexplained progression, a full 24-hour phasing remains essential to capture nocturnal peaks. In patients who cannot ingest a bolus of water for whatever reason, measuring diurnal curve in one day is adequate to show the IOP profile. Alternatively, patients can be scheduled for clinic visits at different time of the day for establish the IOP curve.

Several limitations should be acknowledged. First, the relatively small sample size (21 pairs) reduces generalizability, as confirmed by post-hoc power analysis showing <80% power for fluctuation differences. We recalculated the study power on our actual data which gave a true IOP difference of 4.6 mm Hg instead of 8.6 mm Hg[17] in medically treated eyes, giving only about 32% of power. Similarly, with the true IOP difference of 3.0 mm Hg instead of 4.9 mm Hg[17] in surgically treated eyes, the power of our study is about 40%, well below the desired 80%. Second, central corneal thickness was not measured, which may have introduced small variability in IOP readings. Third, the potential contralateral effect of prostaglandin analogues (PGA) and beta-blocker (BB) on the fellow eye may have lowered IOP readings in surgically controlled eyes[40-41]. In all our patients, PGA was dosed once at night and BB was dosed twice daily, both of which have been shown to significantly reduce the IOP in the contralateral eyes by 2.3–

2.7 mm Hg and 3–6 mm Hg in PGA and BB treated patients respectively in other studies[39-40]. Fourth, lifestyle factors such as sleep position, caffeine intake, and daily activity were not recorded, and continuous IOP monitoring with a contact lens sensor was not performed, leaving nocturnal fluctuations unaccounted for. Lastly, the study population consisted predominantly of Malay males, limiting external validity.

In conclusion, surgically controlled eyes show better IOP profile compared to medically-controlled eyes of the same patient, seen both from 12-DDC and WDT, suggesting that a well-functioning augmented trabeculectomy provides better IOP control in POAG patients. WDT may be used as a reliable time-saving alternative to predict peak IOP and IOP fluctuation in POAG patients. Single day diurnal curve is sufficient to represent everyday diurnal curves of patients.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Miss Chien Joo Lim from the Clinical Research Center, Sarawak General Hospital, and Miss Shirlie Chai from the Pharmacy Department, Miri Hospital, for helping with the statistical analysis; and the Director General of Health, Ministry of Health Malaysia for his permission to publish this manuscript.

Authors' Contributions: Chow TS: proposal development, data collection, writing- original draft; Jaafar F: supervision, data collection; Nasaruddin RA: writing-review and editing; Lam CS: writing-review and editing; Din NM: conceptualization, proposal development, supervision, writing-review and editing.

Data Availability Statement: Data will be available on request.

AI-Generated Content Disclosure: None of the contents have been AI-generated.

Conflicts of Interest: Chow TS, None; **Jaafar F,** None; **Nasaruddin RA,** None; **Lam CS,** None; **Din NM,** None.

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