THE EFFECT OF 24-HOUR INTRAOCULAR PRESSURE FLUCTUATION ON GLAUCOMA PROGRESSION IN PRIMARY ANGLE CLOSURE GLAUCOMA

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DISCLAIMER

I hereby certify that the work in this dissertation is my own except for the quotations and summaries which have been duly acknowledged.

Dated: 28th May 2015

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ABSTRAK

Tajuk

Kajian 24-Jam Fluktuasi Tekanan Mata dalam Glaukoma Primer Sudut Tertutup Maju dan Tidak Maju

Pendahuluan

Glaukoma Primer Sudut Tertutup (GPST) merupakan penyakit yang kerap didiagnosa di kalangan populasi Asia. Bangsa Melayu adalah antara kaum yang dikenalpasti menghidapi GPST dengan prevalens sebanyak 0.12% hingga 2.5%. Sehingga kini, tekanan mata adalah satu-satunya risiko faktor yang boleh dikawal. Dua subkomponen tekanan mata iaitu purata nilai tekanan mata yang tinggi dan nilai jurang turun naik tekanan mata yang luas merupakan faktor penting penyebab kemajuan GPST.

Objektif

Mengenalpasti dan membandingkan purata nilai purata tekanan mata, nilai puncak, nilai dasar, dan nilai turun naik dalam masa 24 jam, di kalangan mata GPST maju dan tidak maju.

Metodologi

Satu kajian keratan rentas telah dijalankan di Hospital Universiti Sains Malaysia, Kelantan yang mana melibatkan seramai 25 pesakit dengan 50 mata yang telah didiagnosa GPST. Mereka dibahagikan kepada 2 kumpulan iaitu mata maju dan mata tidak maju. Kesemua mereka dimasukkan ke dalam wad selama 24 jam. Tekanan mata diukur sebanyak 6 kali selang masa 4 jam, iaitu pada 0800, 1200, 1600, 2000, 2400, dan 0400. Tonometer Aplanasi Goldmann digunakan untuk semua pengukuran tekanan mata. Analisis statistik yang digunakan adalah ujian 'independent t', ujian 'Mann-Whitney U', dan ujian 'Fisher's exact'.

Keputusan

Keputusan kajian mendapati bahawa majoriti dari kumpulan mata GPST maju menunjukkan nilai tekanan mata puncak pada sebelah malam dengan nilai tekanan mata dasar pada sebelah petang, manakala kumpulan mata tidak maju menunjukkan nilai tekanan mata puncak pada sebelah pagi dan nilai tekanan mata dasar pada sebelah malam. Pada selang masa 4 jam, kumpulan mata maju mempunyai nilai purata tekanan mata, nilai puncak, dan nilai dasar yang lebih rendah tetapi jurang nilai turun naik yang lebih luas. Dalam masa 24 jam, tiada perbezaan yang signifikan pada semua variasi tekanan mata. Keseluruhannya, julat nilai purata tekanan mata adalah antara 13.7 ke 15.3 mmHg ($p = 0.202$), julat nilai purata tekanan mata puncak adalah antara 17.0 ke 18.0 mmHg ($p = 0.285$), julat nilai purata tekanan mata dasar adalah antara 11.0 ke 13.0 mmHg ($p = 0.151$), dan julat nilai turun naik tekanan mata adalah 6.0 mmHg ($p = 0.803$).

Kesimpulan

Hasil kajian menunjukkan tiada perbezaan yang signifikan pada semua variasi tekanan mata dalam masa 24 jam dalam kedua-dua kumpulan mata GPST maju dan tidak maju. Walaupun julat nilai turun naik tekanan mata adalah sama dalam masa 24 jam, kumpulan mata maju menunjukkan jurang nilai turun naik tekanan mata yang lebih luas pada selang masa 4 jam.

ABSTRACT

Title

The Effect of 24-Hour Intraocular Pressure Fluctuation on Glaucoma Progression in Primary Angle Closure Glaucoma

Introduction

Primary Angle Closure Glaucoma (PACG) is a common glaucoma type in Asian population. Malays are among affected races in South East Asian with PACG prevalence of 0.12% to 2.5%. To date, intraocular pressure (IOP) is the only modifiable glaucoma risk factor. Two IOP subcomponents; the higher mean IOP and the wider IOP fluctuations are currently being looked upon as important predictors of glaucoma progression.

Objectives

To determine and compare the 24-hour overall mean IOP, mean IOP peak, mean IOP trough, and IOP fluctuation in progressed and non-progressed PACG.

Methodology

A cross-sectional study was conducted in Hospital Universiti Sains Malaysia, Kelantan involving 25 patients with 50 eyes diagnosed with PACG. They were grouped into progressed PACG (11 eyes) and non-progressed PACG (39 eyes). AGIS scoring system was used to determine the progression group. All patients were admitted for 24 hours period. Six IOP measurements were performed at 4-hour time points; at 0800, 1200, 1600, 2000, 2400, and 0400. Goldmann Applanation Tonometer (GAT) was used for all IOP measurements. Statistical analysis used were independent t test, Mann-Whitney U test, and Fisher's exact test.

Results

Majority of progressed eye group of PACG exhibited patterns of night peak with afternoon trough, while non-progressed eye group showed patterns of morning peak with night trough. At 4-hour time points, the progressed eye group had lower mean IOP, mean peak IOP, and mean trough IOP but wider mean IOP fluctuation. Over 24 hour period, there was no significant difference for all IOP variables in both groups. The 24-hour mean overall IOP mean range was 13.7 to 15.3 mmHg ($p = 0.202$), overall mean IOP peak range was 17.0 to 18.0 mmHg ($p = 0.285$), overall mean trough range was 11.0 to 13.0 mmHg ($p = 0.151$), and overall mean IOP fluctuation was 6.0 mmHg ($p = 0.803$).

Conclusion

Progressed and non-progressed eye group of PACG demonstrated no significant difference in terms of all IOP variables over 24-hour period. Despite similar overall mean IOP fluctuation during 24-hour period, the progressed eye group had wider mean IOP fluctuation than the non-progressed eye group at 4-hour time points.

CHAPTER 1
INTRODUCTION

1.0 INTRODUCTION

1.1 Glaucoma

Glaucoma is a progressive optic neuropathy disease with blinding potential. It commonly refers to a group of disorders that exhibit optic nerve head cupping and characteristic visual field loss. Glaucoma in Greek means clouded or blue-green hue, which Hippocrates first used to describe blindness in advanced years associated with pupil's glazed appearance (Fronimopoulos & Lascaratos, 1991).

The understanding of pathogenesis of glaucoma involves 2 theories; mechanical and vascular mechanism. These 2 concepts were introduced in mid-nineteenth century. Muller suggested the mechanical theory in 1858, while von Jeager proposed the vascular theory in the same year (Pinazo-Duran *et al.*, 2011). Elevated IOP is responsible for optic nerve compression and death of the neurons in the mechanical mechanism, where as vascular dysregulation affecting ocular perfusion pressure that leads to optic atrophy is postulated to play the main role in the vascular mechanism. Both eventually share common final sequel: progressive visual field defect hence blindness.

Global impact of glaucoma is devastating. It is costly from both human and economic perspectives. Glaucoma affects quality of vision as well as quality of life. WHO demonstrated that approximately 5.2 million blindness attributable to glaucoma, which represented 15% of total burden of world blindness (Thylefors and

Negrel, 1994). In Malaysia, glaucoma emerged as the fifth leading cause of blindness and low vision according to National Eye Survey 1996 (Zainal *et al.*, 2002). Local survey showed that it was the second leading cause of blindness in urban population after cataract (Reddy *et al.*, 2008). In other South East Asia countries, glaucoma is the second cause of blindness in China, Thailand and Singapore, and the third cause of blindness in Philippines (Rojanapongpun, 2005).

Visual impairment secondary to glaucoma may cause difficulties in mobility, driving and social interactions (Coleman, 1999). Glaucoma patients are also likely at higher risk to involve in motor vehicle collision owing to their restricted visual field (McGwin *et al.*, 2005). Blind glaucoma patients are dependent of activity daily living, thus contribute further to burden people around them, especially the family and relatives. In terms of nation economic burden, cost effectiveness on medications and surgeries is among the issues apart from expenditures spent on regular visits monitoring and compliance, screening and investigation tools purchases, and losing human resource from blindness.

WHO has classified glaucoma into 3 groups: congenital (genetic or development), primary glaucoma (open angle or angle closure), and secondary glaucoma. All these have different etiologies and course of treatment. Worldwide, the distribution of PACG and POAG is both geographically and ethnically variable. PACG is common in Asia, while POAG predominates in other parts of continents. PACG was estimated to blind more people than POAG (Foster *et al.*, 2000).

Despite the alarming figures of glaucoma cases observed each year, the vision loss usually can be delayed with early detection and appropriate management. Factors influencing the increase in glaucoma prevalence are varied and not been fully understood. Among these, IOP remains the most prominent and consistent glaucoma risk factor as concluded by 4 major studies: Ocular Hypertension Treatment Study (OHTS), Early Manifest Glaucoma Trial (EMGT), Advanced Glaucoma Intervention Study (AGIS), and Collaborative Normal Tension Glaucoma Study (CNTG) (Coleman *et al.*, 2004; Bengtsson *et al.*, 2007; Caprioli & Coleman, 2008; Anderson, 2003).

As it is the only modifiable risk factor, lowering IOP has been a mainstay focus of glaucoma treatment, either by pharmacologically, or surgically, or both. The results of the AGIS have proven that lowering IOP prevents further optic nerve damage by maintaining targeted average IOP 12-14 mmHg, as signified by no visual field progression over the 7 years course compared to those who had higher IOP. But keeping IOP at low level is just inadequate. There is other issue beyond the target IOP level to answer why many patients still progress despite achieved target IOP at intervisits. The idea of "IOP stability" concept hence was introduced and frequently emphasized in current studies. Two IOP subcomponent; the mean IOP and IOP fluctuations are now being looked upon as another important predictors of glaucoma progression. Therefore, stabilizing both parameters need to be included and tailored in the management strategy (Asrani *et al.*, 2000; Singh & Shrivastava, 2009).

1.2 Angle Closure Glaucoma

1.2.1 Epidemiology of Angle Closure Glaucoma

WHO data in 1993 shows that about 23 million individuals had confirmed glaucoma while glaucoma suspects reached around 105 million persons. Out of this figure, POAG affects 13.5 million cases and PACG accounts for 6 million people, both seen in subjects over age 40 (Thylefors & Negrel, 1994). The prevalence of glaucoma is increasing and by year 2020, an estimated 79.6 million people worldwide are expected to develop glaucoma (Quigley & Broman, 2006). Population-based data from South East Asia Glaucoma Interest Group Meeting (SEAGIG 2004) showed POAG has higher rate than PACG in Malaysia, Singapore and Thailand, with reverse order for Philippines (Rojanapongpun, 2005). However data for PACG in Asia have increased in past few years (See *et al.*, 2011). Cedrone and colleague analyzed a series of 56 studies on glaucoma prevalence, and concluded that PACG is commonest among Asian ethnic groups whereas POAG is more common in African origin and white population (Cedrone *et al.*, 2008). In Malaysia, ratio of POAG to PACG was approximately 1.5:1.0 (Rojanapongpun, 2005). Prevalence of PACG in adult Asians was 0.75% and more than half of them were female (Cheng *et al.*, 2014). It increases with age (Foster et al., 2000). Malays are among affected races in South East Asian with PACG prevalence of 0.12% to 2.5% (Shen *et al.*, 2009; Bourne *et al.*, 2003; Casson *et al.*, 2007). In a hospital-based study in Malaysia, the prevalence of PACG was once reported 30.0% and the incidence of PACG was once reported 0.86% with Malays accounted one third of the 3 major races (Selvarajah, 1998).

1.2.2 Classification of Angle Closure

According to International Society Geographical & Epidemiological Ophthalmology definition, glaucoma with angle closure is classified and staged into Primary Angle Closure Suspect (PACS), Primary Angle Closure (PAC), and Primary Angle Closure Glaucoma (PACG). In PACS, narrow angle is the only abnormality present. It may progress to PAC with manifested high IOP and other findings, but without glaucomatous optic disc changes. PACG hence, reserved for PAC in presence of glaucomatous optic neuropathy with or without visual field loss (Foster *et al.*, 2002).

1.2.3 Mechanism of Angle Closure

There are 4 main mechanisms of angle closure, each of which may co-exist with another: pupil-block (block at level of iris), anterior non pupil-block that includes plateau iris (block at level of ciliary body), lens-related (block at level of lens), and retrolenticular (block posterior to lens) (Ritch & Lowe, 1996). Identifying mechanism responsible for angle closure is important in addition to establish the disease stage. It is helpful in guiding the appropriate choice of treatment. The two schemes (staging and mechanism) therefore should be used in parallel when managing an angle closure case.

1.2.3.1 Assessment of anterior chamber depth

Anterior chamber depth can be assessed qualitatively using Smith's method and Van Herrick's method. Both use slit lamp biomicroscope. Smith's method estimates the central anterior chamber depth, while Van Herrick's method approximates the peripheral (Smith, 1979; Van Herick *et al.*, 1969). Another method of assessment is by using A-scan, which is quantitative.

1.2.3.2 Assessment of anterior chamber angle

Gonioscopy is the commonest procedure in assessing anterior chamber angle. It uses contact goniolens together with slit lamp biomicroscope. The angle was subsequently graded using Shaffer system, which consists of 5 grades from 0 to 4 (Fellman *et al.*, 2012). Apart from gonioscopy, cross-sectional images of anterior chamber structures, specifically the angles also can be generated using Optical Coherence Tomography (OCT) and Oculus Pentacam. These images can be used to take measurements of the angle.

1.2.4 Risk factors of Angle Closure Glaucoma

Assessing risk factors in a potential angle closure glaucoma patient is essential. Mass screening can be narrowed down to a selected population. It also aids in predicting the incidence of acute attack and long-term glaucoma progression. Ocular biometry risk factors are narrow drainage angles, shorter axial length, shallow anterior chamber depth, lens thickness and position, and thicker iris. Meanwhile, the systemic

risk factors include age of 40 years and above, female gender, ethnicity of Inuit or East Asian, genetic, and environmental such as climate monsoon (Ameraginghe, 2008) (Ch'ng *et al.*, 2013). Amongst these, shallow anterior chamber depth is the leading anatomical risk factor with Chinese ethnicity has the most significant anterior chamber and angle anatomy difference.

1.2.5 Clinical Presentation of Angle Closure Glaucoma

Classic acute primary angle closure (APAC) episode usually brought patient earlier to ophthalmologist due to intolerable eye pain and worsened vision. In such case, IOP reading almost always high and complicated with injected conjunctiva, epithelial edema, shallow anterior chamber, mid-dilated pupil, iris ischemia, and hazy fundal view. However, it is also not uncommon to diagnose cases of advanced PACG at first visit. Painless typical glaucomatous visual field loss and characteristic glaucomatous disc cupping are the common late signs. Nevertheless, both acute and chronic stages are often seen overlapping in the clinical presentation.

1.2.6 Management of Angle Closure Glaucoma

Diagnosis of angle closure glaucoma is mainly clinical and should be made with careful slit lamp examination, which include IOP measurement and gonioscopy. Further investigations may be required such as visual field, ultrasound biomicroscopy, optic nerve head analysis by optical coherence tomography, and central cornea thickness. The aim of treating PAC and PACG is to eliminate the underlying pathophysiological mechanism and to reduce IOP. This can be achieved

medically and/or surgically. Medical treatment consists of laser peripheral iridotomy or iridoplasty, and IOP lowering agents that can be delivered topically, per oral or intravenous. They are available from classes of beta blocker, adrenergic agonist, prostaglandin analog, carbonic anhydrase inhibitor, parasympathomimetic, fixed combination medications, and hyperosmotic agents. Surgically, options include trabeculectomy, lens extraction, combined lens extraction with trabeculectomy, and glaucoma drainage device implantation (See *et al.*, 2011). In case of acute PAC, rapid IOP reduction and control is needed to limit optic nerve insult, hence preventing long-term glaucoma progression.

1.3 Intraocular Pressure

1.3.1 Concept of Normal Intraocular Pressure

Intraocular pressure is determined by balance between aqueous production and outflow. Goldmann equation clearly described the relationship between the IOP and the components of aqueous humor dynamics: Po = (F/C) + Pv ; Po is the IOP in millimeters of mercury (mmHg), F is the rate of aqueous formation, C is the facility of outflow, and Pv is the episcleral venous pressure (American Aceademy of Ophthalmology, 2011). Mean IOP of 15.5 mmHg, with a standard deviation of 2.6 mmHg have been reported in large-scale population-based epidemiologic studies. Therefore “normal” IOP is defined as 2 standard deviations above or below the mean IOP, or approximately 10-21 mmHg. IOP of outside this range is considered pathological and abnormal (Alimuddin, 1956).

1.3.1.1 Aqueous humour formation

There are two steps of aqueous humour production. Firstly, plasma filtrate is formed within the stroma of ciliary body. Secondly, aqueous humour is formed from this filtrate across the blood-aqueous barrier. The aqueous humour subsequently secreted into posterior chamber through two mechanisms, in which active secretion predominates than passive secretion. Active secretion by non-pigmented ciliary epithelium involves metabolic process that is Na+/K+ ATPase pump dependent, whereas passive secretion by ultrafiltration and diffusion are dependent on capillary hydrostatic pressure, oncotic pressure and IOP level (Kanski & Bowling, 2011)

1.3.1.2 Aqueous humour outflow

Aqueous humour flows from the posterior chamber into the anterior chamber via pupil. From there, it exits the eye by two different routes, either through trabecular or uveoscleral. Trabecular route is also known as conventional route as it accounts for approximately 90% of aqueous outflow. From trabecular, aqueous humour then enters Schlemm canal and is subsequently drained by episcleral veins. The remaining 10% will be channeled into uveoscleral route (Kanski & Bowling, 2011).

1.3.2 Measurement of Intraocular Pressure

IOP in general, is indirectly calculated by measuring the amount of force that is required to flatten a section of cornea. Various IOP measurement tools have been developed over decades. Basically, there are 4 types of tonometry available to date: applanation tonometry (Goldmann tonometry, Perkins tonometry, Ocular Response Analyzer, air puff tonometry), indentation tonometry (Schiotz tonometer, Pneumotonometer, Tono-Pen), rebound tonometry (ICare), and Pascal Dynamic Contour Tonometer. Amongst these, Goldmann applanation tonometry remains a gold standard in IOP taking, despite its shortage on numerous ocular biomechanical factors that can erroneously lead to overestimation or underestimation of IOP measurement. Furthermore, it is known that repeated applanation testing using Goldmann-type tonometers might decrease IOP in ipsilateral eye, which cannot fully be explained (Moses, 1961). With emergence of newer inventions, IOP measurements are no longer affected by ocular biomechanical properties that are significant in Goldmann tonometry measurement. Recent development of more

advanced invention using contact lens sensor (SENSIMED Triggerfish), allows short-term reproducibility of continuous 24-hour IOP monitoring (Mansouri *et al.*, 2012). Studies on this device are currently on going in evaluating its clinical safety, tolerability and efficacy.

1.3.3 Factors Affecting Intraocular Pressure Measurement Accuracy

IOP measurements in clinical setting may be affected by numerous ocular biomechanical factors of cornea and tear film such as central cornea thickness, cornea curvature, corneal rigidity and hydration, cornea scarring, thin or thick of tear film (Whitacre & Stein, 1993). False elevated IOP reading may be contributed mechanically such as pressure from a finger on the eyelid while taking the measurement, in squeezed eyes, breath holding and Valsalva maneuver by the patient during measurement. The choice of IOP measurement tools hence needs consideration in different situations.

1.3.4 Goldmann Applanation Tonometer

Goldmann Applanation Tonometer (GAT) is the gold standard of IOP measurement. It requires fluorescein dye to highlight tear film. The force of flattening cornea area of 3.06 mm diameter is measured. The tonometer uses split-imaged prism that generates image of tear meniscus, which divides into superior and inferior arc. When both arcs are aligned in such that their inner margins just touch, IOP is taken. As wide contact surface area is needed for the measurement with fluorescein dye, local

anesthetic eye drop is essential for patient's comfort. GAT needs calibration at frequent interval.

1.3.5 Intraocular Pressure Circadian Rhythm in Primary Angle Closure Glaucoma

Many agreed that IOP fluctuate in rhythmical circadian pattern and eyes with glaucoma were observed to have greater fluctuation. Circadian rhythm of IOP comprises the diurnal and nocturnal curves. Pattern of IOP diurnal curve varies in different types of glaucoma (Wilensky, 1991). IOP circadian rhythm in PACG has been compared to POAG and normal eyes over 24-hour period in few studies. In PACG, documented average IOP peak was 25 mmHg, range of IOP was 12-32 mmHg, and diurnal fluctuation was 6-8 mmHg (Sihota *et al.*, 2005). The 3 parameters did not significantly differ when comparing PACG to POAG, however significant lower values were observed in normal eyes. In PACG and PAC eyes, higher diurnal IOP fluctuation of 4-5 mmHg has been observed in comparison to PACS patients and normal controls (Baskaran *et al.*, 2009). In PACG, IOP peak was observed not only in afternoon, but also at night or early morning, midnight and morning (Sihota *et al*, 2005; Leydhecker, 1976; Shapiro & Zauberman, 1979). Greater IOP dependence was observed for optic nerve damage in PACG than POAG (Gazzard *et al.*, 2003). A diurnal fluctuation of more than 6 mmHg with IOP 21 mmHg was never seen in normal eyes and should be considered pathological if present.

1.3.6 Factors Affecting Intraocular Pressure Fluctuation

IOP physiologically is in a state of flux and therefore it varies in short and long term (Kirstein *et al.*, 2011). There are many factors affecting physiological IOP, and this may exaggerate in glaucoma individuals. Diurnal variation is one of many other factors contributing to short-term fluctuations, apart from body posture, exercise, eye movements, Valsalva maneuvers and various food or drugs consumption. IOP has been observed to have nocturnal variation (Liu, 1998) and most IOP peaks occur outside office hours (Mosaed, 2005). Postural changes have significant effect on IOP (Bill, 1978; Baskaran *et al.*, 2006). On the other hand, long-term fluctuations have been associated with advanced age, season, diet, systemic blood pressure, race, ethnic origin, and body weight. Persistent accumulative short-term variation may lead to long-term fluctuation. It is believed that long-term fluctuation of IOP may be a risk factor for glaucoma progression (Bergea *et al.*, 1999; Asrani *et al.*, 2000; Nouri-Madhavi *et al.*, 2004).

1.3.7 Role of Intraocular Pressure Fluctuation in Glaucoma Progression

At present, recent data suggests that there are more risk factors to consider in glaucoma rather than IOP measurement taken in clinic during office-hour visit. Being an inconstant value, IOP varies considerably and respond to short as well as long-term influences. Despite that, a pattern to IOP variation over 24 hours course seems to be observed in which a given individual has reasonable amount of consistency and reproducibility (Wilensky, 1991). Other diurnal variation in the

body, such as cortisol production, was thought to be related to this pattern (Schwartz, 1966).

Role of 24-hour IOP, thus control plays an important aspect in glaucoma management. Its implication as a risk for progression demonstrated by fluctuation as observed in many published studies. IOP fluctuations have been shown to increase risk of visual field progression in treated eyes (Asrani *et al.*, 2000). AGIS reported that over 7 years, IOP fluctuation of 1 mm Hg increased risk of progression by 30% (Nouri-Mahdavi *et al.*, 2004). Diurnal and nocturnal IOP measured in habitual position provide new insights, although accuracy of measurement technique made is questionable. Treatments have different effects on diurnal and nocturnal IOP. Newest class of glaucoma medications; the prostaglandin analogues, claimed medically lower the IOP, and stabilize the IOP circadian rhythm at the same time. Studies on 24-hour and nocturnal efficacy of glaucoma medications are ongoing (Orzalesi *et al.*, 2000; Liu *et al.*, 1999; Sit *et al.*, 2006; Liu *et al.*, 2005). Current 24-hour IOP monitoring in sleep laboratory is a research tool. Clinical practical 24-hour monitoring of IOP could increase our ability to understand glaucoma progression and its treatment effects.

1.3.8 Monitoring of Intraocular Pressure Fluctuation

There are several indications where 24-hour IOP measurement should be evaluated: in glaucomatous patients with progressive damage whenever single IOP reading is within ‘normal’ range; in patients with ocular hypertension where baseline IOP levels is required to monitor the condition; and in cases where incidental suspicious glaucomatous disc without apparent IOP elevation (David *et al.*, 1992).

1.4 Rationale Of Study

Glaucoma is an unpreventable disease of occurrence, whereby management is aimed to delay and retard its progression. As IOP is the known modifiable risk factor, reducing it has become our mainstay focus of treatment. Wide IOP fluctuation has been demonstrated to be a risk of glaucoma progression. Hence it is essential to determine and compare pattern of 24-hour IOP fluctuation in PACG patients in our local population thus its effect on visual field progression within both groups. This study hopefully will provide an insight on strategizing an aggressive target on lowering mean intraocular pressure, thus potentially minimize and narrow the intraocular fluctuation at identified specific hour.

CHAPTER 2
STUDY OBJECTIVES

2.0 STUDY OBJECTIVES

2.1 General Objectives Of This Study

To study the pattern of 24-hour intraocular pressure fluctuation in primary angle closure glaucoma patients.

2.2 Specific Objectives Of This Study

1. To determine the 24-hour overall mean intraocular pressure, overall intraocular pressure mean peak, overall intraocular pressure mean trough, and overall intraocular pressure fluctuation in progressed eye group of PACG

2. To determine the 24-hour overall mean intraocular pressure, overall intraocular pressure mean peak, overall intraocular pressure mean trough, and overall intraocular pressure fluctuation in non-progressed eye group of PACG

3. To compare the 24-hour overall mean intraocular pressure, overall intraocular pressure mean peak, overall intraocular pressure mean trough, and overall intraocular pressure fluctuation between progressed and non-progressed eye group of PACG

CHAPTER 3
METHODOLOGY

3.0 METHODOLOGY

3.1 Study Design

This is a comparative cross sectional study.

3.2 Research Setting

3.2.1 Study Research Population: Patients diagnosed with PACG, attending regular visits in Ophthalmology Clinic, Hospital Universiti Sains Malaysia

3.2.2 Period of Study : May 2012 till May 2014

3.2.3 Place of Study : 1. Ophthalmology Clinic, Hospital Universiti Sains Malaysia
2. Ophthalmology Ward, 2 Utara, Hospital Universiti Sains Malaysia

3.3 Sampling And Sample Size

3.3.1 Sampling Method

PACG patients in HUSM who fulfilled inclusion criteria and consented to participate in the study were recruited.

3.3.2 Sample Size

Sample size was calculated using PS ("Power and Sample Size") software, version 3.0.43 . t-test formula with independent design was applied.

α : level of significance

SD or σ : standard deviation of mean IOP

DD or δ = the smallest, clinically meaningful difference in mean IOP that is desired to be detected

m : ratio between progress and stable

n : sample size

$\alpha = 0.05$

Power of study = 0.8

SD or $\sigma = 1.24$ (reference: Baskaran *et al.*, 2009)

DD or $\delta = 1.0$

$m = 1$

$n = 25$

n + 10% (expected dropout) = 25 + 3

Total of 28 eyes per arm are required for this study

Total of 56 eyes are required for this study

3.4 Selection Criteria

3.4.1 Inclusion Criteria

i) Age more than 40

ii) Patients with established diagnosis of PACG

iii) At least 2 years of glaucoma clinic follow-up

3.4.2 Exclusion Criteria

i) History of penetrating keratoplasty or filtering surgery

ii) History of cataract surgery within previous 6 months

iii) Patients with secondary glaucoma and glaucoma suspect

iv) Very advanced stage of glaucoma (based on AGIS score)

v) History of severe dry eye syndrome, recurrent corneal epithelial erosion, delayed cornea wound healing, active keratitis or conjunctivitis

vi) BCVA 3/60 and worse

3.5 Ethical Approval

This study received approval from the Research Ethics Committee (Human), School of Medical Sciences, Universiti Sains Malaysia Health Campus. The research protocol adhered to the provision of the Declaration of Helsinki for research involving human subjects.

3.6 Financial Support

This study was supported by the Universiti Sains Malaysia grant. The research short term grant (account number 304/PPSP/61313008) was approved by Timbalan Naib Canselor (Penyelidikan dan Inovasi), Universiti Sains Malaysia.

3.7 Definition Of Terms

3.7.1 Primary Angle Closure Suspect (PACS)

PACS is the initial event that may progress to PAC and subsequently to PACG. There is narrow angle, in the absence of other abnormality. Narrow angle is evidenced on indentation gonioscopy by inability to see posterior (pigmented) trabecular meshwork angled 180^0 to 270^0, which is due to appositional contact between peripheral iris and the posterior trabecular meshwork (Foster *et al.*, 2002; Aung, 2005).

3.7.2 Primary Angle Closure (PAC)

In PAC, the narrow angle is present in combination with consequence of angle closure process such as peripheral anterior synechiae and/or IOP rise. IOP is raised as a result of closure of the narrow angle, and is defined as >2 standard deviations above norm for studied population. Other signs that may present are iris whorling (distorted radially orientated iris), ‘glaucomfleken’, lens opacities, and excessive

pigmented trabecular meshwork. Significant optic nerve damage is absent. Patient can be asymptomatic or symptomatic (Foster *et al.*, 2002; Aung, 2005).

3.7.2.1 Acute Primary Angle Closure (Acute PAC)

Acute PAC is symptomatic PAC in which acute episode of angle closure occurs. This attack may happen at any stage during the disease but leaves no detectable nerve damage following prompt treatment (Foster *et al.*, 2002; Aung, 2005).

3.7.3 Primary Angle Closure Glaucoma (PACG)

PACG is the final sequelae of the event. There is evidence of glaucomatous optic neuropathy with or without visual field loss, in combination with changes seen in PAC (Foster *et al.*, 2002; Aung, 2005).

3.7.4 Peripheral Anterior Synechiae (PAS)

PAS is detectable on gonioscopy. It refers to adhesion of peripheral iris to the anterior angle structures, most commonly the functional trabecular meshwork. Rarely it may extend to the Schwalbe's line. Characteristically, PAS are broad and irregular adhesions, bridge the angle recess, obscure the underlying structures, inhibit posterior movement of iris on indentation, and drag normal iris vessels with it (Nema & Nema, 2014).

3.7.5 Intraocular Pressure (IOP)

IOP is defined as tension inside the eyeball. It is measured with tonometer, either through contact or non-contact method. Bilateral IOP can be symmetric or asymmetric. IOP does fluctuate, throughout the day (short term) or over longer intervals (long term). Normal IOP range is between 10 to 21 mmHg (Alimuddin, 1956). IOP above 21 mmHg is abnormal. IOP is the only modifiable risk factor affecting glaucoma progression (Coleman *et al.*, 2004; Bengtsson *et al.*, 2007; Caprioli & Coleman, 2008; Anderson, 2003).

3.7.5.1 Mean IOP

Mean IOP is defined as average of IOP readings at particular point of time or period (Liu *et al.*, 1999). Mean IOP at 4-hourly interval and overall mean peak IOP during 24-hour period has been described in details of methodology (refer 3.9.2.2).

3.7.5.2 Mean Peak IOP

Peak IOP is defined as maximum IOP reading during 24-hour period (Baskaran *et al.*, 2009). Mean peak IOP at 4-hourly interval and overall mean peak IOP during 24-hour period has been described in details of methodology (3.9.2.3).

3.7.5.3 Mean Trough IOP

Trough IOP is defined as minimum IOP reading during 24-hour period (Baskaran *et al.*, 2009). Mean peak IOP at 4-hourly interval and overall mean peak IOP during 24-hour period has been described in details of methodology (refer 3.9.2.4).

3.7.5.4 Mean IOP Fluctuation

Overall mean IOP fluctuation is defined as the difference between the peak IOP and the trough IOP during 24-hour period (Baskaran *et al.*, 2009). In this study, Mean IOP fluctuation at 4-hourly interval is defined as the difference between IOP values at each interval. IOP at each interval was calculated by subtracting lower IOP value from higher IOP value.

Mean IOP fluctuation at 4-hourly interval and overall mean IOP fluctuation during 24-hour period has been described in details of methodology (refer 3.9.2.5).

3.7.6 Circadian Rhythm of IOP

Circadian rhythm of IOP is defined as daily rhythmic activity cycle based on 24-hour period. It consists of peaks and troughs at different period of daytime (diurnal) and nighttime (nocturnal).

Each eye's circadian rhythm was classified as having one of the following 3 patterns of peak; morning, afternoon and night; and 3 patterns of trough; morning, afternoon, and night (Sihota *et al.*, 2005).