

**CHANGES OF RETINAL NERVE FIBER LAYER
THICKNESS, MACULAR THICKNESS AND
CHOROIDAL THICKNESS IN MIGRAINE PATIENTS
ON TOPIRAMATE**

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DISCLAIMER

I hereby state that the work in this dissertation is entirely mine, with the exception of quotations, some figures, and summaries which have been duly acknowledged. I declare that I have no financial of interest in the instruments and the computer software used in this study.

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(Dr Sruban A/L Suparmaniam)

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ABSTRACT

Introduction:

Migraine is a common primary headache disorder and is ranked as the world's second leading cause of years lived with disability. It is a neurovascular disorder believed to cause altered and permanent structural abnormalities to the optic nerve, retina, and choroid. Topiramate (TPM) is a sulfa-derivative monosaccharide that is effective as a preventive therapy for migraine. TPM may impair retinal function when administered for long periods. Retinal nerve fiber layer (RNFL) thickness measurement can be used as an index to assess ganglion cell and retinal nerve fiber damages while alteration of macular thickness (MT) and choroidal thickness (CT) values due to decreased blood flow in migraine with the usage of TPM can affect the visual functions.

Objectives:

The aim of this study is to assess changes in RNFL thickness, MT, and CT in migraine patients on topiramate (TPM).

Methods:

This cross-sectional study involves migraine patients with and without TPM attending the Neurology Clinic and Ophthalmology Clinic at Hospital USM and Hospital Raja Perempuan Zainab II (HRPZ II) Kota Bharu, Kelantan. The RNFL thickness, MT, CT was measured using Cirrus HD-OCT 5000 and statistical analysis was done using SPSS Inc Version 26.

Results:

A total of 84 migraine patients (42 patients with TPM and 42 patients without TPM) were recruited into the study and were analysed. With respect to all mean values of RNFL thickness and MT in all quadrants, there were no statistically significant differences in migraine patients with TPM and control. For subfoveal CT, there was a significant increase with adjustment of age and gender (adjusted mean 272.26 μ m; 95% CI = 263.73, 280.80 vs 288.14 μ m; 95% CI = 279.60, 296.68; $p = 0.011$).

Conclusion:

This study showed no significant differences between RNFL thickness and MT in migraine patients with and without TPM. Compared to control, there was a significant increase in central subfoveal CT in migraine patients with TPM. The CT measurement during the use of TPM in migraine patients can be considered as a potential non-invasive follow-up method in asymptomatic patients.

ABSTRAK

Pengenalan:

Migrain adalah gangguan sakit kepala utama yang sering berlaku dan disenaraikan sebagai penyebab kedua utama untuk tahun hidup dengan kecacatan. Ia adalah gangguan neurovaskular yang dipercayai menyebabkan perubahan dan keabnormalan kekal kepada struktur di saraf optik, retina, dan koroid. Topiramate (TPM) adalah monosakarida derivatif sulfa yang berkesan sebagai terapi pencegahan untuk migrain. TPM boleh menjejaskan fungsi retina sekiranya di gunakan untuk tempoh yang lama. Pengukuran ketebalan lapisan saraf retina mata (LSRM) boleh digunakan sebagai indeks untuk menilai kerosakan sel ganglion dan lapisan saraf retina manakala perubahan ketebalan makular (KM) dan ketebalan koroid (KK) disebabkan oleh penurunan aliran darah dalam migrain dengan penggunaan TPM boleh menjejaskan fungsi visual.

Objektif:

Matlamat kajian ini adalah untuk menilai perubahan dalam ketebalan LSRM, KM, KK dikalangan pesakit migrain yang mengambil topiramate (TPM).

Kaedah:

Kajian keratan rentas ini melibatkan pesakit migrain yang menggunakan TPM dan tanpa TPM yang menghadiri ke Klinik Neurologi dan Klinik Oftalmologi di Hospital USM dan Hospital Raja Perempuan Zainab II (HRPZ II) Kota Bharu, Kelantan. Ketebalan LSRM, KM, KK diukur menggunakan Cirrus HD-OCT 5000 dan analisis statistik dilakukan menggunakan SPSS Inc Versi 26.

Keputusan:

Sejumlah 84 orang pesakit migrain (42 pesakit menggunakan TPM dan 42 tanpa TPM) telah direkrut ke dalam kajian ini dan telah dianalisis. Secara statistik tidak ada perbezaan yang signifikan untuk LSRM dan KM antara pesakit migrain dengan TPM dan kawalan. Terdapat peningkatan yang ketara dan signifikan untuk KK subfovea selepas melakukan penyelarasan umur dan jantina (purata diselaraskan 272.26 μ m; 95% CI = 263.73, 280.80 vs 288.14 μ m; 95% CI = 279.60, 296.68; $p = 0.011$).

Kesimpulan:

Kajian ini menunjukkan tiada perbezaan signifikan untuk ketebalan LSRM dan KM pada pesakit migrain yang menggunakan TPM dan tanpa TPM. Berbanding dengan kawalan, terdapat peningkatan ketara dalam KK subfoveal untuk pesakit migrain dengan TPM. Pengukuran KK semasa penggunaan TPM dalam pesakit migrain boleh dianggap sebagai kaedah susulan bukan invasif yang selanjutnya untuk pesakit tanpa gejala.

CHAPTER 1

INTRODUCTION

1. INTRODUCTION

1.1 Study Introduction

Migraine is a common and disabling primary headache disorder. In the Global Burden of Disease Study 2016 (GBD2016), it was ranked as the second leading cause of disability in the world in terms of interfering with family, educational, occupational, household, and social responsibilities. The pathogenesis of migraine involving the neurovascular system consists of activation and sensitisation of the trigeminovascular system. It is a neurovascular disorder characterised by headaches, mainly episodic and unilateral dull to throbbing in nature, with various cognitive, autonomic, emotional, and motor disturbances. There can also be the presence of neurological symptoms, including nausea and hypersensitivity to sound, light, and smell, nausea (Nosedá R and Burstein R, 2013).

Topiramate (TOPAMAX[®], Ortho-McNeil Pharmaceuticals, Raritan, New Jersey, USA) (TPM) is a sulfa-derivative monosaccharide known to be effective and safe for treating migraines, seizures, neuropathic pain, and a wide spectrum of psychiatric disorders such as bipolar disorder and post-traumatic stress disorder. It is also an off-label weight reduction agent (Ozturk et al., 2011). However, the range of diverse adverse effects of the drug is increasing; hence it is imperative for neurologists, psychiatrists, and ophthalmologists to be aware of these risks. The Food and Drug Administration approved the use of TPM for migraine prevention in 2004.

The ocular side effects of TPM are well documented and established such as acute angle closure glaucoma, acute onset myopia, suprachoroidal effusions, visual field defects, uveitis,

hyperaemia, mydriasis, ocular headache, blepharospasm, oculogyric crisis, scleritis, and retinal haemorrhage (Hesami et al., 2016).

The pathology involved in migraine can cause permanent structural abnormalities to the brain as well as the retina, choroid and optic nerve. When used over extended periods, TPM may impair retinal function (Abtahi et al., 2012). The retina's function depends on a normal retina's structure and choroidal vasculature, as abnormal choroidal blood volume can compromise flow, resulting in ganglion cell death (Demircan et al., 2015). Retinal nerve fiber layer (RNFL) thickness measurement can be used as an index to assess ganglion cell and retinal nerve fiber damage (Michael et al., 2019). Changes in foveal thickness values due to decreased blood flow can affect the visual functions (Cankaya and Tecellioglu, 2016). Choroidal thickness (CT) affects many ocular diseases and is associated physiological changes of the choroid layer (Kara et al., 2015).

The quantitative measurement of RNFL thickness, MT, and CT parameters can be obtained using optical coherence tomography (OCT). Moreover, OCT is a non-invasive and non-contact imaging technique that can be easily performed in the clinic. RNFL thickness, MT, and CT are likely to be affected by the disease and also with usage of TPM. Therefore, we aim to assess RNFL thickness, MT, and CT changes between migraine patients with and without TPM.

1.2 Study Rationale

The current knowledge regarding the complexity of migraine pathophysiology suggests primary neuronal dysfunction and is still evolving. TPM is the more effective treatment choice in preventive therapy for migraine and the usage of TPM may increase exponentially in the future.

TPM has been found to cause ocular side effects and has also been reported to have structural changes in the retina and choroid (Abtahi et al., 2012; Gok and Ozdemir, 2017). However, very few studies have been performed with migraine patients on TPM and changes in ocular structure, as majority focuses on the anterior part of the eye (Hesami et al., 2016).

This study aims to assess the changes in RNFL thickness, MT, and CT in migraine patients on TPM, which reflect the anatomical integrity of the optic nerve, retina, and choroid. It is also to determine subclinical changes before it leads to progressive and irreversible loss of axons and retinal ganglion cells, which can be reflected in the long-term usage of TPM. Hence, it can contribute to accomplishing better guidelines and added as a routine eye examination in migraine patients with TPM as the treatment of choice.

In this study, we will compare the parameters mentioned as above between migraine patients not on TPM as the control group and migraine patients on TPM.

CHAPTER 2

LITERATURE REVIEW

2. LITERATURE REVIEW

2.1 Migraine

Migraine refers to a primary headache disorder that causes an enormous burden on patients and society. The prevalence of migraine worldwide, according to GBD 2016, is 1 in 7 people. The ratio of female migraine sufferers tends to outnumber males by nearly 3 to 1. In 1996, the prevalence of migraines in Malaysia was 9% (Shaik et al., 2015).

According to the International Classification of Headache Disorder, 3rd edition (ICHD-3) in 2018, migraine has two major types. Migraine without aura is a clinical syndrome characterized by headache with specific features and associated symptoms; migraine with aura is primarily characterized by the transient focal neurological symptoms that usually precede or sometimes accompany the headache. Some patients also experience a prodromal phase, occurring hours or days before the headache, and/or a postdromal phase following headache resolution (Olesen, 2018).

Diagnostic criteria include at least two attacks fulfilling one or more of the following fully reversible aura symptoms such as visual, sensory, speech and/or language, motor, brainstem, or retinal. It also must have at least three of the following six characteristics: at least one aura symptom spreads gradually over more than 5 minutes, two or more aura symptoms occur in succession, each aura symptom lasts 5 to 60 minutes, at least one aura symptom is unilateral, at least one aura symptom is positive, the aura is accompanied or followed within 60 minutes by a headache (Eigenbrodt et al., 2021).

2.2 Pathophysiology of Migraine

Multiple hypotheses have been considered for the pathophysiology of migraine. The initial vascular theory hypothesised that migraine is caused by dilatation of blood vessels, and the aura of migraine from vasoconstriction has receded. With the advancement of science and radio imaging, migraine is viewed as a complex brain network disorder with a strong genetic basis that involves multiple cortical, subcortical, and brainstem regions. Migraine has several phases; premonitory symptoms, aura, headache, and postdrome (Puledda et al., 2017).

In the premonitory phase, which can begin as early as three days prior to migraine headache symptoms, can be wide-ranging from point to the involvement of hypothalamus, brainstem, limbic system, and a certain area of cortical. It displays a diurnal periodicity and is commonly triggered by alteration in homeostasis, which suggests the involvement of chronobiological mechanism and hypothalamus as a potential site of origin of migraine attack (van Oosterhout et al., 2018). There are two theories for this mechanism; the first suggests that increased parasympathetic tone activates meningeal nociceptors, and the second involves modulation of nociceptive signals from the trigeminal nucleus caudalis to supratentorial structures involved in pain processing (Nosedá et al., 2014).

Migraine triggers, for example, stress, awakening, or changes in physiological or emotional homeostasis, activate the nociceptive pathways through increased parasympathetic tone. There will be norepinephrine release from the sympathetic outflow into the meninges that leads to nociceptive signalling through actions on dural afferents and dural fibroblasts. These will project to preganglionic parasympathetic neurons in the superior salivatory nucleus, causing

peripheral nociceptor activation by releasing neuropeptide transmitter (Burstein and Jakubowski, 2005).

In the aura phase, a phenomenon known as Cortical Spreading Depression (CSD) which Aristides Leão first described in 1944, is thought to be the neurophysiological association of migraine. It is characterised by a slow (2–6 mm/min) propagating wave of depolarisation in neuronal and glial cell membranes that is followed by inhibition of cortical activity for up to 30 minutes, corresponding with the initiation and progression of aura symptoms (Charles and Brennan, 2009).

The pathophysiology of headache in migraine involves activating the trigeminovascular system that conveys nociceptive information from the meninges to the central areas of the brain and subsequently to the cortex. These nociceptive fibers originate from the trigeminal ganglion and upper cervical dorsal roots (Bartsch and Goadsby, 2003). The vast majority of the innervation of the anterior structures is via the ophthalmic division of the trigeminal nerve and upper cervical roots to posterior structures with convergence at the trigeminal nucleus caudalis. The convergence of afferent projections with neurons from extracranial structures explains the referred pain perception in the regions of the periorbital, occipital, and cervical neck (Bartsch and Goadsby, 2005). Activation of the trigeminovascular pathway involves the stimulation of the trigeminal ganglion, resulting in the release of vasoactive neuropeptides such as calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating polypeptide-38 and neurokinin A, which cause vasodilation and plasma protein extravasation (Amin et al., 2014).

This neurogenic inflammation leads to a process of sensitization. It is a process in which neurons become responsive to nociceptive and non-nociceptive stimulation, causing their response threshold to decrease and the magnitude of their response to increase (Burstein and Jakubowski, 2005). Peripheral sensitization in the primary afferent neurons mediates the throbbing perception of headache. Central sensitization happens within second order neurons in the trigeminal nucleus caudalis, and higher order neurons in the central nervous system are responsible for cephalic and extracephalic allodynia (Burstein et al., 2015).

Migraine attacks impose both functional and structural retinal changes. The functional changes are fully reversible after the aura, but the structural ones are not reversible. Thus, active prevention of migraine attacks would be protective for the retina (El-Shazly et al., 2017).

2.3 Topiramate in Migraine

TPM is a sulfamate-substituted monosaccharide derived from D-fructose. TPM acts by inactivating voltage-gated sodium channels, which leads to hyperpolarisation of potassium currents. In addition, it inhibits kainate-mediated conductance and activates GABA(A) postsynaptic receptors, subsequently enhancing the inhibitory effects. Furthermore, TPM inhibits some subtypes of the enzyme carbonic anhydrase (Shank et al., 2000).

In migraineurs, TPM shows an array of pharmacodynamic effects that could explain its efficacy, such as reducing cortical hyperexcitability that leads to cortical spreading depression. It also inhibits glutamatergic signalling by trigeminal afferent nerves or modulates nociceptive signalling through GABA-receptors in the trigeminal nucleus caudalis or in descending brain pathways (Shank et al., 2000).

Treatment for migraine falls into two categories: acute and preventive. The main aim of preventive therapy is to reduce the frequency of the attacks, duration, and severity. TPM is used in preventive therapy to improve responsiveness to acute treatment, enhance functional status, and reduce disability. Typically, the TPM dose used in migraine is 50 to 200 mg (Linde et al., 2013).

2.4 Ocular side effects of topiramate

The common ocular side effects due to TPM, are acute-onset angle closure glaucoma, acute myopia, suprachoroidal effusions, peri-orbital oedema, scleritis, blepharospasm, oculogyric crisis, nystagmus, and diplopia. The sulfonamide moiety of TPM is the responsible factor for these side effects (Fraunfelder and Fraunfelder, 2004).

The side effects can be wide-ranging, from the anterior up to the posterior segment of the eye. TPM's common ocular side effect is the acute onset of ciliochoroidal effusion syndrome. Ciliochoroidal effusion syndrome can be defined as a spectrum of clinical manifestations ranging from transient TPM-induced myopic shift to severe bilateral TPM-induced acute angle closure glaucoma (AACG) (Abtahi et al., 2012).

In the TPM shift of refractive error to myopia, there are case reports of myopia up to -8.75D. A few mechanisms for the pathophysiology of acute myopia have been postulated regarding the lens osmotic disturbance and swelling causing shallowing of the anterior chamber (9– 16%). Another study shows TPM causes an increase in central cornea thickness (Ozturk et al., 2011).

TPM-induced AACG has been reported to occur within two weeks of commencing treatment (range 1-49 days). It is not dose-related and occurs with doses ranging from 50 mgs to more than 100 mgs (Fraunfelder and Fraunfelder, 2004). The mechanism of this secondary AACG is related to ciliary body oedema, which causes a forward rotation of the ciliary body hence causing the iris to displace forward (Liebmann et al., 1998).

2.5 Retina Nerve Fiber Layer (RNFL) thickness on topiramate

The RNFL is a structure in the eye as it is an extension of the ganglion cell axons, which courses along the inner portion of the retina and aggregates to form the optic nerve which continues to form the optic chiasm and optic tract. The optic nerve head is described as the point where the retinal axons exit in the eye. The RNFL axons are unmyelinated within the retina, and they are ideal for the visualising and analysis of any potential neurodegeneration process (Galletta et al., 2011).

The average RNFL thickness scanned by OCT in healthy Malaysians residing in Kelantan was 95.94 (± 14.77) μm (Abd Hamid et al., 2021). Study showed RNFL thickness significantly thinner in migraineurs' eyes in Malaysia (Michael *et al.*, 2019). There was no significant difference of RNFL thickness in average and all quadrants between subgroups of migraine with aura and migraine without aura (Demircan *et al.*, 2015; Gunes *et al.*, 2016). However, no analysis was done based on the migraine medications for both groups. Based on evidence and consensus agreed upon, preventive migraine treatment can be divided; into established effective such as beta-blocker propranolol, TPM, and valproic acid, probably effective such as amitriptyline, and possibly effective such as carbamazepine (Loder *et al.*, 2012). Changes in RNFL thickness in using propranolol, valproic acid, amitriptyline, and

carbamazepine in migraine patients are not yet established. However, the usage of valproic acid and carbamazepine did not alter any RNFL thickness in epilepsy treatment (González de la Aleja et al., 2019).

TPM side effects on the retina has been investigated. In a prospective cohort study with a follow-up period of 3 months, there was a significant increase in RNFL thickness (Ozturk et al., 2011). In another study, which was done via retrospective observation shows there was a significant decrease of RNFL thickness in one quadrant, but no significant difference was found when the quadrants were averaged (Kara et al., 2015).

2.6 Macular Thickness (MT) on topiramate

Macular is a small area at the centre of the retina bound by temporal vascular arcades that is responsible for central, high resolution and colour vision. MT is the volumetric measurement in three dimensions using OCT based on the Early Treatment Diabetic Retinopathy Study (ETDRS) map. It consists of macular mapping of the posterior pole with the fovea as the central locus. The central macula thickness is the central 1 mm area of a 6 mm mapping as described in the ETDRS study (Adhi et al., 2012).

MT profiles are a common tool for diagnosing and monitoring macular diseases. The overall mean MT as scanned by OCT in healthy Asians was 276.1 (± 13.4) μm (Wong et al., 2019). The MT is significantly thinner in migraine patients (Yurtoğulları et al., 2021; Cankaya and Tecellioglu, 2016). There are case reports regarding TPM maculopathy, and some even report irreversible visual loss. Cases reported showed the presence of cystoid macular oedema and macular striae. The majority of the cases reported stated that maculopathy resolved after

cessation of TPM (Dacosta and Younis, 2016). A study showed a reduction in MT over three months of usage of TPM but was statistically insignificant (Ozturk et al., 2011).

2.7 Choroidal Thickness (CT) on topiramate

The choroid is a pigmented vascular tissue that extends from the ora serrata anteriorly to the optic nerve head posteriorly. Anatomically, it forms the posterior portion of the uveal tract, which continues anteriorly with the ciliary body and the iris. It comprises Bruch's membrane, the choriocapillaris, the medium diameter choroidal vessels (Sattler's layer), the large diameter vessels (Haller's layer), and suprachoroidal space (Ryan, 2006).

In view of choroidal changes having a significant role in the development and progression of various disorders, CT, which reflects choroidal changes, can give clinicians meaningful information (Shin et al., 2012). The most common measurement used in daily practice is subfoveal choroidal thickness and can be done with the use of OCT, enabling detailed in vivo cross-sectional visualisation of the choroid, which is simple, reproducible, high-resolution, and non-invasive (Sezer et al., 2016). The mean subfoveal CT as scanned by Spectralis SD- OCT in healthy Asians ranged from 261.93 μm to 340 μm and a study done in Malaysia showed the overall mean subfoveal CT was 320.08 μm (± 56.08) and thicker in males (Jeffrey et al., 2017).

In migraine, transitory and recurrent constriction of the retinal and ciliary arteries will occur. It may cause ischemic damage to the optic nerve, retina, and choroid. Consequently, CT may decrease, resulting in retinal pigment epithelium and photoreceptors dysfunction (Ascaso et al., 2017).

There have been studies done to evaluate CT in patients with TPM that show an increase in CT. Two prospective cohort-based studies show a prominent increase in CT in migraine patients with TPM (Gok and Ozdemir, 2017; Karalezli et al., 2015). Another study also showed an increase in CT after just being on TPM for 2 weeks but it was not significant (Kara et al., 2015).

In view of changes in RNFL thickness, MT and CT in the migraine patients, only migraine patients were selected in this study to compare and analysed the changes that happened with the usage of TPM. To the best of our knowledge, this is the first study done in the Malaysian population.

CHAPTER 3

OBJECTIVES

3. OBJECTIVES

3.1 Objectives

3.1.1 General Objectives

To assess changes in retina nerve fiber layer thickness (RNFL), macular thickness (MT) and choroidal thickness (CT) in migraine patients on topiramate (TPM).

3.1.2 Specific Objectives

- i. To compare changes of RNFL in patient with migraine on TPM treatment and control group.
- ii. To compare changes of MT in patient with migraine on TPM treatment and control group.
- iii. To compare changes of CT in patient with migraine on TPM treatment and control group.

3.2 Research Questions

- i. Is there any difference between the RNFL thickness measurement in patients having migraine on TPM compare to patients with migraine?
- ii. Is there any difference between the MT measurement in patients having migraine on TPM compare to patients with migraine?
- iii. Is there any difference between the CT measurement in patients having migraine on TPM compare to patients with migraine?

3.3 Research Hypotheses

- i. There are significant changes in the parameters of RNFL measurement in patients having migraine on topiramate.
- ii. There are significant changes in the parameters of MT measurement in patients having migraine on topiramate.
- iii. There are significant changes in the parameters of CT measurement in patients having migraine on topiramate.

CHAPTER 4

RESEARCH METHODOLOGY

RESEARCH METHODOLOGY

4.1 Study Design

A cross sectional study was conducted in the Ophthalmology Clinic Hospital Universiti Sains Malaysia (USM) from December 2020 till June 2022. The study population involved all migraine patients attending Neurology Clinic and Ophthalmology Clinic at Hospital USM and Hospital Raja Perempuan Zainab II (HRPZ II) Kota Bharu, Kelantan during the study duration and fulfilled the selection criteria. A control group of migraine patients, who attended both clinics as above were recruited in the study for comparison.

4.2 Ethical Approval

This study was conducted after approval by the local Human Research Ethics Committee (Universiti Sains Malaysia [USM]/ Jawatankuasa Etika Penyelidikan Manusia [JEPeM]; Registration Number: 20090483 (Appendix A), and from Medical Research and Ethics Committee (MREC); Registration number: NNMR-20-2043-56214(IIR) (Appendix B) with the highest respect for subjects according to the study protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP).

4.3 Selection Criteria

The study group included patients diagnosed with migraine according to ICHD-3, aged 18 years old and above, and indicated for TPM and taken the medication for at least 2 months. Any patients with retinopathy or maculopathy due to hereditary or acquired, refractive error greater than 6.00DS, media opacity including cornea scar, significant cataract and vitreous

haemorrhage that affect the quality of OCT image, optic neuropathy, or optic disc abnormality of other causes such as glaucoma or optic neuritis, history of ocular trauma, history of intraocular surgery was excluded. Patients on systemic oculo-toxic drugs (chloroquine, hydroxychloroquine, allopurinol, ethambutol, oral contraceptive pills, and steroids) were excluded. Patients with systemic disease; concurrent demyelinating disease such as Multiple sclerosis, Parkinsonism, previous cerebral vascular accident or intracranial lesion, brain trauma were also excluded. For the control group, they included migraine patients not on TPM, aged 18 years old and above. The exclusion criteria for control group were same as the study group.

4.4. Sample Size Estimation

This study involved 2 group of subjects: migraine with TPM and migraine without TPM. Sample size for each group was calculated accordingly. For objective i to iii to compare changes of RNFL, MT, CT in patient with migraine on TPM treatment and control group the sample size was calculated based on formula using Power and Sample Size Calculation software version 3.1.2 (Copyright 1997-2009 by Dupont WD and Plummer WD), accessible for free download via the website <http://biostat.mc.vanderbilt.edu/PowerSampleSize>.

Objective i)

Level of significance, α of 0.05 and power of 0.8.

α – level of significant : 0.05

β – power of study : 0.8

clinical meaningful difference : 14.5

Standard deviation : 15.3 (Ozturk et al., 2011)

n = 15 + 10% drop out

= 17 patients for each group

Objective ii)

Level of significance, α of 0.05 and power of 0.8.

α – level of significant : 0.05

β – power of study : 0.8

clinical meaningful difference :33.3

Standard deviation : 22.6 (Ozturk et al., 2011)

n = 35 + 10% drop out

= 40 patients for each group

Objective iii)

Level of significance, α of 0.05 and power of 0.8.

α – level of significant : 0.05

β – power of study : 0.8

clinical meaningful difference 49

Standard deviation : 55.6 (Karalezli et al., 2015)

n =23 + 10% drop out

= 25 patients for each group

The total number of subjects required for this study was taken based on the highest number of sample size calculation in each group. The total sample size was 80 (Migraine with TPM was 40 and the control group migraine without TPM was 40)

4.5 Sampling Method and Subject Recruitment

A convenience sampling method was applied to participant who were attending the Ophthalmology Clinic and Neurology Clinic at Hospital USM and HRPZ II who fulfil the criteria along the duration of study. All selected participants were checked if they fulfil the inclusion and exclusion criteria. Any chosen participant who did not fit the study criteria was dropped, and the next participant was selected. This was done until the desired number of participants required for the study was attained.

4.6 Definition of Terms

4.6.1 Migraine

Migraine refers to a primary headache disorder. It is caused by the activation of a mechanism deep in the brain that leads to release of pain-producing inflammatory substances around the nerves and blood vessels of the head. Migraine is recurrent, often life-long, and characterised by recurring attacks with can include hypersensitivity to sound, light, and smell, nausea.

4.6.2 Topiramate (TPM)

TPM is a sulfa-derivative monosaccharide which known to be effective and safe for the treatment of migraine and commonly use as preventive.

4.6.3 Retinal nerve fiber layer (RNFL)

The RNFL is formed by the radial expansion of the fibers of the optic nerve. Character of this structure around peripapillary area can facilitate optic neuropathies. They are ideal for the visualizing and analysis of any potential neurodegeneration process.

4.6.4 Macular thickness (MT)

Macular is a small area at the centre of retina that. It is important as it is responsible for central, high resolution and color vision. Any defect at macular region can even lead to irreversible legal blindness

4.6.5 Choroidal thickness (CT)

The choroid is a pigmented vascular tissue which extends from the ora serrata anteriorly to the optic nerve head posteriorly. The measurement used in daily practice is subfoveal CT, by using the software's caliper tool to draw a line connecting the outer border of the RPE and the inner border of the sclera at subfoveal region (Margolis and Spaide, 2009).

4.7 Research Tools

4.7.1 Instruments

Refraction set (Snellen Chart, retinoscope, trial frame and trial lens) was used to assess any refractive error prior to fundus examination. Slit lamp biomicroscope with Superfield and 78D lenses (Volk double aspheric) were used in this study for comprehensive ophthalmic examination. Intraocular pressure test done using Goldman Applanation Tonometer (Haag-Streit Bern, Swiss). RNFL thickness, MT and CT were measured using Cirrus HD-OCT 5000 (Carl Zeiss Meditec, Dublin, California, USA)

4.7.2 Topical Anaesthesia

- Gutt Proparacaine 0.5% (Alcon Laboratories, Texas, USA)

Topical proparacaine 0.5%, was used as a topical anaesthetic agent prior to application of the pupil dilation medications.

4.7.3 Dilating eye drops

Dilating eye drops that were used for pupil dilatation were Gutt Tropicamide 1% and Gutt Phenylephrine 2.5%.

- Gutt Tropicamide 1% (Alcon Laboratories, Texas, USA)

Topical tropicamide 1% is a mydriatic agent which is a parasympatolytic agent that inhibit the acetylcholine, resulting in relaxation of sphincter pupillary muscle.

- Gutt Phenylephrine 2.5% (Alcon Laboratories, Texas, USA)

Topical phenylephrine 2.5% is a mydriatic agent which is a sympathetic agonist that act directly on alpha-adrenergic receptors in the eye resulting in contraction of dilator pupil muscle.

4.8 Data collection method

4.8.1 Participant Recruitment

The study was conducted after obtaining approval from the Ethical Committee of Universiti Sains Malaysia and from Medical Research and Ethics Committee (MREC). All migraine patients who come for their follow up in Hospital USM and HRPZ II was selected according to inclusion and exclusion criteria. Patients were counselled regarding the purpose of the study and all steps of procedure for completion of study. Any known adverse reaction related to study procedure and anticipated benefits were informed as well. Patient information sheets were also provided to all patients prior to obtaining a written consent (Appendix D and F). The above information (Patient information sheet and consent) was provided in Bahasa Malaysia for patients who were unable to understand the English language (Appendix E and G). All the data of the consented patient was entered into the patient's demographic data form. In this study, only one eye was selected for each migraine patient.