A STUDY OF EFFECTIVENESS AND ADHERENCE BETWEEN FIXED COMBINATION DORZOLAMIDE / TIMOLOL MALEATE AND NON-FIXED DORZOLAMIDE AND TIMOLOL XE IN 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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ABBREVIATIONS

ACG	Angle closure glaucoma
ANOVA	Analysis of variance
CCT	Central corneal thickness
CI	Confidence interval
CNTGS	Collaborative Normal-Tension Glaucoma Study
EMGT	Early Manifest Glaucoma Study
FCDT	Fixe-combination dorzolamide/ timolol meleate
FDA	Food and Drug Administration
GAT	Goldmann applanation tonometer
GMASES	Glaucoma Medication Adherence Self-Efficacy Scale
IOP	Intraocular pressure
NFDT	Non-fixed combination dorzolamide and timolol XE
NO	Nitric oxide
NTG	Normal tension glaucoma
OAG	Open angle glaucoma
OHTS	Ocular Hypertension Treatment Study
POAG	Primary open angle glaucoma
RCT	Randomised controlled trial
SD	Standard deviation
SDAS	Subjective drug adherence score
SE	Standard error
SEAGIG	South East Asia Glaucoma Interest Group

VCDR	Vertical cup disc ratio

ABSTRAK

PENGENALAN

Rawatan yang berkesan dan kepatuhan kepada ubatan adalah faktor penting untuk menentukan kejayaan rawatan penyakit glaukoma. Banyak bukti menunjukkan penurunan tekanan intraokular (IOP) membantu mencegah and merencat kemusnahan saraf optik dan medan penglihatan.

OBJEKTIF

Untuk mengenalpasti dan membandingkan kesan penurunan tekanan intraokular dan skor kepatuhan kepada ubatan di antara kombinasi tetap dorzolamide/timolol maleate (FCDT) dan kombinasi secara berasingan dorzolamide dan timolol XE (NFDT) dalam glaukoma sudut terbuka.

METODOLOGI

Kajian ini merupakan kajian klinikal terkawal rawak, kumpulan selari dan kajian buta satu yang melibatkan 55 orang pesakit glaukoma sudut terbuka. Pesakit disampelkan secara rawak kepada kumpulan FCDT yang menerima kombinasi tetap dorzolamide/ timolol maleate dan kumpulan NFDT yang menerima kombinasi secara berasingan dorzolamide dan timolol XE selama 3 bulan. Pre-kajian pemberian ubat timolol dijalankan selama 2 minggu. Tekanan intraokular asas diambil pada waktu pagi. Pesakit diberi temujanji pada bulan pertama dan bulan ketiga. Tekanan intraokular dan keselamatan ubatan dinilai semasa temujanji. Skor kepatuhan kepada ubatan yang mengandungi peratusan ubat titis yang digunakan berdasarkan timbangan berat botol ubatan, Skala Kecekapan Diri Terhadap Kepatuhan Ubat Glaukoma dan Skor Kepatuhan Ubatan Secara Subjektif. Ia direkodkan semasa temujanji bulan ketiga.

Data dianalisa menggunakan ‘repeated measures ANOVA’, ujian T bebas dan ujian ‘Pearson Chi Square’.

KEPUTUSAN

Data demografik adalah serupa di antara kumpulan. Kumpulan FCDT dan NFDT secara statistik yang signifikan menurunkan tekanan intraokular pada bulan pertama dan ketiga dengan penurunan tekanan intraokular min pada bulan pertama adalah 4.9 mmHg dengan 95% interval keyakinan (CI) (4.0 ke 5.9) dalam FCDT, 4.9 (95% CI 4.0 ke 5.8) mmHg dalam NFDT, pada bulan ketiga adalah 5.2 (95% CI 4.2 ke 6.2) mmHg dalam FCDT dan 4.9 (95% CI 3.9 ke 5.8) mmHg dalam NFDT. Min peratusan perbezaan intraokular pada bulan pertama dan bulan ketiga menunjukkan tiada perbezaan signifikan di antara kumpulan rawatan. Tiada perbezaan yang signifikan di antara kumpulan dari segi min skor kepatuhan total.

KESIMPULAN

Kesan penurunan tekanan intraokular dalam kumpulan FCDT adalah setanding dengan NFDT. Kedua-duanya menunjukkan penurunan tekanan intraocular yang signifikan pada bulan pertama dan ketiga rawatan. Skor kepatuhan total adalah tinggi dan standing untuk kedua kumpulan.

ABSTRACT

INTRODUCTION

The effective treatment and adherence to medication are important factors for successful management of glaucoma. Many evidences showed that lowering the IOP could prevent and halt the progression of optic nerve damage and visual field loss.

OBJECTIVES

To determine and compare the pressure lowering effects and adherence score between fixed-combination dorzolamide/ timolol maleate (FCDT) and non-fixed combination dorzolamide and timolol XE (NFDT) in open angle glaucoma.

METHODS

This randomised controlled trial, parallel groups and single-blinded study involved 55 patients of OAG. Patients were randomised to FCDT group who received fixed-combination dorzolamide/ timolol maleate and NFDT group that received concomitant dorzolamide and timolol XE for 3 months. Pre-study run-in timolol was given for 2 weeks. Baseline IOP was taken in the morning. Patients were follow-up at month 1 and month 3. IOP and safety of medication were assessed during follow-up. The adherence score consists of percentage of eye drops used based on bottle weight measurement, Glaucoma Medication Adherence Self-Efficacy Scale and Subjective Drug Adherence Score were recorded at month 3 follow-up. Data were analyzed using repeated measures ANOVA, independent t-test Pearson Chi Square test.

RESULTS

The demographic data were similar between the groups. FCDT and NFDT were statistically significant reduced the IOP at month 1 and month 3 with mean IOP reduction at month 1, 4.9 mmHg with 95% confidence interval (4.0 to 5.9) in FCDT, 4.9 (95% CI 4.0 to 5.8) mmHg in NFDT, at month 3 were 5.2 (95% CI 4.2 to 6.2) mmHg in FCDT and 4.9 (95% CI 3.9 to 5.8) mmHg in NFDT. The mean percentage of IOP difference between treatments groups at one month and three months were no significant different. There was no significant difference of mean total adherence score between the groups.

CONCLUSION

The pressure lowering effects of fixed-combinations dorzolamide/ timolol maleate and non-fixed combination dorzolamide and timolol XE was comparable. Both provide a significant reduction of IOP at one month and three months treatment. The total adherence score was high in both treatment groups and comparable.

CHAPTER 1

INTRODUCTION

CHAPTER 1: INTRODUCTION

1.1 Open angle glaucoma

1.1.1 Definition of Open Angle Glaucoma (OAG)

Glaucoma is a progressive optic neuropathy characterised by excavation of optic nerve heads and specific patterns of visual field defect. The evidence of optic nerve damage derives either from the optic disc or retinal nerve fibre layered structural abnormalities or reliable and reproducible visual field abnormality or from both (Panel, 2010). As open angle glaucoma, the gonioscopy findings are open anterior chamber angles.

There occur multiple factors involved in the pathogenesis of glaucoma. The initial insult primary result derived from the elevated intraocular pressure (IOP) and vascular dysregulation leads to secondary insult include excitotoxic damage caused by glutamate or glycine released from injured neurons and oxidative damage caused by the over-production of nitric oxide (NO) and other reactive oxygen species (Agarwal *et al.*, 2009).

Glaucoma has been classified as open angle or closed angle and as primary or secondary. Primary open angle glaucoma (POAG) can occur with or without elevation of IOP. POAG is open angle glaucoma with elevation of IOP while the category consisting of open angle without elevation of IOP is termed normal tension glaucoma (NTG) .

1.1.1.1 Definition of Primary Open Angle Glaucoma (POAG)

Primary open-angle glaucoma (POAG) is chronic progressive optic neuropathy with characteristic patterns of optic nerve damage and visual field loss with the absence of secondary causes (SEAGIG).

POAG is lacks of identifiable contributing factors of the secondary open-angle glaucoma such as pigment dispersion in pigmentary glaucoma or exfoliated material observed in exfoliation syndrome in an eye with open anterior chamber drainage angles on gonioscopy and elevated intraocular pressure (IOP). The Ocular Hypertension Treatment Study (OHTS) found an increased risk of the onset of POAG was associated with increased age , increased vertical and horizontal cup-disc ratio, pattern deviation and IOP at baseline. However, the most powerful predictor is central corneal thickness (CCT) which increases the relative risk of POAG by 81% for every 40 μm thinner (Kass *et al.*, 2002) .

The diagnosis of glaucoma according to cross sectional prevalence studies is based on three levels of evidence (Foster *et al.*, 2002). The highest level of evidence requires optic disc abnormalities (VCDR > 97.5 th percentile in the normal population) and visual field defect compatible with glaucoma. As for second, if the visual field cannot be obtained satisfactorily, a severely damaged optic disc (VCDR > 99.7 th percentile of normal population) would be sufficient to make a diagnosis. Lastly, if the optic disc cannot be examined because of media opacity (and hence no visual field test is possible), an IOP exceeding 99.5 th percentile of the normal population , or evidence

of previous filtering surgery, may be taken as sufficient for the diagnosis of glaucoma (Foster *et al.*, 2002).

The characteristic visual defects are defined as asymmetrical points across the horizontal line, located in the mid-periphery, clustered in the neighbouring test points, reproducible on at least two occasions, not explained by any other disease and a valid representation of the subject's functional status. In severe optic disc damage, these principles fail to be applied. Therefore a group of researchers interested in psychophysics of glaucoma adopted the glaucoma hemifield test graded 'outside normal limits' using the threshold test strategy with the 24-2 test patterns of the Zeiss-Humphrey field analyser 2 as a gold standard of glaucomatous visual field loss (Foster *et al.*, 2002).

1.1.1.2 Definition of Normal Tension Glaucoma (NTG)

Normal-tension glaucoma (NTG) is a form of open-angle glaucoma characterized by glaucomatous optic disc and defined type and severity of visual field defect with a median IOP of 20 mmHg or less in 10 baseline measurements (Anderson, 2003). The diagnosis of NTG is essentially based on the optic nerve and visual field defect of glaucoma with diurnal IOP measurement (Deborah Kamal and Hitchings, 1998) . Phasing should be performed in order to rule out POAG with diurnal variation.

However, NTG has several distinguishing features. As the name implies, NTG patients have a higher propensity for optic nerve damage at relatively low levels of IOP. There are other IOP independent mechanisms of retinal ganglion cells loss that is associated with NTG. These include myopia, older age, vasospasm, ischaemia, vascular insufficiency and complex genetic factors disorder that involves genetic, epigenetic and environmental factors (Shastry, 2013)

Optic disc examination in NTG exhibited narrower neuroretinal rim particularly inferiorly and inferotemporally (Caprioli and Spaeth, 1985). Other frequent findings found in NTG are disc haemorrhage and beta zone peripapillary atrophy, disc haemorrhage has significantly poor prognostic indicator (Tezel *et al.*, 1996; Ishida *et al.*, 2000). Visual field defects typically appear deeper, steeper and closer to fixation in patients with NTG than in patients with POAG (Song and Caprioli, 2014)

The progressive nature of the disease will distinguish the NTG from an isolated optic neuropathy such as compressive optic neuropathy, ischaemic optic neuropathy, congenital disc abnormality and toxic optic neuropathy. Therefore, clinical assessment of systemic comorbidities and brain imaging may be necessary.

Although IOP is within the normal range, it is still postulated that IOP is the risk factor in the development and progression of the disease. The Collaborative Normal-Tension Glaucoma Study (CNTGS) revealed that a 30% reduction in IOP can prevent the progression of visual field loss in most patients with previously documented progression or a fixation threat(Anderson, 2003).

1.1.2 Prevalence of OAG

The estimated number of people with OAG and ACG reached 60.5 million in 2010 and increased to 79.6 million people in 2020 (Quigley and Broman, 2006). From the estimated number of people with glaucoma, 74% are OAG. South East Asia represents 4.7 % (2.1 million) of worldwide OAG (Quigley and Broman, 2006).

The prevalence of POAG reported in population-based studies in Asia range from between 0.5% in Hovsgol, Mongolia to 3.9% in Tamiji, Japan (Cho and Kee, 2014). Singapore Malay Eye Study (SiMES-1) reported that 3.2% of the study population were afflicted with primary open angle glaucoma followed by secondary glaucoma (0.8%) and primary angle closure glaucoma (0.2%)(Rosman *et al.*, 2012).

However, NTG is most prevalent within the Japanese (3.6%) and Korean (2.04%) populations rather than Caucasian inhabitants(0.6%)

Bilateral blindness from OAG comprised 5.8 million people in 2020 in contrast with ACG sufferers estimating about 5.2 million (Quigley and Broman, 2006). The number of people with glaucoma is estimated to increase to 111.8 million in 2040 on a global scale (Tham *et al.*, 2014). This data is imperative for the planning of glaucoma screening, treatment and estimated the public health burden.

1.2 Treatment of OAG

1.2.1 Medical treatment

The treatment of glaucoma must be weighted between the risks of therapy and the anticipated benefits. Prevention and modification of risk factors particularly the raised intraocular pressure is the primary goal of the management of glaucoma. Early Manifest Glaucoma Trial (EMGT) reported that a reduction in each mmHg IOP will reduce 10% risk of the visual field defect progression .The study also discovered that the predictive factors for glaucoma progression include higher baseline IOP, exfoliation, bilateral disease, worse mean deviation, older age and frequent disc haemorrhage during follow-up (Leske *et al.*, 2003). The Ocular Hypertension Treatment Study (OHTS) evaluated the safety and efficacy of topical ocular hypotensive medication in delaying or preventing the onset of primary open angle glaucoma. OHTS found a 22.5% decrease in IOP in the treatment group and 4.0% in the control group, this was associated with a reduction in the development of POAG from 9.5% in controls to 4.4% in treated patients at 60 months follow-up (Kass *et al.*, 2002). There was also evidence proving that reducing the IOP could preserve the vision, this was reported by the Collaborative Normal Tension Glaucoma Study (CNTGS). The study concluded that by reducing the IOP by at least 30% lowered the rate of visual field progression significantly from 35% to 12% (Anderson, 2003) .

Medical treatment of glaucoma can be divided into several groups of ocular hypotension based on chemical structure and pharmacologic action. These include:

- β - adrenergic antagonists

- Prostaglandin analog
- carbonic anhydrase inhibitors
- parasympathomimetics
- adrenergic agonist (selective and non-selective α_2- agonist)

There are many factors required for consideration before initiating the treatment of glaucoma, which include selecting the appropriate medication, establishing the target IOP and follow-up evaluations to establish efficacy and most important the safety of the treatment. The selection of appropriate medication is exceedingly individualised. It is most appropriate begin with monotherapy, easier to comply with, less side effects and is undeniably more cost effective.

As the elevated IOP is the vital risk factor for glaucoma development and progression, the physicians must establish a target pressure that can prevent further glaucomatous damage. The target pressure is based on the status of optic nerve heads and other risk factors associated with progression.

1.2.1.1 Non-fixed combination treatment

The ocular hypotensive medications can be administered in a non-fixed combination, fixed combinations or systemic medication. The non-fixed medication is a single type of ocular hypotensive medication that derived from the group mentioned above. Table 1.1 illustrates ocular hypotensive medication according to chemical structure.

Table 1.1: Ocular hypotensive medications

Drug Classification	Methods of Action	IOP Reduction*	Side Effects	Contraindications
Prostaglandin analogs	Increase uveoscleral and/or trabecular outflow	25%–33%	- Cystoid macular edema - Conjunctival injection - Increased eyelash growth - Periocular hyperpigmentation - Iris color change - Uveitis - Possible herpes virus activation	- Macular edema - History of herpetic keratitis
Beta-adrenergic antagonists (beta-blockers)	Decrease aqueous production	20%–25%	- Corneal toxicity - Allergic reactions - CHF (classic teaching, although cardiologists use beta-blockers as first line treatment in CHF) - Bronchospasm (seen with nonselective) - Bradycardia - Depression - Impotence	- Chronic obstructive pulmonary disease (nonselective) - Asthma (nonselective) - CHF (check with cardiologist) - Bradycardia - Hypotension - Greater than first degree heart block
Alpha-adrenergic agonists	Nonselective: improve aqueous outflow Selective: decrease aqueous production; decrease episcleral venous pressure or increase uveoscleral outflow	20%–25%	- Conjunctival injection - Allergic reactions - Fatigue - Somnolence - Headache	- Monoamine oxidase inhibitor therapy - Infants and children younger than 2 years
Parasympathomimetic agents	Increase trabecular outflow	20%–25%	- Increased myopia - Eye or brow ache/pain - Decreased vision - Cataract - Periocular contact dermatitis - Corneal toxicity - Paradoxical angle closure	- Neovascular, uveitic, or malignant glaucoma - Need to regularly assess fundus
Carbonic anhydrase inhibitors (mainly with systemic use)	Decrease aqueous production	15%–20%	With topical route: - Metallic taste - Allergic dermatitis/conjunctivitis - Corneal edema With oral route: - Stevens-Johnson syndrome - Malaise, anorexia, depression - Serum electrolyte imbalance - Renal calculi - Blood dyscrasias (aplastic anemia, thrombocytopenia) - Metallic taste	- Sulfonamide allergy - Kidney stones - Aplastic anemia - Thrombocytopenia - Sickle cell disease

Table derived from Preferred Practise Pattern Guidelines. Primary Open Angle Glaucoma, San Francisco, CA: American Academy of Ophthalmology; 2010.

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Timoptic-XE is a timolol maleate ophthalmic gel forming solution and a non-selective beta-adrenergic receptor blocking agent. The gel forming solution contains a purified anionic heteropolysaccharide derived from gellan gum. Upon contact with the precorneal tear film, timoptic-XE forms a gel that is subsequently removed by the flow of tears.

Pharmacologically, it reduced IOP by a reduction in aqueous formation. The ocular side effects of Timoptic-XE are pain, conjunctivitis, crusting discharge, foreign body sensation, itching and tearing. The systemic side effects include headache, dizziness, and upper respiratory infection.

Dorzolamide or generic name Trusopt® is a dorzolamide hydrochloride ophthalmic solution 2%. It is a carbonic anhydrase inhibitor that decreases the aqueous humor secretion. Therefore it reduces the intraocular pressure by presumably slowing the formation of bicarbonate ion with subsequent reduction in sodium and fluid transport.

The most frequently reported adverse reactions are ocular burning, stinging,and discomfort immediately following the instillation of the eye drops. Approximately one-quarter of patients reported a bitter taste, 10-15% developed superficial punctate keratitis and 10% experienced symptoms and signs of ocular allergic reaction. Other ocular and systemic adverse reactions were reported infrequently, including headaches, nausea, asthenia/fatigue; and there occurred rare complication of, skin rashes, urolithiasis and iridocyclitis.

1.2.1.2 Fixed combination medication

In recent years, fixed combination IOP lowering agents has gained its popularity. The fixed combinations contain two medications in a single bottle and offer several advantages over concurrent medication used. The fixed combination was more convenience, received better adherence, reduced exposure to preservative, reduced the effects of " washout" when

instilling multiple doses and is possibly more cost effective compared to the two separate bottles (Bell *et al.*, 2010).

The fixed combination dorzolamide/timolol maleate available as Cosopt® (Merck & Co.Inc.) was proved by the Food and Drug Administration (FDA) in 1998. It is a combination of dorzolamide 2% and timolol maleate 0.5%. Pharmacologically, it reduced the IOP by decreasing aqueous humour production, they tend to have an additive and synergistic effect when administered together either as a fixed combination or concomitantly. The ocular side effects are the same as for both drugs individually. Table 1.2 represents fixed-combination ocular hypotensive medication. The mode of action and side effects are similar to the individual drug. Intraocular pressure-lowering effects of commonly used fixed combination drugs with timolol in the management of POAG were studied by Ozer M.A et al. They discovered that brinzolamide/ timolol, dorzolamide/timolol and latanaprost/timolol revealed analogous lowering efficacies on an IOP level (Ozer M.A *et al.*, 2014).

Table 1.2: Fixed combination ocular hypotensive medications.

Class/compound	**Brand name**	**Dosage**	**Mode of action**	**IOP decrease**
Timolol / dorzolamide	Cosopt	bid	Decrease aqueous production	25% -30%
Timolol / Latanaprost	Xalacom	qd	Decrease aqueous production and increase uveoscleral outflow	Greater than monotherapy with each individually
Timolol / Travoprost	DuoTrav	qd	Decrease aqueous production and increase uveoscleral outflow	Same as above
Timolol / Bimatoprost	Ganfort	qd	Decrease aqueous production and increase trabecular and uveaoscleral outflow	Same as above
Timolol / brimonidine tartrate	Combigan	bid	Decrease aqueous production and increase uveoscleral outflow	Same as above

Table information adapted from American Academy of Ophthalmology: Glaucoma. 2011-2012

1.2.2 Surgical treatment

Surgical treatment for glaucoma is undertaken when medical therapy has failed, not tolerated well, is ineffectual and if glaucoma remains uncontrolled with documented progressive damage. Trabeculectomy is the gold standard of surgical intervention for POAG. It is a creation of fistula between the anterior chamber to the subconjunctival space to providing alternative drainage of aqueous outflow.

The use of low dose concentration of mitomycin intraoperatively has favourable outcomes in primary glaucoma patients after a 2 years follow-up.(Huang *et al.*, 2013)

The glaucoma drainage device implant should be considered in POAG patients who failed trabeculectomy with antifibrotics, patients with inadequate conjunctiva who had undergone severe trauma or extensive retinal detachment surgery and patients with associated active uveitis, neovascular glaucoma or aphakic eyes.

The Collaborative Initial Glaucoma Treatment Study (CIGTS) compared initial treatment of newly diagnosed open-angle glaucoma with either medications or immediate filtration surgery. After 5 years, trabeculectomy lowered IOP marginally more effectively than initial medical therapy. Both groups resulted IOP reduction of 37% and the outcome was a very low incidence of visual field progression (Lichter *et al.*, 2001).

1.3 Intraocular Pressure (IOP) and its measurement

Intraocular pressure is an essential modifiable risk factor in preventing the development and progression of glaucoma. The IOP is determined by the balance between the rate of aqueous secretion and aqueous outflow. Any circumstances that effect the aqueous humour formation and outflow causes changes to the IOP. These include the local and systemic disorders, medication and surgeries.

There exist multitudinous methods of IOP measurement. These methods are applanation tonometers, indentation tonometers, dyanamic contour tonometer, pneumotonometer (air puff) and transpalpebral tonometer. Goldmann Applanation Tonometer (GAT) is the most commonly used and is considered the gold standard of IOP measurement (Yilmaz *et al.*, 2014). The applanation tonometer system calculates the IOP by measuring the flattened corneal area with constant force. However ,Goldmann Applanation Tonometer reading can be affected by corneal thickness, corneal curvature, modulus of elasticity (ocular rigidity) and tears films (Chihara, 2008). GAT underestimates the IOP in thin corneas and overestimates IOP in thick corneas (ElMallah and Asrani, 2008).

There are numerous advances in the development of tonometry, such as dynamic contour tonometry which measures IOP with less dependence on corneal properties compared to GAT. Other convenient and easy to use tonometry is rebound tonometer which can be utilized at home and the reading is well correlated with GAT (ElMallah and Asrani, 2008).

1.4 Adherence of Medication

1.4.1 Defination of Adherence

Patient adherence was recognised as an imperative tool to effective treatment and successful management of the chronic diseases. Adherence to medication is the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen (Cramer *et al.*, 2008). The term is used interchangeably with compliance to medication. Medication persistence refers to the act of continuing the treatment for the prescribed duration or may be defined as the duration of time commencing from initiation to discontinuation of therapy (Cramer *et al.*, 2008). Glaucoma medication adherence can be measured in several ways, including self- report, pharmacy refill reports, electronic monitoring and direct observation (Sleath *et al.*, 2011) .

1.4.2 Measurement of adherence

The gold standard of monitoring the adherence in glaucoma is by electronic monitoring. During a one month study of adherence, the self- reported adherence was 100% whereas, microchips documented actual adherence of only 76% (Okeke *et al.*, 2009). The electronic monitoring provides additional information than prescription refill rate or alternative methods because it incorporates a time component (Robin *et al.*, 2007).

Sleath, Blalock et al have developed a Glaucoma Medication Self-efficacy Questionnaire which examines adherence to glaucoma medication and self-confident eye drops technique. They found that the 10 items Glaucoma Medication Adherence Self- efficacy Scale was significantly associated with the objective electronic measure of adherence (β coefficient

8.52%, 95% CI 1.94 to 15.1) .Patients who are expected to be non-adherent will have a lower score in the scale (Sleath *et al.*, 2011).

Hong S et al implemented a subjective drug adherence score in their study of patients' attitudes towards anti-glaucoma medication and their association with adherence. They reported that patients with negative approaches towards anti-glaucoma drugs tend to exhibit lesser degree adherence than patients with positive attitudes.(Hong *et al.*, 2010).

1.4.3 Factors affecting adherence

Adherence to medication was associated with patient's understanding of the disease and rationale of the treatment and complexity of the treatment regime. Additional of second medication and complexity of glaucoma therapy was associated with a decrease in adherence by increasing intervals until refilling of medication. Many reasons for non-adherence or non-persistence include cost ,tolerability, difficulty in administering drops, denial, lack of education, forgetfulness, schedule and travel issue (Schwartz and Quigley, 2008)

Study conducting on adherence by Tsai J.C, identified 4 major types of barriers to adherence. The barriers are medication regimen, patient factors including the elderly, reduced cognition and musculoskeletal problems, provider factors and situational or environment factors (Tsai, 2009). Okeke et al conducted a study on patients with once a day administered glaucoma medication, found that interventional strategies consisting of education and reminder systems

improved adherence rates from 54% to 75% . IOP does not correlate with adherence (Okeke *et al.,* 2009)

1.5 Rationale Of The Study

There are a few studies which centre on comparing the effectiveness between fixed combinations dorzolamide/timolol maleate and non-fixed dorzolamide and timolol maleate completed previously.

However, during the course of our study, we compared the effectiveness of fixed combinations to the non-fixed of dorzolamide and timolol XE within our population. We would also like to compare the adherence to medication between these 2 groups. We hope that this study will assist in improving our management of glaucoma patients.

CHAPTER 2

OBJECTIVE

CHAPTER 2: OBJECTIVE

2.1 General Objective

To study the effectiveness and adherence of fixed combinations dorzolamide/ timolol maleate (FCDT) and non-fixed dorzolamide and timolol XE (NFDT) in open angle glaucoma.

2.2 Specific Objectives

2.2.1 To determine the pressure lowering effects of fixed combinations dorzolamide / timolol maleate (FCDT) and non-fixed dorzolamide and timolol XE (NFDT)

2.2.2 To compare the pressure lowering effects of fixed combinations dorzolamide / timolol maleate (FCDT) and non-fixed dorzolamide and timolol XE (NFDT) at month 1 and month 3 from the baseline.

2.2.3 To determine the adherence score (i.e Glaucoma Medication Adherence Self-Efficacy Scale , bottle weight and subjective drug adherence score) of fixed combinations dorzolamide / timolol maleate and non-fixed dorzolamide and timolol XE.

2.2.4 To compare the total adherence score to medication of fixed combinations dorzolamide / timolol maleate and non-fixed dorzolamide and timolol XE at month 3.

CHAPTER 3

METHODOLOGY

CHAPTER 3: METHODOLOGY

3.1 Study Design

Randomised, single blinded involving two parallel groups clinical trial.

3.2 Population, location and duration

3.2.1 Study population

All patients from Hospital Universiti Sains Malaysia(USM), Kelantan whom fit the inclusion criteria.

3.2.2 Study location

Eye Clinic, Hospital USM, Kota Bharu, Kelantan

3.2.3 Study duration

From August 2012 to October 2014

3.3 Ethical Approval

This study was approved by the Research and Ethics Committee (Human) Universiti Sains Malaysia (USM), Clinical Science Research Platform, USM Health Campus on 8th August 2012 (reference no USMKK/PPP/JEpeM) [252.3(6)] (Appendix E). This study was conducted in accordance to Declaration of Helsinki for Human Research.

3.4 Randomisation Method

Non probability sampling was applied in the study. Block of 4 randomization method was used to assign patient into fixed combinations dorzolamide/ timolol maleate (FCDT) group and non-fixed combinations dorzolamide and timolol XE (NFDT) group. A randomized block size of 4 was chosen, balanced combination of 6 (AABB, ABAB, ABBA, BAAB, BABA, BBAA). Block was randomly chosen by using random number 1-6 to determine the assignment of all 58 participants. This procedure results in 29 participants in each group.

3.5 Sampling and Sample Size

3.5.1 Sampling Method

All POAG and NTG patients attending glaucoma clinic, HUSM between August 2012 and October 2014 who fulfilled the selection criteria were recruited through non-probability sampling.

3.5.2 Sample size calculation

1. a) To determine the pressure lowering effect of fixed combination dorzolamide and timolol maleate (FCDT)

Sample size determination using single mean formula

$$n = \left[\frac{z\,\sigma}{\Delta} \right]^2$$

n = sample size σ= standard deviation Δ= precision

σ = 3.9 mmHg (Choudhri S et al ,2000), Δ = 1.2 mmHg , z = 1.96

n = 41

to consider 10 % drop out during the study , (41 + 4), n = 45

1. b) To determine the pressure lowering effect of non-fixed dorzolamide and timolol meleate

$$n = \left[\frac{z\,\sigma}{\Delta} \right]^2$$

σ = 4.1 mmHg (Chouldri S et al , 2000) , Δ = 1.2 mmHg , z = 1.96

n = 45

to consider 10 % drop out during the study , (45 + 5), n = 50

2. a) to compare the pressure lowering effect of fixed combination dorzolamide and timolol malaete (FCDT) and non-fixed dorzolamide and timolol XE (NFDT) at month 1

Sample size per group by two mean formula,

$$n : \frac{2\sigma^2 (Z\alpha + Z\beta)^2}{\Delta^2}$$

n = required sample size σ= standard deviation Δ= precision

Zα= value of standard normal distribution cutting off probability α

Zβ= value of standard normal distribution cutting probability β

Zα = 1.96 for α = 0.05 (two tailed) , zβ = 1.28 for 90% power

Δ = 3.5 mmHg, σ = 3.9 mmHg (Chouldri S et al 2000)

n = 26

to consider 10% drop out during the study, (26 + 3) = 29

therefore sample size for 2 groups are 58

2. b) to compare the pressure lowering effect of fixed combination Dorzolamide and timolol malaete (FCDT) and non-fixed Dorzolamide and Timolol XE (NFDT) at month 3

Sample size per group by two mean formula,

$$n : \frac{2\sigma^2 (Z\alpha + Z\beta)^2}{\Delta^2}$$

$Z\alpha = 1.96$ for $\alpha = 0.05$ (two tailed) , $z\beta = 1.28$ for 90% power

$\Delta = 3.2$ mmHg, $\sigma = 3.5$ mmHg (Strohmaier K et al, 1998)

n = 25

to consider 10% drop out during the study, (25 + 3) = 28

therefore sample size for 2 groups are 56

3. a)To determine the adherence to medication of fixed combination Dorzolamide/ timolol meleate

Sample size calculation using single proportion formula

$$n = \left[\frac{z}{\Delta} \right]^2 p\,(1-p)$$

n = required sample size, p= anticipated population proportion, Δ= absolute precision

P= 0.9, $\alpha = 0.05\%$, $\Delta = \pm 12\ \%$

n = 24,

to consider 10% drop out during the study, (24 +2) , n = 26

3. b) To determine the adherence to medication non-fixed dorzolamide and timolol XE.

Sample size using single proportion formula

$$n = \left[\frac{z}{\Delta} \right]^2 p\,(1-p)$$

P= 0.65, $\alpha = 0.05\%$, $\Delta = \pm 15\ \%$

n = 38,

to consider 10% drop out during the study, (38+ 4) , n = 42

4.a) To compare the adherence to medication of fixed combination dorzolamide and timolol melaete and non-fixed dorzolamide and timolol XE.

Sample size calculation using two proportions formula

$$n = \frac{P_1 (1- P_1) + P_2 (1-P_2)}{(P_1 – P_2)^2} (Z\alpha + Z\beta)^2$$

n = required sample size,

Zα= value of standard normal distribution cutting off probabilily α

Zβ= value of standard normal distribution cutting off probability β

Zα = 1.96 for α = 0.05 (two tailed), Zβ = 0.84 for 80% power

P_1 = 0.65, proportion of adherence to non-fixed glaucoma therapy (pilocarpine, QID doses) (Kass MA et al, 1986)

P_2 = 0.94, expected proportion of study outcome

n = 26

to consider 10% drop out during the study, (26+3 =29)

Therefore, n= 58

3.6 Selection Criteria

3.6.1 Inclusion Criteria

- Age more than 40 years old
- Unilateral or bilateral open angle glaucoma, if bilateral eyes were eligible for the study the right eye will be chosen.
- Glaucoma patients who received monotherapy or dual therapy.

3.6.2 Exclusion Criteria

- Secondary open angle glaucoma
- Contraindication to use beta blocker antiglaucoma drug such as patient with chronic obstructive pulmonary disease, asthma, bradycardia and second and third degree heart block
- IOP more than 35 mmHg on dual therapy during follow-up
- Known hypersensitivity to any product of investigational product such as benzylkonium chloride or sulphonamide.