THE ROLE OF 24-HOUR INTRAOCULAR PRESSURE FLUCTUATION ON GLAUCOMA PROGRESSION IN PRIMARY OPEN ANGLE GLAUCOMA

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DISCLAIMER

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

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(In the name of ALLAH, the Most Beneficent, the Most Merciful)

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TABLE OF CONTENTS

5. List of Tables

6. List of Figures

ABBREVIATIONS

1	AGIS	Advanced glaucoma intervention study
2	ANOVA	Analysis of variance
3	CCT	Central corneal thickness
4	CI	Confident interval
5	CNTGS	Collaborative Normal Tension Glaucoma study
6	DM	Diabetes mellitus
7	EMGT	Early Manifest Glaucoma Study

8	GAT	Goldmann applanation tonometer
9	HPT	Hypertension
10	HUSM	Hospital Universiti Sains Malaysia
11	HVF	Humphrey visual field
12	IOP	Intraocular pressure
13	JOAG	Juvenile open angle glaaucoma
14	LCI	Lower confidence interval
15	mmHg	Millimeter mercury
16	NTG	Normal tension glaucoma
17	OAG	Open angle glaucoma
18	OHTS	Ocular Hypertension Study
19	POAG	Primary open angle glaucoma
20	SD	Standard deviation
21	SE	Standard error
22	UCI	Upper confidence interval
23	VCDR	Vertical cup disc ratio

7. ABSTRAK

PENGENALAN

Pengukuran tekanan intraokular (IOP) yang tepat sangat penting dalam merawat pesakit glaukoma primer jenis terbuka. Walaupun penyakit ini mempunyai banyak faktor penyebab, pengawalan IOP sahaja sahaja yang boleh mengelakkan kebutaan. Pada masa sekarang, flaktuasi tekanan dikaitkan sebagai salah satu penyebab yang memburukkan medan penglihatan. Mengenal pasti fluktuasi tekanan penting terutama pada pesakit glaukoma yang mencapai target IOP tetapi masih kehilangan

medan penghilatan. Oleh yang demikian, satu bacaan di klinik mata tidak dapat mengesan fluktuasi tekanan pada pesakit glaukoma.

OBJEKTIF

Kajian ini bertujuan untuk mengkaji corak tekanan mata dalam tempoh 24 jam dan membandingkan purata tekanan mata, tekanan mata tertinggi, tekanan mata terendah dan fluktuasi tekanan mata dengan dua kumpulan yang dibahagikan berdasarkan AGIS skor

METODOLOGI

Kajian melibatkan pesakit glaukoma primer jenis terbuka di mana mereka terbahagi kepada kumpulan yang mempunyai medan penglihatan yang semakin buruk dan kumpulan yang mempunyai medan penglihatan yang stabil berdasarkan AGIS skor. Pesakit dimasukkan ke hospital untuk pengukuran mata setiap 4 jam selama 24 jam. Purata tekanan mata, tekanan mata tertinggi, tekanan mata terendah dan fluktuasi tekanan mata direkodkan. Analisa telah dibuat menggunakan ujian T dan ‘repeated measure ANOVA’.

KEPUTUSAN

Seramai 68 pesakit (32 pesakit glaukoma yang progres dan 36 pesakit glaukoma yang stabil telah terlibat dalam kajian ini. Purata usia pesakit dalam kajian ini ialah 68.3±8.6 tahun. Pesakit lelaki adalah lebih tinggi dalam kumpulan progres (P=0.022). Purata tahun pesakit mendapatkan rawatan untuk pesakit progres ialah

6.7±3.8 tahun manakala 5.0±2.6 tahun untuk pesakit yang stabil. Pesakit progres kebanyakannya terdiri dari peringkat pesakit yang sederhana kepada peringkat yang teruk (P=0.001) dan kebanyakannya mempunyai ubat glaukoma lebih dari dua (P=0.010). Purata tekanan mata tertinggi (peak) dalam 24 jam adalah lebih tinggi (P=0.001) dan purata fluktuasi tekanan mata dalam 24 jam lebih besar untuk kumpulan pesakit progres (P=0.005). Manakala, purata tekanan mata lebih tinggi pada pukul 1200 untuk kumpulan pesakit progress (P=0.003).

KESIMPULAN

24 jam pengukuran tekanan mata menunjukkan purata mean tertinggi tekanan mata dan fluktuasi tekanan mata lebih tinggi untuk kumpulan pesakit progres. Kedua-dua kumpulan menunjukkan peak (bacaan tekanan tertinggi) pada waktu tengah hari.

8. ABSTRACT

INTRODUCTION

The accurate assessment of patient’s intraocular pressure profile is critical in the management of primary open angle glaucoma. Although it is a multifactorial disease, IOP remain the only treatable risk factor for the condition. Currently, wide diurnal IOP fluctuation has been identified as an independent risk factor of glaucoma progression. Therefore a single IOP reading taken in our clinic will failed to detect diurnal IOP fluctuation in glaucoma patients. The recognition of diurnal

IOP may also explain the progression of visual field in patients who appear to be controlled.

OBJECTIVES

To study the pattern of 24-hour intraocular pressure fluctuation in primary open angle glaucoma patients and compare the 24 hours mean intraocular pressure, peak trough and IOP fluctuation between POAG patients with and without visual field progression.

METHODS

A comparative cross sectional study was conducted involving POAG patients. They divided into non-progressed and progressed group based on AGIS score. Patients were admitted in the ward and IOP measured by GAT at 4-hourly interval for 24-hour. Mean intraocular pressure, peak trough and IOP fluctuation IOP were compared between non-progressed and progressed groups. Analysis was conducted using repeated measure ANOVA and independent t-test.

RESULTS

A total of 68 patients (36 non-progressed and 32 progressed) were recruited. Mean age for all recruited patients were 68.3±8.6 years old. There was significant more Male among patient with progressed group than in non-progressed group (P=0.022). Mean follow-up was 6.7±3.8 years in progressed group and 5.0±2.6 years in non-progressed group. Patient in progressed group has significantly more moderate to

severe glaucoma (P=0.001) and 71.9% of them were on more than two topical pressure lowering agents (P=0.001). There was significantly higher 24-hour mean peak IOP (P=0.001) and wider 24-hour mean IOP fluctuation (P=0.003) in progressed group compared to non-progressed group. There was significant higher mean IOP at 1200 hour in progressed group (P=0.003). Both group showed afternoon peak pattern.

CONCLUSION

24-hour IOP profile showed that there was significant higher 24-hour mean peak IOP and wider 24-hour mean IOP fluctuation found in progressed group. Both group showed pattern of afternoon peak.

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Assoc Prof Dr Azhany Yaakub: Supervisor

Professor Dr Liza Sharmini Ahmad Tajuddin: Co-Supervisor

Chapter 1

Introduction

1.1 GLAUCOMA

Glaucoma is a worldwide leading cause of irreversible vision loss. It constitutes a diverse group of disorders associated progressive optic neuropathy and visual field loss which the main risk factor for glaucoma is raised intraocular pressure (IOP). However, 40% of people with glaucoma have normal IOP and only 10% of people with raised IOP are at risk of optic nerve damage (Shah n.d, 2011). The prevalence of glaucoma increased exponentially with age.

Glaucomas are often divided into primary and secondary types as well as open and closed angle type. Open angle is related to an anatomically open angle while closed angle related to an anatomically closed angle. Primary glaucoma which is in open angle category includes Primary Open Angle Glaucoma (POAG), Juvenile Open Angle Glaucoma (JOAG), Congenital Glaucoma and Normal Tension Glaucoma (NTG).

POAG is defined as open angle glaucoma without secondary features and IOP >21 mmHg with glaucomatous disc changes and visual field defect. NTG is defined as an optic neuropathy characterized by optic disc excavation and corresponding visual field loss in the setting of an open anterior chamber angle and normal IOP. Some consider that NTG is part of the spectrum of POAG. Primary congenital glaucoma is term generally applied to children who present with classic features such as cloudy and/or enlarged corneas with Haab's striae. Newborn or birth-onset congenital glaucoma presents at birth or prior to 1 month of age. The most common age of

presentation after 1 month until 2 years of age, is known as infantile-onset primary congenital glaucoma. Late onset primary congenital glaucoma is typically used to refer to patients who develop after 2 years of age. JOAG is an autosomal dominant form of glaucoma that occurs in patients who develop open angle glaucoma in late childhood or early adulthood without signs of ocular enlargement.

The secondary glaucomas occur in association with a wide variety of ocular and systemic disorders. Secondary open angle glaucoma includes pseudoexfoliation syndrome, pigment dispersion syndrome, traumatic glaucomas, iridocorneal endothelial syndrome, the phakomatoses, elevated episcleral venous pressure. The secondary angle closure glaucoma includes neovascular glaucoma, lens induced glaucoma, malignant glaucoma and nanopthalmos related (Jacobiec, 1994).

1.2 PRIMARY OPEN ANGLE GLAUCOMA

1.2.1 Epidemiology of primary open angle glaucoma

Recent studies have provided valuable information about prevalence and subtype of glaucoma in Asian regions (View, 2007; Shen et al, 2008; View, 2003). Shen et al showed that prevalence of POAG among Malay people in Singapore is 2.5% while in Chinese 2.4%.

Prevalence of POAG Asia is 2.3%, 2.5% and 2.6% in Rom Klao, Thailand, Dhaka Bangladesh and Andra Pradesh, South India respectively (Quigley & Broman, 2006).

The prevalence of primary open-angle glaucoma (POAG) has been increasing, and this trend is undoubtedly due at least in part to advances in diagnostic technology. (Cedrone et al, 2008)

1.2.2 Risk Factor of Primary Open Angle Glaucoma

1.2.2.1 Age

Older age is consistently associated with POAG (Mitchell et al, 1996; Leske et al, 1995). The prevalence of glaucoma increases dramatically with age, particularly among Blacks. (Tielsch et al, 1991). In the Collaborative Initial Glaucoma treatment Study (CIGTS), visual field defects were seven times more likely to develop in patients aged 60 years or older than in those younger than 40 years.

1.2.2.2 Genetic and Race

Von Graefe in 1869 described a heritable form of glaucoma and noted that the accurate etiology of this disease remained to be investigated. First-degree family members of POAG patients are estimated to have as much as a tenfold increased risk of the disease compared to general population (Wolfs et al, 1998)

Many loci have been identified. The currently known genes (MYOC (Stone et al, 1997), OTPN (Rezaie et al, 2002), WDR36 (Monemi et al, 2005) probably contribute to pathogenesis of POAG. More than 80 MYOC mutations have been identified in different ethnic groups worldwide (Hewitt

et al. 2008) Some (the Pro370Leu, Tyr437His, and Ile477Asn mutations) are particularly associated with severe early onset forms of POAG (Shimizu et al. 2000). A study of large Malay pedigree found that the Asn480Lys mutation and the IVS2 730+35>A polymorphism increased susceptibility to JOAG (Mimivati et al, 2014).

Although genetic factors are important factor for POAG, environment factors may play a role. Black race is another risk factor for POAG. The prevalence of POAG is 3 to 4 times greater in blacks than in others. Blindness from glaucoma is at least 4 times more common in blacks than in whites (Tielsch et al, 1991). However, recent meta-analysis demonstrating no significant differences in POAG prevalence among black populations from America, Europe, West Indies, or Africa (Rudnicka et al, 2006). (Coleman & Kodjebacheva, 2009) suggested that poor socioeconomic status is associated with higher risk of glaucoma in African American. The income disparities may have limited knowledge regarding eye disease and lower access to care. African American are less likely to undergo glaucoma surgery (Devgan et al, 2000) and treatment compliance are difficult due to lower access to health care (Wang et al, 1997).

1.2.2.3 Myopia

Myopia is associated with twofold to threefold increased risk of glaucoma especially in moderate to high myopic eye compared to low myopia (Blue & Eye, 2010) . The link between glaucoma and myopia has been postulated by

a number of mechanisms. The optic nerve head in myopic eyes are more susceptible to glaucomatous damage from elevated or normal IOP (Chen et al, 2012; Perkins & Phelps, 1982). Myopic eyes also have thinner sclera and found to have higher sclera tension across lamina cribrosa. This may lead to high susceptible to optic nerve damage (Cahane & Bartov, 1992). Similar connective tissue changes may also occur and both glaucoma and myopia have a strong familial basis and may share a common genetic link.

(Galassi et al, 1997; Shimada et al, 2004) demonstrated that there is impaired retrobulbar and retinal circulations in glaucomatous eyes with myopia. There is also reduction in ocular pulse amplitude and pulsatile ocular blood flow in severe myopia (Ravalico et al, 1996). (Samra et al, 2013) demonstrated reduced subfoveal choroidal circulations in patient with myopia in comparison with age-matched glaucomatous patients without myopia. It has been assumed that the reduced choroidal blood flow might be partly due to increased vascular resistance because of anatomically in pathological myopia's eyes mostly have straightening of retinal vessels, small caliber and scarce choroidal arteries, thinning and loss of choriocapillaris.

1.2.2.4 Intraocular Pressure (IOP) and Central Corneal Thickness (CCT)

Central corneal thickness known to affects intraocular pressure measurement. In Ocular Hypertension Treatment Study found that central corneal thickness alone is a powerful predictor of the development of POAG (Gordon et al, 2002). When CCT is thin, underestimation of IOP may occur.

It is known that increasing age was associated with thinner CCT (Aghaian et al, 2004). Racial variation of CCT has been reported. There are ethnic differences in distribution of CCT in a multi-ethnic Asian population reported (Chua et al. 2014). More percentage of Malays had CCT reading less than 555µm compared to Chinese and Indians in Singapore. CCT was also reported to be one of the risk factor for visual fields progression (Mehdizadeh et al, 2007).

1.2.2.5 Diabetes Mellitus

Studies have reported a higher prevalence of both elevated IOP and POAG among persons with diabetes mellitus (DM) (Mastropasqua et al, 1988) Glaucoma patients also have been reported to have a higher prevalence of abnormal glucose metabolism. Some authorities believe that small-vessel involvement in diabetes may cause the optic nerve to become more susceptible to pressure related damage (Wong et al, 2011). However, prospective population based study by (de Voogd et al, 2006) showed that DM was not a risk factor for POAG. DM also was not associated with an increased risk of progression to glaucoma in OHTS.

1.2.2.6 Cardiovascular disease

Cardiovascular disease has been associated with POAG, blood pressure and perfusion pressure of the eye. Systemic hypertension may have microcirculatory effects on the optic nerve and will increase susceptibility to

glaucoma. Recent evidence suggests that lower systolic perfusion pressure, lower systolic blood pressure and cardiovascular disease history are risk factors for glaucoma progression (Leske et al, 2007).

1.2.3 Clinical Presentation of Primary Open Angle Glaucoma

In most cases, glaucoma develops in midlife or later, and the onset is usually gradual and asymptomatic. The IOP may be elevated only slightly in the early stages, but it generally becomes higher when the disease is more advanced (Jakobiec, 2000). The likelihood that optic nerve damage will occur varies from one individual to the next, depending on the level of IOP and on the presence of other risk factors. It is estimated that approximately 1% of all individuals with elevated IOP will acquired glaucomatous damage each year. The rate is higher if high IOP is present (Jakobiec, 2000).

In POAG, the gonioscopy appearances of the angle of anterior chamber are no different from those found in normal eyes. The examination of the optic nerve head is important. Findings that have significance including an asymmetry of the optic nerve cups, thinning or notching of the neural rim of the disc, slight bending of the vessels at the margin, saucerization of the disc, disc margin hemorrhage and a documented progressive change in the appearance of the disc. Nerve fiber layer defects may be present.

Visual field defect may include arcuate defect, nasal steps, paracentral scotomas, and a generalized depression of the field.

The IOP may vary in the course of a day from normal to significantly elevated levels. The mean value of IOP in a large normal population is approximately 16 mm Hg, with a standard deviation of about 3 mm Hg. The clinical relevance of this number to glaucomatous damage is not clear-cut, 16% of patients with glaucoma have not had demonstrable or repeated elevations of IOP greater than 21 mmHg, whereas many individuals with IOP repeatedly greater than 21 mmHg do not have and may never have optic nerve damage during their lifetimes (Jakobiec, 2000).

1.2.4 Management of Primary Open Angle Glaucoma

Management of POAG is to give treatment after taking into account the risks and rate at which glaucomatous optic nerve damage and visual impairment are likely to occur, the patient's expected lifespan and his or her tolerance of effective treatment.

In management of glaucoma, it is helpful to select a target pressure in which this level of IOP if achieved will presumably prevent future optic nerve damage. Treatment modalities for glaucoma consist of topical and systemic medication, laser treatment and conventional surgical procedures. Traditionally, the maximal medical therapy that can be tolerated has been used before laser therapy and conventional filtering surgery (Jakobiec, 2000).

1.3 INTRAOCULAR PRESSURE

1.3.1 IOP and Aqueous humor dynamic

A fine balance between the production, circulation and drainage of ocular aqueous humor from the posterior chamber (aqueous humor dynamics) is essential to maintain intraocular pressure (IOP) at a steady state level. Aqueous humor is produced in the posterior chamber and flows through the pupil into the anterior chamber. Aqueous humor exits the eye by passing through trabecular meshwork and into Schlemm's canal before draining into the venous system through a plexus of collector channels, as well as through the uveoscleral pathway, which is proposed to exit through the root of iris and the ciliary muscle, into the suprachoroidal spaces and through the sclera. The Goldmann equation summarizes the relationship between many of these factors and the IOP in the undisturbed eye: $P_0 = (f/C) + P_{v;}$ where P0 is the IOP in millimeters of mercury (mmHg), F is the rate of aqueous formation in microliters per minute (uL/min), C is the facility of outflow in microliters per minute per millimeter of mercury (uL/min/mmHg) and Pv is the episcleral venous pressure in mmHg.

1.3.1.1 Aqueous humor formation

Aqueous humor formation is a biological process that is subject to circadian rhythms. Aqueous humor is formed by the ciliary processes, each of which is composed of a double layer of epithelium over a core of stroma and a rich supply of fenestrated capillaries. Each of the 80 or so processes contains a large number of capillaries, which are supplied mainly by branches of the

major arterial circle of the iris. The apical surfaces of both the outer pigmented and the inner non-pigmented layers of epithelium face each other and are joined by tight junctions, which are an important component of the blood- aqueous barrier. The inner non-pigmented epithelial cells, which protrude into the posterior chamber, contain numerous mitochondria and microvilli; these cells are thought to be the actual site of aqueous production. The cilliary processes provide a large surface area for secretion. Aqueous humor formation and secretion into the posterior chamber result from active secretion, ultrafiltration and simple diffusion. Aqueous formation varies diurnally and drops during sleep. It also decreases with age, as does outflow facility.

Aqueous humor is produced at an average rate of 2.0-2.5uL/min. The rate of aqueous formation is affected by a variety of factors including integrity of the blood aqueous barrier, blood flow to cilliary body and neurohumoral regulation of vascular tissue and cilliary epithelium. Aqueous humor production may decrease following trauma or intraocular inflammation and following administration of certain drugs such as general anaesthetics and some systemic hypotensive agents. Carotid occlusive disease may also decreased aqueous humor production.

1.3.1.2 Aqueous humor outflow

Aqueous humor outflow occurs by 2 major mechanisms: conventional or unconventional outflow. The aqueous humor leaves the eye at the anterior

chamber angle through the system consisting of trabecular meshwork, schlemm's canal, intrascleral channels and episcleral and conjuctival veins. This pathway is referred to as conventional or trabecular outflow. In the unconventional pathway or uveoscleral outflow, aqueous humor exits by passing through the root of the iris between the cilliary muscle bundles then through the suprachoroidal-scleral tissues. In general, the trabecular outflow account for approximately 70-95% of aqueous humor egress from the eye. The facility of outflow varies widely in normal eyes. The mean value reported ranges from 0.22 to 0.30 uL/min/mm Hg.

1.3.1.3 Episcleral venous pressure

Episcleral venous pressure is relatively stable, except with alteration in body position and with certain disease of the orbit, the head and the neck that obstruct venous return to the heart or shunt blood from the arterial to the venous system. The usual range of values is 8-10 mmHg. The pressure in the episcleral veins can be measured with specialized equipment. In acute condition, according to Goldmann equation, IOP rises approximately 1mm Hg for every 1mm Hg increase in episcleral venous pressure.

1.3.2 Measurement of intraocular pressure

1.3.2.1 Goldmann Applanation Tonometer (GAT)

Goldmann applanation tonometer (GAT) is reference standard for tonometry. Theo Schmidt introduced the GAT in 1957. The IOP is estimated by measuring the force required to flatten a fixed area of the cornea. The optimal applanation area derived from empirical experimentation and the Imbert-Fick principle. The Imbert-Fick principle states that the pressure (P) of a body of fluid encapsulated within a sphere is directly proportional to the force (W) required to applanate an area (A) of the sphere: W = PA. The principle holds provided that the surface encapsulating the fluid is infinitely thin, perfectly elastic, dry and perfectly flexible and that the only force being exerted upon it is from the applanating surface.

However, with respect to the cornea, none of these assumptions is true. Goldmann recognized that the equation would need to be modified to account for certain corneal characteristics (a finite thickness, measureable rigidity and capillary attraction forces of the precorneal tear film). An assumption was made that, in the absence of corneal pathology, the central corneal thickness (CCT) did not vary much around 500um. The modified equation included factors to account for resistance of the cornea to applanation and the action of surface tension from the tear meniscus on tonometer prism. W+s=PA+b where W= tonometer forces, s=surface tension of precorneal tear film, P= intraocular pressure, A= area of applanation, and

b= corneal rigidity to bending. The effects of corneal rigidity and tear film surface tension forces approximately cancel when the area of applanated is 7.35mm^2. When applanating this area, a force of 0.1g corresponding to an IOP of 1 mmHg.

1.3.2.2 Factors affecting IOP measurement accuracy

Sources of IOP measurement error using GAT technique includes excessive tears, insufficient tears, corneal astigmatism more than 3 diopters, corneal edema, breath-holding, tight clothing around neck causing increased venous pressure, sustained accommodation and deviation of gaze from primary position.

Overestimation of IOP is due to excessive tears that causing broad fluorescein rings and against the rule of astigmatism. Underestimation of IOP is due to insufficient tears, with the rule astigmatism and corneal edema. Increase in IOP occurred when there is deviation of gaze from primary position and when increased in venous pressure in breathe holding or tight clothing around the neck. While, sustained accommodation cause reduction of IOP.

Other sources of error include ‘digit preference’- a subconscious bias towards certain digits, eyelid squeezing, patient obesity (may give high readings). Typical repeatability coefficients are 2.2-5.5 mm Hg for GAT. For

different observers measuring IOP in the same subjects, the 95% limits of agreement have been reported to be ±2.2-3.8 mmHg for GAT.

1.3.3 Factors Affecting Intraocular pressure

There are three categories of IOP fluctuation: ultra-short term fluctuation (those occurring within seconds and minutes), short-term fluctuation (those occurring over hours and days), and long term fluctuation (those occurring over months and years).

IOP fluctuation is best understood in the context of aqueous dynamics and the relationship between intraocular volume and IOP, described by the modified goldmann and Friednenwald equations, respectively. Ff= (Pi –Pe) C + Fu, where Ff is aqueous humor flow rate, Pi is the intocular pressure, Pe is the episcleral venous pressure, C is trabecular facility and Fu is uveoscleral outflow. K = dP/dV where , K is the rigidity coefficient (-0.021 mmHg/uL), dP is the change in pressure (mmhg) and dV is the change in volume (uL). In a non-steady state, the friedenwald equation explains ultra-short term IOP fluctuation, such circumstances include: increased choroidal blood flow volume during systolic cardiac cycle, external ocular pressure, and the Valsalva maneuver. These all lead to sudden IOP spikes due to the scleral rigidity.

However, during a steady state, the IOP is explained by the Goldmann equation. The formula may be rearranged: Pi = (Ff- Fu+ Pe)/C. The steady state IOP is therefore dependent on aqueous humor flow rate, episcleral venous pressure, trabecular

outflow and uveoscleral outflow. Any changes in these parameters will result in an IOP changes.

Aqueous flow averages about 2.9uL/min in young healthy humans. Drinking a large amount of water over a short time, as in classic water drinking test, can induce hypotonicity of the plasma and increase the aqueous production rate over an ultra-short time period. It is possible that IOP variation itself may affect the aqueous production rate in the ultra-short term. This is conceptualized as “pseudo-facility” – the effect of increased IOP during tonography measurement causing a reduction in aqueous production rate. This effect is probably fairly small and has not been shown to be significant in a fluorophotometry study. There is a slight reduction of aqueous flow rate with age, with an estimated reduction of 2,4% per decade, reaching a mean level of only 2.2ul/min in octogenarians. Aqueous flow also has a distinctive circadian rhythm. The flow rate at night, during sleep, is only 43% of the rate in the morning after awakening. If all other parameters were stable, the highest IOP would be first thing in the morning on waking while the lowest would be when one is sleeping.

Episcleral venous pressure in healthy humans is in the range of 7 to 14 mmhg. This parameter is liable to ultra- short term fluctuation as this is the only component of aqueous humor dynamics that is affected by body position. Episcleral venous pressure increases by 3.6mmHg by changing body position from seated to supine. Otherwise, when body position does not change, episcleral pressure appears to be relatively stable. A change in episcleral venous pressure of 0.8mmHg corresponds to

a change in IOP of 1 mmHg. Long term fluctuation of episcleral venous pressure remains unknown.

Trabecular outflow facility (rate at which fluid can be expressed from the eye by pressure) in healthy human eyes in the range of 0.1-0.4uL/min/mmHg. There is some evidence of diurnal variation in outflow facility. In addition, trabecular outflow resistance increases with age. Outflow facility is reduced in POAG, ocular hypertension and exfoliation and pigment dispersion syndromes with secondary ocular hypertension.

Uveoscleral outflow is 25-57% of total aqueous flow in young healthy subject of 20-30 years of age. Uveoscleral outflow is reduced in ocular hypertension with and without pseudoexfoliation syndrome and increased in uveitis. There are no data on diurnal variation of uveoscleral outflow.

1.3.3.1 Ultra-Short Term Fluctuation of IOP

Ultra-short term IOP fluctuation can be caused by the systolic cardiac cycle, changing external ocular pressure, episcleral venous pressure, and aqueous flow, and by other unknown factors. One of the most important factors determining the IOP spike height in the ultra-short term is sclera rigidity. Experimental data suggest sclera rigidity increases significantly with age, and this leads to greater spikes in IOP, other parameters being equal. However, the clinical significance of ultra-short term fluctuation of IOP is unclear.

1.3.3.2 Short Term Fluctuation of IOP

Short-term IOP fluctuation is variation occurring over 24-hour. This fluctuation is likely to be caused by changes in aqueous outflow rate, episcleral venous pressure, trabecular outflow, and other factors. Of these, the most important variables are aqueous flow rate and episcleral venous pressure. The circadian pattern of aqueous flow rate has been known for many years and has a marked effect on the IOP, if all other parameters remained unchanged.

1.3.3.3 Long Term Variation of IOP

Factors are thought to exert a sustained influence on IOP throughout the lifetime of the individuals are genetics, age, gender, refractive error and ethnicity.

The IOP within the general population appears to be under hereditary influence, possibly through a polygenic, multifactorial mode (Armaly et al, 1968). In general, IOP increase with age. In adults, the IOP distribution is according to Gaussian distribution in aged between 20-40 years (Armaly, 1965).

IOP is equal between the gender in ages 20-40 years. In older age groups, the apparent increase in the mean IOP with age is greater in women (Armaly, 1965).

Race may occasionally influence IOP distribution. Study in Singapore found that Chinese have the thickest CCT but lowest IOP among Malays and Indians (Chua et al. 2014). In addition, there is a higher proportion of Malays with IOP ≥21 mmHg and CCT <555 μm compared with Chinese or Indians (Chua et al. 2014). Black populations have been reported to have slightly higher pressure than whites (Hiller et al, 1982). However, in Japanese adult, IOP is found to be low was negatively correlated with age.

There are two means of assessing 'true' long term IOP fluctuation: performing repeated diurnal IOP curves over a period of few years or by measuring IOP at the same time of the day over a few years.

1.3.4 Effect of 24-hour intraocular pressure on glaucoma progression

IOP is not a constant value. IOP is a dynamic parameter with a circadian rhythm and spontaneous changes (Weinreb & Khaw, 2004). Despite stable IOP measured in clinic, some glaucoma patient still developed visual field progression (Caprioli & Coleman, 2008). The IOP variables such as peak IOP and fluctuations (both short term and long term fluctuation) have been known to adversely impact the disease progression even in cases with statistically normal or controlled pressure (Hong et al, 2007; Medeiros et al, 2002; Rao et al, 2013).

Current studies showed that there is diurnal variation in normal and glaucomatous eyes. IOP fluctuation of as much as 4-5 mmHg in healthy individual and higher in some glaucoma patients are common (Liu et al, 1999; Liu et al, 2003). Large diurnal IOP fluctuation has been identified as an independent risk factor of glaucoma progression (Caprioli & Coleman, 2008; Asrani et al, 2000).

Normal individual and patients with glaucoma experienced peak IOP at night. The shift of posture from upright to supine position was to be one of the main factors causing night peak. It is due to changes in episcleral venous pressure and redistribution of body fluid in the eye during supine position. In aging population and glaucoma patients, nocturnal slow-down of aqueous flow not sufficient to counterbalance the elevation of IOP at night (Liu et al. 1999). However, liu et al. found similar patent of nocturnal peak IOP reading in younger subjects (Mosaed et al. 2005) .

Study that measure IOP several times over entire days found that approximately two-third of glaucoma patients had highest IOP outside regular clinic most frequently during the nocturnal/sleeping period (Barkana et al, 2006). However, morning peaks were also reported more frequently in POAG patients compared to PACG patients (Sihota et al. 2005)

POAG patients also found to have different IOP peak time before and after treatment of topical timolol. Time peak IOP that were not receiving treatment was 10 am and in treatment phase the diurnal curve were flatter and peak was observed at 6am and 6pm (Agric, 2006).

Although varies studies agree that rhythmic pattern of diurnal variation does occur in POAG patient, no agreement as to the time of peak pressure and pattern in POAG patients.

Some proposed theories regarding how fluctuation IOP leads to visual field progression. First, there is possibility that kinking of axons occurred during IOP fluctuation of 5-7 mmHg. Morgan et al. found that, there was maximum movement of lamina cribrosa portion during the IOP fluctuation (Morgan et al, 2002). A paper presented at International congress of eye research postulated that it was related to an ischaemic reperfusion injury where higher IOP fluctuation demonstrated damaged of DNA in the circulating lymphocytes (Flammer et al, 2002).

Fluctuation may occur in phenomenon of IOP spike that occur when people awake. Normal trabecular meshwork typically experience a spike of approximately 6 mmHg

upon awakening. The IOP rise in about 12 minutes and reduce to presleep level. However, in a patient with glaucoma the spike of IOP may be higher and may take much longer to dissipate.

Therefore, current management of glaucoma were targeted to modify all three parameters of IOP peak, mean IOP and IOP fluctuation that only available when 24-hour IOP were measured.

1.3.5 Monitoring of Intraocular Pressure Fluctuation

Saller-Huguenin first reported the concept of diurnal IOP variation in 1898 and this was refined by Maslenikow in 1904. There is currently no clinical tool for continous monitoring of normal variations and spontaneous fluctuations of IOP. In studies, subject either undergo repeated IOP measurement during office (clinic) hours, or are admitted for regular IOP measurement over 24-hour period. There have also been studies in which patients performed ‘self-tonometry’ using a device during their waking hours. The main advantage of this paradigm is that patients are in their natural environment, although the tonometer may not be as accurate and precise as the Goldmann tonometer.

1.4 RATIONALE OF STUDY

Although POAG is multifactorial disease, IOP remains the only treatable risk factor for this condition (Boland & Quigley, 2007). In Early Manifest Glaucoma Trial Study stated that 25% reduction in IOP will reduced progression from 30-49% at 4 years (Heijl 2002). However despite adequate controlled IOP measured in clinic, there is still clinical deterioration (Katz et al, 1997). Here, intraocular pressure fluctuation is considered the risk factor for the glaucoma progression (Asrani et al. 2000).

Liu et al were the first to demonstrate that in majority of normal and glaucoma patients, the peak IOP occur during nocturnal period (Liu et al. 2003). Barkana et al showed peak 24-hour IOP was higher than the peak IOP noted during office hour visit and IOP measurements during office hours failed to detect peak IOP in up to 62% of glaucoma patients (Barkana et al. 2006). Some study showed IOP fluctuation in POAG patients was between 4-6mmhg (Liu et al, 2003).

24 hour IOP assessment is importance to measure IOP not only in the morning but at other times of the day as current trend of treatment in progressed POAG patients was identification of peak IOP, mean IOP and reduction of IOP fluctuation.

The aim of this study is to determine 24-hour IOP fluctuation and pattern in progressed and non-progressed groups of POAG patients.

Chapter 2

Objectives

2.1 GENERAL OBJECTIVE

To investigate the 24-hour intraocular pressure fluctuation pattern in primary open angle glaucoma patients.

2.2 SPECIFIC OBJECTIVE

2.2.1 To determine the 24 hours mean intraocular pressure, peak, trough, fluctuation and pattern in POAG patients with non-progressive visual field changes.

2.2.2 To determine the 24 hours mean intraocular pressure, peak, trough, fluctuation and pattern in POAG patients with visual field progression.

2.2.3 To compare the 24 hours mean intraocular pressure, peak trough, IOP fluctuation and pattern between POAG patients with and without visual field progression

Chapter 3

Material and Methods

3.1 STUDY DESIGN

A cross sectional comparative study

3.2 STUDY SETTINGS

3.2.1 Study population

Patients diagnosed with POAG, attended regular follow up visits in glaucoma clinic, Hospital Universiti Sains Malaysia (HUSM).

3.2.2 Study period

November 2012 to November 2014 (2 years)

3.2.3 Study Place

Glaucoma clinic and 2 Utara ward, Hospital Universiti Sains Malaysia, Kelantan

3.3 SAMPLING METHOD AND SAMPLE SIZE

3.3.1 Sampling method

Consecutive sampling of all POAG patients who attended glaucoma clinic in Eye clinic, HUSM. Eligible patients according to inclusion and exclusion criteria were divided into 2 groups (progress and non-progress group) based on AGIS score of their visual field. Progress and non-progress group were further defined in (3.7.3.1)