EVALUATION OF OPTIC NERVE HEAD PARAMETERS AND VISUAL EVOKED POTENTIAL AMONG BREAST CANCER PATIENTS ON TAMOXIFEN

BY

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MD (USM)

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FORMAT B

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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.

Dated: 23rd May 2017

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Dr. Tan Chai Lee

P-UM 0099/13

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ABSTRAK

Latar belakang:

Retinopati dan neuropati optik merupakan kesan sampingan yang telah dikenal pasti disebabkan oleh rawatan dengan tamoxifen. Pemeriksaan dengan konfokal laser oftalmoskopi skan (*Scanning confocal laser ophthalmoscopy*) pada kepala saraf optik mendapati saiz cawan optik yang lebih kecil di kalangan pesakit yang menerima rawatan tamoxifen tanpa menunjukkan simtom masalah penglihatan. Ujian elektrofisiologi merupakan salah satu pemeriksaan yang tidak invasif untuk mengkaji fungsi retina dan ujian ini boleh membezakan antara masalah kerosakan retina atau saraf optik. Kajian ini bertujuan untuk mengkaji kesan awal tamoxifen pada parameter kepala saraf optik dan elektrofisiologi di kalangan pesakit menerima rawatan tamoxifen.

Kaedah:

Ini merupakan kajian prospektif melibatkan jumlah 76 mata dari 38 orang pesakit kanser payudara yang menerima rawatan ubat tamoxifen di Hospital Universiti Sains Malaysia, Kelantan, Malaysia. Pesakit menjalani pemeriksaan oleh hanya seorang doktor dan semua ujian dilakukan oleh seorang juruteknikal perubatan. Ketajaman penglihatan, fungsi saraf optik, medan penglihatan, pemeriksaan mata, pengukuran parameter kepala saraf optik dengan *Heidelberg Retinal Tomograph III* (HRT III) dan corak potensi ransangan visual (*pattern visual evoked potential*) diperiksa ke atas pesakit sebelum dan 3 bulan selepas rawatan tamoxifen dimulakan.

Keputusan:

Didapati tiada kesan sampingan okular di kalangan pesakit selepas 3 bulan menerima rawatan tamoxifen. Tahap ketajaman visual dan fungsi saraf optik tidak menunjukkan perubahan selepas rawatan. Tiada perubahan signifikan dikenalpasti dalam parameter kepala saraf optik dan latensi P 100 dan amplitud pada ujian corak potensi rangsangan visual di kalangan pesakit selepas menerima tamoxifen.

Kesimpulan:

Kesan toksik okular merupakan kesan sampingan rawatan tamoxifen. Optik neuropati disebabkan oleh tamoxifen berkemungkinan sukar dibaikpulih dan memberi kesan penglihatan yang teruk. Jangka masa yang lebih panjang perlu untuk memerhati kesan tamoxifen kepada perubahan peringkat awal yang mungkin berlaku ke atas saraf optik dan fungsi visual melalui ujian berkala dengan HRT III dan corak potensi ransangan visual (*Pattern VEP*).

ABSTRACT

Background:

Tamoxifen retinopathy and optic neuropathy is a known complication of tamoxifen treatment. Scanning confocal laser ophthalmoscopy of optic nerve head demonstrated smaller optic cup in visually asymptomatic patients on tamoxifen. Electrophysiology study is a non-invasive method of evaluating retinal function and facilitate differentiation between retinal and optic nerve dysfunction. The present study aims to evaluate early optic nerve head parameter and electrophysiology changes in patients receiving tamoxifen.

Method:

This is a prospective study involving 76 eyes of 38 breast cancer patients treated with Tamoxifen in Hospital Universiti Sains Malaysia, Kelantan, Malaysia. These patients were examined by a single doctor and the investigations were done by a single technician. The visual acuity, optic nerve function, visual field, anterior and posterior segment ocular examination, optic nerve head parameters measurement on Heidelberg Retinal Tomograph III (HRT III) and Pattern VEP were assessed. The examination was performed before and three months after treatment initiation.

Results:

There was no tamoxifen ocular toxicity found 3 months post treatment with tamoxifen. There was no change in visual acuity and optic nerve function post treatment initiation. There were no statistically significant changes found in optic nerve head parameters on HRT III and P 100 peak latency and amplitude on PVEP within study duration.

Conclusion:

Ocular toxicity is a recognized complication of tamoxifen treatment. Tamoxifen optic neuropathy is a potentially irreversible, visually disabling complication. Tamoxifen ocular toxicity was not found 3 months after tamoxifen treatment initiation among breast cancer patients. No early changes in optic nerve head parameters and P 100 peak latency and amplitude changes found after 3 months of treatment. Longer duration of monitoring with HRT III and Pattern VEP may be needed to adequately observe for early, subclinical changes in optic nerve head parameters and visual function among tamoxifen users.

Chapter 1

Introduction

Tamoxifen is a selective estrogen receptor modulator. It is used as a hormonal therapy in early invasive and advanced estrogen receptor (ER) positive breast cancer. Tamoxifen acts by competing with estrogen for estrogen receptor, prevents binding and halts the tumour growth. The duration of treatment with tamoxifen is currently recommended for 5 years as it was found superior to shorter duration of period in improving survival rate.

Tamoxifen is also being used in treatment of gynecomastia, malignant melanoma, hepatocellular carcinoma, and a chemopreventive agent for breast cancer prevention in high risk patients.

The incidence of tamoxifen related ocular toxicity were reported as 6.3% and 12% in 2 different prospective studies. Tamoxifen related ocular toxicities were reported as corneal subepithelial deposits, cataract, intraretinal refractile crystals and retinopathy, macular edema and optic neuritis. Systemic side effects include thromboembolism, memory impairment, premature growth plate closure and increased risk of endometrial carcinoma.

Detection of the ocular toxic effects before occurrence of symptoms is of great value to prevent irreversible optic nerve damage. Regular ophthalmic examination which includes optic functions test (consists of visual acuity, visual field, colour vision, light brightness and red desaturation), ophthalmoscopy and photography has been used to detect ocular toxicity in the clinical practice. However, these assessments may not be useful in detecting subclinical tamoxifen-induced optic neuropathy or

retinopathy. With the advancement of technology, newer imaging techniques and equipment provide the tools to examine the possibility of any early anatomical changes in the optic nerve head or early electrophysiology changes.

Optic neuritis is a less common but potentially irreversible visual morbidity from tamoxifen ocular toxicity. It affects bilaterally and occur at range of 3 weeks to 7 months of tamoxifen treatment. Several case reports showed prolonged latency in patients with tamoxifen induced optic neuritis. Visual evoked potential (VEP) is an electrophysiology test which is recognized as a sensitive measure of optic nerve pathologies. It is more sensitive for diagnosis of resolved optic neuritis than visual acuity, contrast sensitivity, Goldmann perimetry or magnetic resonance imaging.

In a study by Eisner et. al. utilized confocal laser scanning ophthalmoscopy, optic cups of short term (less than 2 years) tamoxifen users were found to be significantly smaller in both the lateral and axial directions than the optic cups of control subjects whom are not using any hormonal medication. We are keen to evaluate possible early optic nerve head changes related to tamoxifen treatment which may not be detectable clinically in routine ocular examination.

The Heidelberg Retina Tomograph III (HRT III) is a confocal laser scanning system for acquisition and analysis of three-dimensional images of the posterior segment of the eye. Data from the HRT III can quantitatively describe the retinal topography and the follow-up topographic changes. Using a series of optical section images at different locations of a focal plane, a three-dimensional image is acquired. In

evaluation the optic nerve head, the HRT III provides optic nerve head parameters (disc area, rim area, cup disc area ratio, cup volume, disc volume and rim volume). In this study, we expect to observe possible early changes in the optic nerve head parameters.

Visual Evoked Potential (VEP) is a cortical response to reflect generated by an electrical potential gradient recorded clinically by placing wire electrodes adjacent to the occipital cortex and to a non-visual area of the brain. It reflects the patency of visual pathway and to assess optic nerve function and its projection to the visual cortex. In pattern reversal VEP, the stimulus used to generate the wave is an alternating high contrast checkerboard.

A typical pattern-reversal VEP waveform consists of N75, P100 and N135 peaks. These peaks are designated as negative and positive followed by the typical mean peak time. The standard measure of VEP amplitude is the height of P100 from the preceding N75 peak. P100 is usually a prominent peak that shows relatively little variation between subjects, minimal within-subject interocular difference, and minimal variation with repeated measurements over time. The responses stimulate by these stimuli have less intra- and inter-individual variability and more sensitivity in detecting minor visual pathway abnormality compare to Flash VEP. In this study, we aim to evaluate for early changes in pattern VEP among patients receiving tamoxifen treatment.

Chapter 2

Study Protocol

2.1 BACKGROUND

Tamoxifen is an anti-estrogen medication. It is used as a hormonal therapy in early invasive and advanced Estrogen Receptor positive (ER positive) breast cancer[1]. In breast cancer, estrogen induces the proliferation of tumor cells and disease progression. It acts by competing with estrogen for its receptor, preventing estrogen binding and halts the tumor growth[2]. The duration of treatment with Tamoxifen is currently recommended for 5 years as it is more superior to shorter duration of period in improving survival rate[1].

Tamoxifen is also being used in treatment of gynecomastia, malignant melanoma, hepatocellular carcinoma. It is also being use as chemopreventive agent for breast cancer prevention in high risk patients[3].

The incidences of tamoxifen-related ocular toxicity were reported as 6.3% and 12% in 2 different prospective studies[4, 5]. Tamoxifen related ocular toxicities were reported as corneal subepithelial deposits, cataract, intraretinal refractile crystals and retinopathy, macular edema and optic neuropathy[4-10]. Systemic side effects include thromboembolism, memory impairment, premature growth plate closure and increased risk of endometrial carcinoma.

In a study by Eisner et. al optic cups of short term Tamoxifen users (less than 2 years) were found to be significantly smaller in both the lateral and axial directions than the optic cups of control subjects whom are not using any hormonal medication.[11]

Optic neuritis is a less common but potentially irreversible visual morbidity from tamoxifen ocular toxicity. It affects bilaterally and occur at range of 3 weeks to 7

months of tamoxifen treatment[9,10]. Several case reports showed prolonged latency in patients with tamoxifen induced optic neuritis[9,10]. Visual evoked potential (VEP) is an electrophysiology test which is recognized as a sensitive measure of optic nerve pathologies. It is more sensitive for diagnosis of resolved optic neuritis than visual acuity, contrast sensitivity, Goldmann perimetry or magnetic resonance imaging[12,13].

Tamoxifen toxic optic neuropathy was thought to be a rare side effect of treatment. However, it can cause potentially irreversible visual morbidity. We are keen to evaluate further for subclinical presentation of tamoxifen-related ocular toxicity which may not be detected in typical ocular examination. Detection of the ocular toxic effects before occurrence of symptoms is of great value to prevent extensive optic nerve damage and furthermore allow the complete recovery of normal function.

The regular ophthalmic examination which includes optic functions test (consists of visual acuity, visual field, color vision, light brightness and red desaturation), ophthalmoscopy and photography has been used to detect ocular toxicity in the clinical practice. However, these assessments may not be useful in detecting subclinical Tamoxifen-induced optic neuropathy or retinopathy. With the advancement of technology, newer imaging techniques and equipment provide the tools to examine the possibility of any early anatomical changes in the optic nerve head or possible electrophysiological changes.

The Heidelberg Retina Tomograph III (HRT III) is a confocal laser scanning system for acquisition and analysis of three-dimensional images of the posterior segment of

the eye. Data from the HRT III can quantitatively describe the retinal topography and the follow-up topographic changes. The typical application of the HRT III is the assessment of the glaucomatous optic nerve head. Using a series of optical section images at different locations of a focal plane, a three-dimensional image is acquired. In evaluation the optic nerve head, the HRT III provides many details regarding the disc are, rim area, cup disc area ratio, cup volume, disc volume and rim volume.

VEP is a cortical response to reflect generated by an electrical potential gradient recorded clinically by placing wire electrodes adjacent to the occipital cortex and to a non-visual area of the brain. It reflects the patency of visual pathway and to assess optic nerve function and its projection to the visual cortex. In pattern reversal VEP, the stimulus used to generate the wave is an alternating high contrast checkerboard.

A typical pattern-reversal VEP waveform consists of N75, P100 and N135 peaks. These peaks are designated as negative and positive followed by the typical mean peak time. The standard measure of VEP amplitude is the height of P100 from the preceding N75 peak. P100 is usually a prominent peak that shows relatively little variation between subjects, minimal within-subject interocular difference, and minimal variation with repeated measurements over time. The responses stimulate by these stimuli have less intra- and inter-individual variability and more sensitivity in detecting minor visual pathway abnormality compare to Flash VEP.

In this study, we aim to evaluate the optic nerve head parameter changes and pattern VEP changes among breast cancer patients pre-treatment and 3 months of Tamoxifen treatment.

2.2 RATIONALE OF STUDY

There are reported cases of optic neuropathy and optic neuritis in patients receiving Tamoxifen treatment[7, 9, 10]. Ashford et al. reported the reversibility of bilateral optic disc swelling upon treatment cessation in a patient. Colley SM et al[9]. and Pugesgarrd T. et al.[10] reported improvement of visual symptoms in their patient with optic neuropathy after cessation of treatment however in both cases, the sequele of optic atrophy and vision reduction were also reported. It is postulated that at most of the time it is subclinical and not diagnosed by the typical optic nerve function test.

Eisner et. al studies the optic cups of short term tamoxifen users (less than 2 years) and found significantly smaller optic cups in both the lateral and axial directions than the optic cups among patients treated compared to control subjects whom are not using any hormonal medication[11].

Tamoxifen optic neuropathy reported to occur as early as 3 weeks after treatment initiation[7]. If the changes of tamoxifen-induced optic neuropathy can be detected early in the course of treatment, it may be possible in preventing the possible permanent damage to optic nerve and the potential outcome of irreversible vision reduction.

The aim of this study is to evaluate early changes in optic nerve head parameters and the electrophysiology test using HRT III and pattern VEP among breast cancer patients treated with tamoxifen in Hospital Universiti Sains Malaysia (HUSM).

2.3 RESEARCH OBJECTIVE

2.3.1 General Objective

To study the optic nerve head parameters and ocular electrophysiology among breast cancer patients on tamoxifen treatment.

2.3.2 Specific Objectives

i. To evaluate the optic nerve head parameters using HRT III pre and 3 months of treatment with tamoxifen among breast cancer patients.

ii. To evaluate the pattern visual evoked potential pre and 3 months of treatment with tamoxifen among in breast cancer patients.

2.4 RESEARCH QUESTIONS

i. Is there significant change in optic nerve head parameters in HRT III pre and 3 months of treatment with tamoxifen in breast cancer patients?

ii. Is there a significant change in pattern visual evoked potential pre and 3 months of treatment with tamoxifen in breast cancer patients?

2.5 RESEARCH HYPOTHESIS

i. There is a significant change in optic nerve head parameters in HRT III pre and 3 months after treatment with tamoxifen in breast cancer patients

ii. There is significant change in pattern visual evoked potential after treatment with tamoxifen in breast cancer patients.

2.6 METHODOLOGY

2.6.1 Study Design

Cross-Sectional Study

2.6.2 Study Location

Eye Clinic, Hospital Universiti Sains Malaysia (Hospital USM)

2.6.3 Study Duration

January 2015 - May 2016

2.6.4 Study Reference Population

Patients diagnosed with breast cancer in Malaysia

2.6.5 Source population

Patients diagnosed with breast cancer and are planned for tamoxifen treatment in Hospital Universiti Sains Malaysia (HUSM)

2.6.6 Sampling Frame

Patients diagnosed with breast cancer in HUSM and planned for tamoxifen treatment from January 2015 till May 2016

2.6.7 Inclusion and Exclusion Criteria

Inclusion Criteria:

- Breast cancer patients whom are planned for tamoxifen treatment
- Patients aged 18 years old and above

Exclusion Criteria:

- Patients with underlying ocular diseases
- Cornea opacity or presence of dense ocular opacity
- Patients with abnormal HRT III or pattern VEP on first time evaluation before treatment
- Patients with Diabetes Mellitus, Hypertension or renal impairment
- Patients with past history of intake of other neurotoxic drug
- Mentally challenged patients
- Developmental brain disease or brain metastasis
- Active brain disease

2.6.8 Sample Size Calculation

Objective 1 and Objective 2: Literature reviews on the mean and SD for optic nerve head parameters, pattern VEP in breast cancer patients on tamoxifen treatment were not found.

Sample size was calculated using G*Power 3.1.9.2

T tests – Dependent T-test, within factor, with medium size effect (Cohen, 1988)

Tails	= two
Effect size	= 0.5
α err prob	= 0.05
Power (1-β err prob)	= 0.80
Number of groups	= 1
Nonsphericity correction ε	= 2.92
Critical t	= 2.03
Df	= 33
Total sample size	= 34

Estimated 10% of drop-out:

Total sample size, n = 34/ (1-0.1)

= 38

2.6.9 Sampling Method

Non-probability sample selection of all breast cancer patients attending Eye Clinic, Hospital USM

2.6.10 Examination Procedure

The study will be conducted after obtaining approval from the Human Research Ethics Committee USM (HREC).

1. The study will be conducted in the Eye Clinic of Hospital Universiti Sains Malaysia between January 2015 and May 2016.
2. Patients who fulfill the inclusion and exclusion criteria will be invited to participate. Informed written consent will be obtained from patient.
3. In the Eye Clinic, distance visual acuity will be measured monocularly using a Snellen chart for distance (Reichert, NY, USA) at 6 meters
4. A comprehensive eye examination, including pupillary examination, optic nerve function tests, Humphrey visual field test and slit lamp biomicroscopy will be performed to rule out any associated ocular conditions which would have precluded participation in the study.
5. Intraocular pressure will be assessed with applanation tonometry.
6. After dilation with topical Phenylephrine 2.5% and Tropicamide 1%, fundus will be examined using a slit lamp bio microscopy and a 90 D condensing lens or binocular indirect ophthalmoscope (BIO) and a 20 D condensing lens by principle investigator.
7. Bilateral fundus photograph will be captured by one identified trained medical operator using a digital fundus camera.

8. Optic nerve head parameters will be captured by one identified trained medical operator using Heidelberg Retinal Tomograph III (Heidelberg Engineering, Germany). Both eyes optic nerve head image will be acquired three-dimensionaly with the pre-determined acquisition parameters. The size of the field of view is fixed at 15° x 15°, and the digitization is performed in frames of 384 x 384 pixels. The mean topography images are computed automatically. The operator will draw the contour line manually using both the reflectance and topography image as guide for placement of contour line. Contour line will be drawn at the inner edge of the scleral ring. A good quality image will be considered when the following criteria are fulfilled: 1) the optic disc image appeared centrally, 2) minimal eye movement detected during image capture, 3) absence of artifact and 4) topography standard deviation less than 50 micrometers. The Overall Quality Score from the software combines Image and Imaging Quality Score to determine quality of image. Only images with good and acceptable overall quality score will be used for analysis.
9. Pattern VEP recording will be done using Granzfield PVEP (Roland-Consult, RETI-port 32, Germany). Recording will be based on standard ISCEV PVEP protocol 2009[15].The placement of electrode is based on the "10-20 International System" in proportion to the size of the head. Patient was asked to sit at 1.5m from the video monitor. PVEP was tested monocular with appropriate refractive correction. The test was elicited by checkerboard stimuli with large 1° (60 min of arc) checks. Peak latency of P100, N75 and N135; and amplitude of N75- P100 and P100 – N135 will be measured
10. Statistical analyses will be performed using SPSS version 22.0. Paired T-test will be performed to determine the changes of optic nerve head parameters,

respective latencies and amplitudes of pattern VEP pre and 3 months of Tamoxifen treatment.

2.6.11 Research Tools

1. Snellen chart for distance (Reichert, NY, USA)
2. Slit Lamp Biomicroscopy (Clement Clark International, UK) with 90D and 78D lenses (Volk, USA)
3. Binocular Indirect Ophthalmoscope (Heine, Germany) with 20D and 28D lenses (Volk, USA)
4. Digital Retinal Camera (VX-10/KOWA/Japan)
5. Humphrey Visual Field Analyzer Statpac2 (Carl Zeiss Meditec Inc, USA).
6. Heidelberg Retinal Tomograph III (Heidelberg Engineering, Germany)
7. Granzfield PVEP (Roland-Consult, RETI-port 32, Germany)
8. Gutt Tropicamide 1%
9. Gutt Phenylepinephrine 2.5%
10. Gutt Proparacaine 0.5%

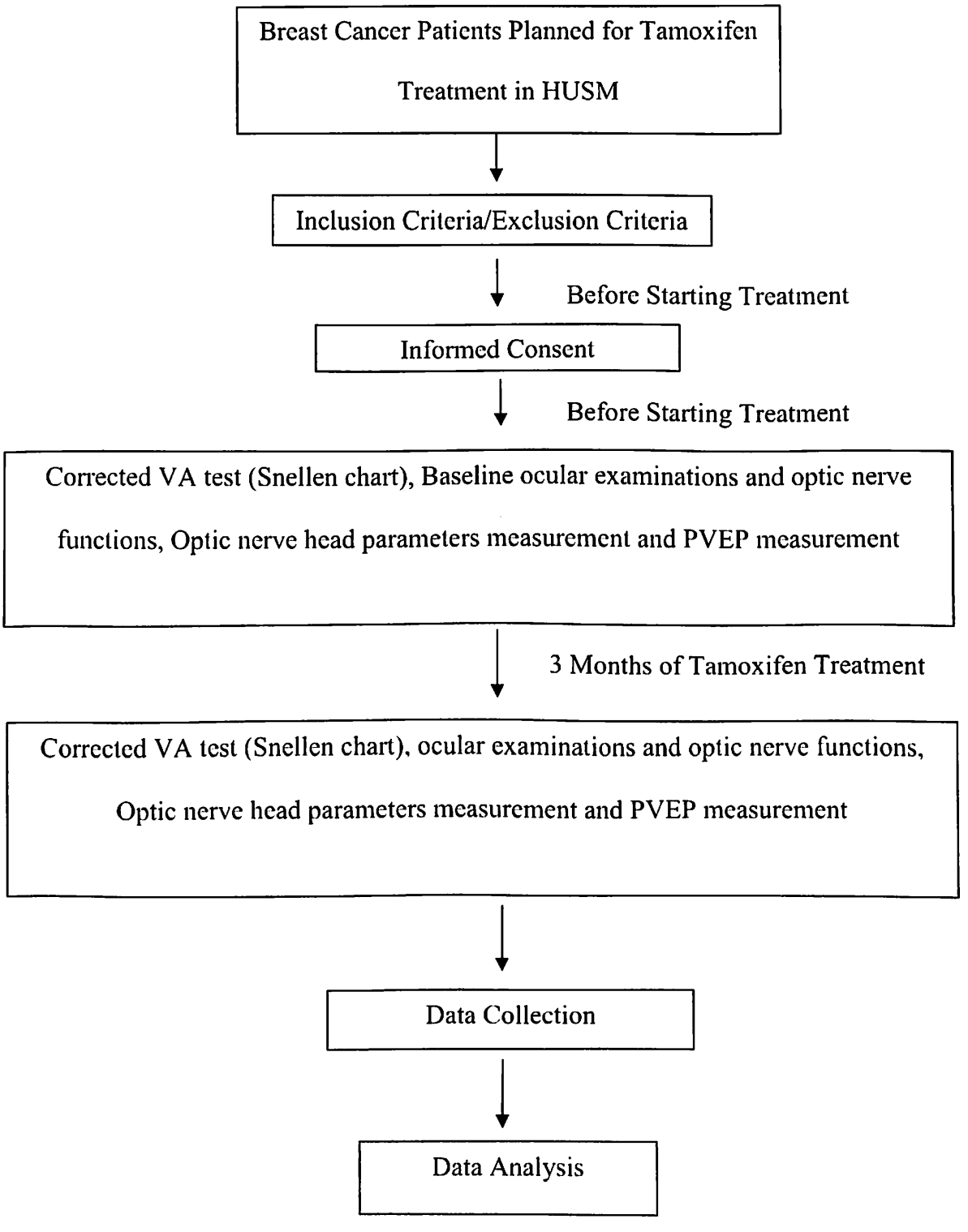
2.6.12 Statistical Analysis

All data will be entered and analyzed using SPSS version 22.0. For descriptive statistics, data will be presented by mean (SD) for numerical variables and frequency (percentage) for categorical variables. For objective number 1 and 2, we will use paired T-test for analysis to compare means of variables.

2.6.13 Ethical Considerations

This study will be submitted to the Ethical Committee of USM. An information form will be given to all participants prior to data collection. Written consent will be obtained from the patient.

2.6.14 Flow Chart



2.6.15 Dummy Tables

Objective 1: Optic nerve head parameters using HRT III pre and 3 months of treatment with Tamoxifen among breast cancer patients.

Right eye

Variables	Pre	Post	Mean Difference	t-statistics	P value
	Mean (SD)		(95% CI)	(df)	
Disc area					
Cup area					
Rim area					
Cup volume					
Rim volume					
Cup disc area ratio					
Mean cup depth					
Maximum cup depth					
Cup shape measure					
Height variation contour					
Mean RNFL thickness					
RNFL cross section area					

Left eye

Variables	Pre	Post	Mean Difference	t-statistics	P value
	Mean (SD)		(95% CI)	(df)	
Disc area					
Cup area					
Rim area					
Cup volume					
Rim volume					
Cup disc area ratio					
Mean cup depth					
Maximum cup depth					
Cup shape measure					
Height variation contour					
Mean RNFL thickness					
RNFL cross section area					

Objective 2: To evaluate the pattern visual evoked potential pre and 3 months of treatment with Tamoxifen among in breast cancer patients.

Right eye

Variables	Pre	Post	Mean Difference	t-statistics	P value
	Mean (SD)		(95% CI)	(df)	
N1 Latency					
P1 Latency					
N2 Latency					
N1 P1 Amplitude					
P1 N2 Amplitude					

Left eye

Variables	Pre	Post	Mean Difference	t-statistics	P value
	Mean (SD)		(95% CI)	(df)	
N1 Latency					
P1 Latency					
N2 Latency					
N1 P1 Amplitude					
P1 N2 Amplitude					

2.7 GANTT CHART

	2015						2016											
	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D
Data collection																		
Data analysis																		
Report writing																		
Submission																		

2.8 REFERENCES

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2.9 APPENDICES

APPENDIX A : ETHICAL APPROVAL

Jawatankuasa Etika Penyelidikan Manusia USM (JEPeM)

Universiti Sains Malaysia

24th September 2014

Assoc. Prof. Dr. Wan Hazabbah Wan Hitam
Department of Ophthalmology
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan.

JEPeM Code : USM/JEPeM/1403118
Protocol Title : Evaluation of Optic Nerve Head Structures, Function and Electrophysiology in Breast Cancer Patients on Tamoxifen.

Dear Dr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM). Your study has been assigned study protocol code **USM/JEPeM/1403118** which should be used for all communication to the JEPeM-USM related to this study. This ethical clearance is valid until **September 2016.**

The following documents have been approved for use in the study

1. Summary of Research Proposal

In addition to the abovementioned documents, the following technical document was included in the review on which this approval was based:

1. Patient Information Sheet and Consent Form (English version)
2. Patient Information Sheet and Consent Form (Malay version)
3. Data Collection Sheet

Attached document is the list of members of JEPeM-USM present during the full board meeting reviewing your protocol.

While the study is in progress, we request you to submit to us the following documents:

1. Any changes in the protocol, especially those that may adversely affect the safety of the participants during the conduct of the trial including changes in personnel, must be submitted or reported using **JEPeM-USM FORM 3(A) 2014: Study Protocol Amendment Submission Form.**
2. Reports of adverse events (if any) including from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2014: Adverse Events Report.**
3. Notice of early termination of the study and reasons for such using **JEPeM-USM FORM 3(E) 2014.**
4. Any event which may have ethical significance
5. Any information which is needed by the JEPeM-USM to do ongoing review
6. Notice of time of completion of the study using **JEPeM-USM FORM 3(C) 2014: Final Report Form.**
7. Application for renewal of ethical clearance 90 days before the expiration date of the approval through submission of **JEPeM-USM FORM 3(B) 2014: Continuing Review Application Form.**