

**HYPERTENSIVE RETINOPATHY AND THE RISK OF HEMORRHAGIC
STROKE**

by

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LIST OF ABBREVIATIONS

	Abbreviation	Description
1.	HR	Hypertensive Retinopathy
2.	HS	Hemorrhagic Stroke
3.	C	Capsular
4.	p	Posterior limb
5.	a	Anterior Limb
6.	V	Ventricle
7.	Th	Thalamus
8.	n	Total Number
9	SD	Standard Deviation
10	BP	Blood Pressure
11	AV	Arteriovenous
12	ARIC	Atherosclerosis Risk in Communities
13	RR	Relative Risk
14	CI	Confidence Interval
15	ICH	Intracerebral Hemorrhage
16	GCS	Glasgow Coma Scale
17	CT	Computed Tomography

Abstrak

Latar Belakang

Pendarahan otak dan retinopati hipertensi merupakan kerosakan organ sasaran akhir, dan pendarahan otak mempunyai akibat merbahaya kepada pesakit. Kajian ini adalah untuk mengaitkan antara retinopati hipertensi dan pendarahan otak akibat penyakit darah tinggi.

Kaedah kajian

Semua pesakit yang ada penyakit darah tinggi dengan pendarahan otak dan tanpa pendarahan otak di kaji. Pemeriksaan mata dilakukan dan dikelaskan tahap keparahan mengikut klasifikasi retinopati hipertensi Wong dan Mitchell. Maklumat demografi pesakit, tanda pemantauan penting, tahap kesedaran pesakit semasa kemasukan, saiz darah beku, skor pendarahan otak (*ICH-score*), dan tahap kecacatan pesakit (*GOS-score*) direkodkan.

Keputusan

50 pesakit darah tinggi tanpa pendarahan otak, dan 51 pesakit dengan pendarahan otak dikaji. Bagi kumpulan pendarahan otak, 21 mengalami keparahan rendah, (perubahan retinopati biasa dan ringan) menyumbang kepada 41.2%, 30 pesakit mempunyai keterukan yang tinggi (retinopati sederhana dan teruk). Dalam kumpulan pesakit tanpa pendarahan otak, 49 mempunyai keparahan yang rendah dan 1 mempunyai keparahan yang tinggi ($p = 0.001$). Keterukan yang rendah menunjukkan skor kesedaran (GCS) yang lebih baik pada kemasukan berbanding dengan tahap keterukan yang tinggi ($p = 0.003$). Keterukan tahap rendah juga menunjukkan jumlah darah beku kurang daripada 30 ml ($p = 0.001$). Skor pendarahan otak (*ICH score*) antara 0-2 dalam kebanyakan pesakit ($p = 0.006$). Akhir sekali, kami membandingkan dengan tahap kecacatan pesakit (*GOS score*). Kami mendapati hasil yang baik dari skor GOS 4-5, keterukan retinopati rendah menyumbang kepada 17 pesakit, dan hanya 4 mempunyai hasil yang tidak

memuaskan (*GOS 1-3*). Bagi keterukan yang tinggi, 23 pesakit mempunyai hasil yang tidak baik dengan 7 mempunyai hasil yang baik (p 0.001)

Kesimpulan

Retinopati keterukan yang rendah didapati mempunyai jumlah darah beku yang rendah dan kemungkinan besar dirawat oleh pengurusan perubatan dan kecacatan yang kurang. Manakala retinopati keterukan tahap yang tinggi mempunyai jumlah darah beku yang besar dan mungkin memerlukan rawatan pembedahan dan kecacatan yang teruk.

Abstract

Background

Hemorrhagic stroke and hypertensive retinopathy are known end organ damage, with hemorrhagic stroke having deleterious consequence to the patients. This study is to correlate between hypertensive retinopathy and hemorrhagic stroke.

Methods

All patients with with hypertension with and without hemorrhagic stroke were recruited. Funduscopy examination was performed and then graded based on Wong and Mitchell hypertensive retinopathy classification. Clinical and radiological parameter included are demography, vital signs, Glasgow Coma Scale(GCS) on admission, clot volume, site of clot, Intra-Cerebral Hemorrhage (ICH) score and Glasgow Outcome Scale (GOS) score. Data were collected and correlated with the severity of hypertensive retinopathy.

Results

Fifty hypertensive patient without hemorrhagic stroke and fifty one patients with hemorrhagic stroke were recruited. In the hemorrhagic stroke group, 21 had low severity (normal/mild retinopathy changes) accounting for 41.2% and 30 patients had high severity (moderate and severe retinopathy). In the non hemorrhagic stroke patients 49 had low severity and 1 had high severity (p value 0.001). Low severity showed better GCS score on admission as compared to high severity, (p value of 0.003). Low severity also showed a clot volume less than 30ml, (p value 0.001) and also statistically significant with an ICH score of between 0-2 in most of the patients, (p value 0.006). Lastly, we compared the GOS score of patients and found a favourable outcome of GOS score 4-5 in low severity retinopathy for 17 patients with only 4 having unfavourable outcome (GOS score 1-3). As for high severity, 23 patients had

unfavourable outcome with 7 having favourable outcome, this was statistically significant, (p value of 0.001).

Conclusion

Low severity retinopathy were found to have small clot volume and most likely treated by medical management and better outcome. With high severity retinopathy had larger clot volume and requiring surgical intervention and poorer outcome.

1. INTRODUCTION AND LITERATURE REVIEW

Spontaneous intracranial hemorrhage accounts for up to 15% of the total case worldwide in regard to hemorrhagic stroke (HS) with a mortality about 38% within the first year. In the world population there is a higher percentage of hemorrhagic stroke's (HS) amongst the Southeast Asian population. Studies comparing the Caucasian population in Australia, with Asian population shows a 5 times higher incidence of developing HS in the latter.¹

The data above reveals that HS is a serious non-communicable disease that has a devastating impact towards the individual, family and the community, as well as a burden to the healthcare system. Hypertension is a major disease that affects our population. It has a prevalence of 42.6% above the age of 30 years old in the year 2006 and has increased to 43.5% in 2011, with 60.6% of patients being 'undiagnosed'. Malaysia, being a multicultural society also shows a disparity among the ethnic and major race group in the development of hypertension, with the indigenous race from the state of Sabah and Sarawak accounting for a prevalence of 36.4%, followed by Malays at 34%, Chinese at 32.3% and lastly Indian 30.6%. Hypertension being a chronic disease results in end target organ damage, contributing as a risk factor for other disease up to 42.6%, namely myocardial infarction, cerebral stroke, heart failure and kidney disease.² While mortality remains high in patients with HS, the prognostic outcome in morbidity fairs better as compared to ischemic stroke, this due to the pathogenesis of the disease.

Hypertension is defined as a persistent elevation of systolic blood pressure (BP) of 140 mmHg or greater and/or diastolic BP 90mmHg or greater². These values are then staged accordingly based on the BP reading that was taken during the clinic visit. The higher the stage of hypertension, the higher the risk end organ damage or end organ complication. The organ

most involved would be the heart, resulting in heart failure, coronary heart disease and left ventricular hypertrophy. The brain on the other hand may develop transient ischemic attack, stroke, followed by peripheral vasculature disorder and kidney failure. Lastly, the retina may develop hemorrhage and exudative changes.³ Hypertensive changes in the eye are usually chronic in nature. Many studies were conducted,⁴⁻⁷ to relate the eye findings with other target organs damage, the most recent study was conducted in 2013, by *Ong Yt et al, Hypertensive Retinopathy and Risk of Stroke*, was a long term follow up over 13 years on hypertensive patients and the risk of stroke based on hypertensive retinopathy, the study showed the risk of cerebral infarction within the study population, that was more prevalent with a higher grade of retinopathy. But there has not been any study conducted within the hemorrhagic stroke patients, a subset of stroke patients and hypertensive retinopathy. This gap of knowledge is the purpose of this study, as hemorrhagic stroke is a common problem with our community.

Stroke is one of the leading causes of death that has been projected to surpass coronary artery disease in patients with chronic hypertension, as a risk factor in the near future. This has occurred mainly due to the acute symptoms that occur with stroke without any warning sign as compared to heart disease, where subtle symptoms and signs may be picked up in many patients during regular clinic follow up.⁸ Hypertension has been placed as a traditional cause for stroke along with diabetes, and cigarette smoking, which was associated with patients age less than 45 years, of which cryogenic stroke was diagnosed in one third of them.⁹ While hypertension as a risk factor is well established it is difficult to quantify it in order to help predict stroke and more importantly, to help in prevention of target end organ complication apart from lowering of blood pressure.¹⁰⁻¹²

Retinopathy changes in the eye due to hypertension is a chronic process, affecting the structure and function of the eye. The patho-physiological changes that occur in the retinal,

choroidal and optic nerve circulation are all in response to elevated blood pressure producing retinopathy changes in these structures.¹³ As for the pathogenesis of hypertensive hemorrhagic stroke, it is the affection of the arteriole of a diameter of less than 300 micrometer, resulting in tiny lipo-hyalinotic aneurysm formation, known as Charcot-Bouchard aneurysm. These lenticulostriate arteriole's which supply the basal ganglia region are those that rupture resulting in intra-parenchymal hemorrhage.¹⁴ The vasculature system of the two organs share similar anatomical, physiological and embryological characteristics. Firstly, the blood-retinal barrier is identical to the brain-blood barrier, and secondly, the retina is also an extension of the diencephalon. Thus, we could hypothesize that the changes experienced in the cerebral vessel could be similar to the retinal vessel, with the added benefit of a non-invasive visualization of the eye vessel by fundoscopic examination. This also provides an opportunity to study retinal vessel and the development of stroke.¹⁵⁻¹⁷

Blood pressure elevation leads to a spectrum of pathophysiological changes in the retinal vasculature, resulting in retinopathy.^{15,18} These signs are divided into stages, of which the initial stage is the vasoconstrictive stage, resulting in an increase in vasomotor tone and vasospasm due to the rise of blood pressure, with clinically evident signs of generalized retinal-arteriolar narrowing, affecting the pre-capillary arteriole. These changes are more common in younger patients with hypertension than the older population.¹⁹ As the blood pressure remains elevated, it undergoes the sclerotic stage, resulting in hyperplasia of the tunica media and hyaline degeneration of the arterial wall. These changes are evident clinically by generalized arteriolar narrowing, arteriovenous (AV) nicking, focal arteriolar narrowing, alteration of the arteriolar light reflex, arteriolar tortuosity and increase in the arteriolar branching angle.²⁰ The exudative stage occurs with sustained hypertension; it is described as a disruption of the blood-retinal barrier, with degeneration of vascular smooth muscle and endothelial cell necrosis

leading to blood and fluid exudation. However, exudation has been seen without concomitant endothelial necrosis. Other pathological changes found are fibrinoid necrosis of the arteriolar wall, arteriolar lumen narrowing, impaired blood flow, and ischemic complications. The features seen are micro aneurysms and retinal hemorrhages, occurring in the superficial nerve fiber layer, corresponding to flame-shaped hemorrhages, while the deeper layers of the retina result in blot and dot hemorrhages. In the subhyaloid space boat-shaped pre-retinal hemorrhage sometimes appear. There is also leakage of plasma lipoproteins, phospholipids, cholesterol and triglycerides (hard exudates), and disruption of axoplasmic transport mechanism with ischemia of the nerve fiber layer causing cotton-wool spots.²¹⁻²³ Despite development of the pathophysiology of the hypertensive retinopathy, a few issues have been identified. The pathophysiology does not correspond with the natural history to the disease. In addition, there has been no human models available as all current research were focused on animal models. Because of these issues, the retinopathy changes may not correspond to clinical findings based on the natural history.⁴ In this study we hope that by studying the retinopathy changes, we may be able to determine its association with chronic hypertension.

Classification of hypertensive retinopathy, as developed by Keith-Wagener and Baker in 1939, showed that there was a correlation between signs of retinopathy severity with the predictor of mortality. While many modern classifications retain the name of the classification, it has been modified to include four groups of retinopathy, placed in increasing severity. Grade 1, consists of generalized retinal arteriolar narrowing; grade 2 consists of generalized narrowing, focal areas of arteriolar narrowing and AV nicking; grade 3 consists of grade 1 and 2 signs plus the presence of retinal hemorrhages, micro aneurysms, hard exudates and cotton-wool spots; in grade 4, sometimes referred to as accelerated 'malignant' hypertensive retinopathy, consists of signs in the preceding three grades plus optic disk swelling and macular

edema. This classification established clinical mortality predictor in 3 years survival of persons with grade 1 hypertensive retinopathy as 70%, the survival was only 6% in those with grade 4 retinopathy. The major limitation of this classification system is the difficulty in distinguishing early hypertensive retinopathy severity (i.e. grade 1 from grade 2), and it's prognostic implication is unclear, therefore several proposals for a new systems have been made.^{4,15} A new classification was proposed to simplify hypertensive retinopathy into a three grade classification. This consists of mild retinopathy, which would be identified by retinal–arteriolar signs, such as generalized and focal arteriolar narrowing, arteriolar wall opacification, and arteriovenous nipping. In addition to these signs, moderate retinopathy would be recognized by flame-shaped or blot-shaped hemorrhages, cotton-wool spots, hard exudates, micro aneurysms, or a combination of all of these factors. Severe retinopathy would display some or all of these signs, as well as swelling of the optic disc.¹⁸ This classification is used in this study and has been named the Wong and Mitchell classification of hypertensive retinopathy.⁷

This classification was then used in many studies to correlate hypertensive retinopathy and risk of cardiovascular mortality and morbidity, stroke and less on renal disorder. Many studies have shown to demonstrate a strong association between hypertensive retinopathy and stroke and cerebrovascular disease²⁴⁻²⁷ In the Atherosclerosis Risk in Communities (ARIC) study, individuals with moderate retinopathy changes according to this Wong and Mitchell classification, were two to four times more likely to develop an incident clinical stroke within 3 years, even when controlling for the effects of blood pressure, cigarette smoking, lipids and other risk factors.²⁸ Among the participants without stroke or transient ischemic attack, hypertensive retinopathy signs were also associated with cognitive dysfunction, based on standardized neuropsychological tests over a 6 year period,²⁹ and were susceptible to cerebral white matter hyper intensity lesions and atrophy, as defined from MRI scans. One of the key

observations was that the presence of hypertensive retinopathy may offer additional predictive value of clinical stroke risk in individuals with MRI-defined subclinical cerebral disease.³⁰ In the ARIC study, individuals with both MRI-defined white matter lesions and hypertensive retinopathy were 18 times more likely [relative risk (RR) 18.1; 95% confidence interval (CI) 5.9–55.4] to develop an incident clinical stroke event than those without either white matter lesions or hypertensive retinopathy.³¹ The most recent study conducted on the ARIC subjects by *Ong YT et al in 2013*⁷, with a mean follow up of 13 years, of the 2907 subject, revealed 1406 (48.4%) subjects had no retinopathy changes, 1354 (46.6%) subjects had mild retinopathy changes and 47 (5.1%) subjects had moderate/severe retinopathy changes, of which 146 developed cerebral infarctions and 15 were hemorrhagic strokes. The incidence of stroke events for the whole population was 0.436 (95% CI, 0.42–0.45) per 100 person-years, 0.322 (95% CI, 0.305–0.339) per 100 person- years for the group with no retinopathy, and 0.493 (95% CI, 0.466–0.519) per 100 person-years and 1.073 (95% CI, 0.899–1.246) per 100 person-years for the group with mild and moderate hypertensive retinopathy, respectively.⁷ This study showed long term effects of hypertension to end organ damage, which is to the eye and the brain. However many studies conducted concentrated on cerebral infarction, and the main pathogenesis is based on atherosclerosis. There have not been any studies correlating hypertensive retinopathy with hemorrhagic stroke. The disease is based on the existence of essential hypertension changes on the vessel of both organs, therefore it can be postulated that there is an association with the pathogenesis of hemorrhagic stroke and eye signs.

The proposed study would be a collection to evaluate the significance of intracranial hemorrhage in the population of Sabah. The regional neurosurgery center in Kota Kinabalu, covers a great deal of the state, which includes the capital state, Kota Kinabalu and around 25 district primary center, where Hospital Queen Elizabeth is the tertiary center for referral. This

covers approximately a population of 1.8 million people, giving a good demographic study of the population of Borneo, which consist of indigenous native, (Kadazan, Dusun, Murut, Bajau, Murut), Malays, Chinese, and other minority.

The study aim is to determine the correlation of hypertensive retinopathy changes and hypertensive hemorrhagic stroke, based on the severity of hypertensive retinopathy, compliance of medication, Glasgow Coma Scale score, Intracerebral Hemorrhagic score (ICH score), clot volume and site of HS. No studies were conducted among hemorrhagic stroke, this will be the first study conducted, that will help the association of hypertensive retinopathy changes among hemorrhagic stroke patients. The retinopathy changes may be associated with clinical findings, the possibility of intervention and also outcome of the patients. Therefore retinopathy screening will provide a better understanding to the pathogenesis and importance in clinical practice in regards to hemorrhagic stroke.

2. STUDY PROTOCOL

Research Question : Is there association between hypertensive retinopathy and hemorrhagic stroke?

Hypothesis : Higher severity of retinopathy causes hemorrhagic stroke.

General objective

1. To study the hypertensive retinopathy changes in patients with hemorrhagic stroke.

Specific objective

1. To compare severity of hypertensive retinopathy in groups of hypertensive patients with and with out hemorrhagic stroke.
2. To look for association between clinical and radiological feature of subject with hemorrhagic stroke and hypertensive retinopathy changes.

3. To look for association between Glasgow's Outcome Scale in hemorrhagic stroke subject and severity of hypertensive retinopathy.

Study design:

Specific objective 1: Case control study

Specific objective 2 and 3: cross sectional study

Hemorrhagic Stroke Group

Inclusion criteria

1. All patient with spontaneous intracranial haemorrhage due to hypertension referred to Hospital Queen Elizabeth, Kota Kinabalu.
2. Age of ranging from 35-70 years old.

Exclusion criteria

1. Patient's with intracranial hemorrhage due to trauma, coagulopathy, vascular abnormality, infective cause, tumoral bleed and cerebral amyloid angiopathy.
2. Patient's with spontaneous intracerebral haemorrhage but not known to be hypertensive.
3. Patient with co-morbid of Diabetes Mellitus, Ischemic heart disease, previous stroke and on anticoagulants, and hemorrhagic transformation of ischemic stroke.

For Control Group (Hypertension alone)

Inclusion criteria

1. Patients with no hemorrhagic stroke with hypertension follow up in Putatan Community Clinic.
2. Age ranging from 35 till 70 years old.

Exclusion criteria

1. Patient with cerebral infraction, on any anticoagulant medication, brain tumour and any form of cerebral vascular malformation.
2. Patients with co morbid of Diabetes Mellitus and Ischemic Heart disease.

Source of population:

For Hemorrhagic Stroke

All patients referred to Neurosurgery Department Hospital Queen Elizabeth, Kota Kinabalu with hypertensive hemorrhagic stroke from May 2016 till May 2018.

For Control Group

Patients from Putatan Community Clinic, Kota Kinabalu, Sabah, for hypertension follow up from May 2016 till May 2018.

Methods:

1. Patients, not randomised were diagnosed with hypertensive hemorrhage based on CT scan on admission who fulfilled the inclusion and exclusion criteria were recruited. Patients underwent treatment in accordance to standard protocol for hypertensive hemorrhagic stroke.
2. Clinical and radiological parameter were collected in a standard collection data entry form, the parameter includes Blood Pressure, that was taken during the acute stage of the disease, Glasgow Coma Scale (GCS), clot volume, site of haemorrhage, Intracerebral Hemorrhage (ICH) score, and Glasgow Outcome Score (GOS).

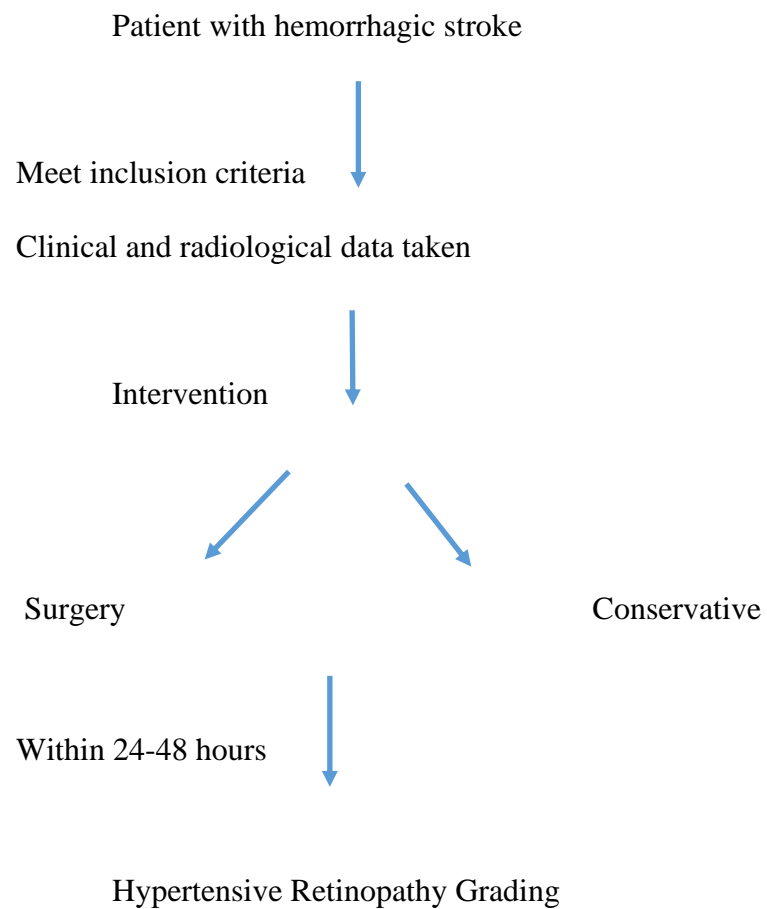
3. Retinal examination picture was taken with a digital fundoscopic camera apparatus using Pan-Optic Ophthalmoscope WELCH ALLYN, USA, that was recorded and stored as photo or image, within the first 24-48 hours, after the patients were clinically stabilised.
4. The severity was graded on both the fundi, based on *Wong and Mitchell classification of Hypertensive Retinopathy*,^[35] The retinal picture was accessed by two independent ophthalmologist that were blinded to the patient clinical condition.

Control group

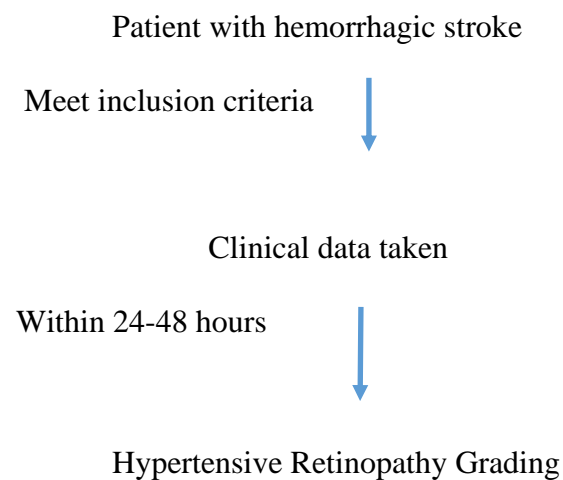
1. Control group, consisting of patients having hypertension without hemorrhagic stroke and not randomised who fulfilled the inclusion and exclusion criteria were recruited during their follow up hypertension visit in the community clinic.
2. The clinical parameter were taken, such as blood pressure, during the visit to the clinic, after matching statistically with the hemorrhagic stroke patients, and retinal examination picture of the fundi were carried out and accessed by two independent ophthalmologist that were blinded to the patient clinical condition based on *Wong and Mitchell classification of Hypertensive Retinopathy*.^[35]

Study Flow Chart

Hemorrhagic Stroke Group



Non Hemorrhagic Stroke / Control Group



Sample size calculation

Size was calculated based on the study Hypertensive retinopathy and the risk of stroke⁷ and prevalence and risk factor of hypertensive retinopathy in hypertensive patients.³²

Using PS sample size software

Power = 0.8

$\alpha = 0.05$

$P_0 = 0.14$ (Hypertensive Retinopathy in Hypertensive patients)³²

$P_1 = 0.4$ (Hypertensive Retinopathy in Stroke patients)⁷

The calculated sample size was 45, with a drop out rate of 10%, the total sample require is 50 subjects for each group for the specific objective 1.

As there were no prior studies for specific objective number 2 and 3, we took the sample size of the 50 patients from the hemorrhagic stroke group to analyse this was based on the specific objective 1 sample size calculation.

Results analysis:

Statistical analysis was performed with the use of commercially available software SPSS Inc., version 22. Numerical variables will be presented in mean and standard deviation whereas categorical variables will be presented in frequency and percentage. Association between HR and HS will be assessed by chi-square test or Fisher exact test.

Hypertensive Retinopathy and the Risk of Hemorrhagic Stroke

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Abstract

Background

Hemorrhagic stroke and hypertensive retinopathy are known end organ damage, with hemorrhagic stroke having deleterious consequence to the patients. This study is to correlate between hypertensive retinopathy and hemorrhagic stroke.

Methods

All patients with with hypertension with and without hemorrhagic stroke were recruited. Fundoscopic examination was performed and then graded based on Wong and Mitchell hypertensive retinopathy classification. Clinical and radiological parameter included are demography, vital signs, Glasgow Coma Scale (GCS) on admission, clot volume, site of clot, Intra-Cerebral Hemorrhage (ICH) score and Glasgow Outcome Scale (GOS) score. Data were collected and correlated with the severity of hypertensive retinopathy.

Results

Fifty hypertensive patient without hemorrhagic stroke and fifty one patients with hemorrhagic stroke were recruited. In the hemorrhagic stroke group, 21 had low severity (normal/mild retinopathy changes) accounting for 41.2% and 30 patients had high severity (moderate and severe retinopathy). In the non hemorrhagic stroke patients 49 had low severity and 1 had high severity (p value of 0.001). Low severity showed better GCS score on admission as compared to high severity, (p value of 0.003). Low severity also showed a clot volume less than 30ml, (p value 0.001) and also statistically significant with an ICH score of between 0-2 in most of the patients, (p value 0.006). Lastly, we compared the GOS score of patients and found a favourable outcome of GOS score 4-5 in low severity retinopathy for 17 patients with only 4 having unfavourable outcome (GOS score 1-3). As for high severity, 23 patients had unfavourable outcome with 7 having favourable outcome, this was statistically significant, (p value of 0.001)

Conclusion

Low severity retinopathy were found to have small clot volume and most likely treated by medical management and better outcome. With high severity retinopathy had larger clot volume and requiring surgical intervention and poorer outcome.

Keyword: hypertensive retinopathy, hemorrhagic stroke

Introduction

Spontaneous intracranial hemorrhage accounts for up to 15% of the total case worldwide in regards to hemorrhagic stroke (HS) with a mortality about 38% within the first year. In the world population there is higher percentage of hemorrhagic stroke (HS) in Southeast Asia. Studies in contrast to the Caucasian population in Australia, with the Asian population showing a 5 times higher incidence of developing HS.¹ Malaysia being a multicultural society also shows a disparity among the ethnic and major race group, with the indigenous race from the state of Sabah and Sarawak accounting for a prevalence of 36.4%, followed by Malays at 34%, Chinese at 32.3% and lastly Indian 30.6%. While mortality remains high in patient with HS, the prognostic outcome in morbidity fares better as compared to ischemic stroke, this is due to the pathogenesis of the disease itself.

Retinopathy changes in the eye due to hypertension is a chronic process, affecting the structure and function of the eye, the pathophysiological changes that occur in the retinal, choroidal and optic nerve circulation are all in response to elevated blood pressure resulting in retinopathy changes in these structures.¹³ As for the pathogenesis of hypertensive hemorrhagic stroke, is the affection of the arteriole having a diameter of less than 300 micrometer, that caused tiny lipohyalinotic aneurysms formation called Charcot-Bouchard aneurysm. These are the lenticulostriate arteriole supplying the basal ganglia region which then rupture, resulting in intra parenchymal hemorrhage.¹⁴ The vasculature system of the two organs, share similar anatomical, physiological and embryological characteristic. Possessing a blood-retinal barrier which is identical to brain-blood barrier, the retina is an extension of the diencephalon, thus we could hypothesize the changes in the cerebral vessel could be similar to the retinal vessel. This is an added benefit as non visualization of the eye vessel is non invasive and can be performed by fundoscopic examination. This also provide an opportunity to study retinal vessel and the development of stroke.¹⁵⁻¹⁷

The most recent study conducted on the ARIC subjects by *Ong YT et al in 2013*⁷, with a mean follow up of 13 years, of the 2907 subject, revealed 1406 (48.4%) subjects had no retinopathy changes, 1354 (46.6%) subjects had mild retinopathy changes and 47 (5.1%) subjects had moderate/severe retinopathy changes, of which 146 developed cerebral infarctions and 15 were hemorrhagic strokes. The incidence of stroke events for the whole population was 0.436 (95% CI, 0.42–0.45) per 100 person-years, 0.322 (95% CI, 0.305–0.339) per 100 person- years for the group with no retinopathy, and 0.493 (95% CI, 0.466–0.519) per 100 person-years and 1.073 (95% CI, 0.899–1.246) per 100 person-years for the group with mild and moderate hypertensive retinopathy, respectively. ⁷ This study showed long term effects of hypertension to end organ damage especially to the eye and to the brain. Although many studies were conducted, it has mostly concentrated on cerebral infarction, and the main pathogenesis is atherosclerosis. There have not been any studies correlating hypertensive retinopathy with hemorrhagic stroke. As the disease is based on the existence of essential hypertension of the patients, therefore it can be postulated that there is an association of the pathogenesis of hemorrhagic stroke and eye signs. The proposed study would be a collection to evaluate the significance of intracranial hemorrhage in the population of Sabah. The regional neurosurgery center in Kota Kinabalu, covers a great deal of the state. This includes the capital state, Kota Kinabalu and around 25 district primary centers, where Hospital Queen Elizabeth is the tertiary referral centre. This covers approximately a population of 1.8 million people, giving a good demographic study of the population of Borneo, which consist of indigenous native, (Kadazan, Dusun, Murut, Bajau,), Malays, Chinese, and other minority. The study aims to determine the prevalence of hypertensive retinopathy changes and hypertensive hemorrhagic stroke based, on the severity of hypertensive retinopathy, compliance of medication, Glasgow Coma Scale score, Intracerebral Hemorrhagic score (ICH score), clot volume and site of HS. No studies

were conducted among hemorrhagic stroke, this will be the first study conducted, and will help will help determine the association of hypertensive retinopathy changes among hemorrhagic stroke patients. The retinopathy changes will be associated with clinical findings, possibility of intervention and also outcome of the patients. Therefore retinopathy screening will provide a better understanding to the pathogenesis and importance in clinical practice in regards to hemorrhagic stroke.

Methodology and Materials

2 group of patients were recruited

For Hemorrhagic Stroke

All patients referred to Neurosurgery Department Hospital Queen Elizabeth, Kota Kinabalu with hypertensive hemorrhagic stroke from May 2016 till May 2018.

For Control Group (hypertension without hemorrhagic stroke)

Patients from Putatan Community Clinic, Kota Kinabalu, Sabah, for hypertension follow up from May 2016 till May 2018.

The study was approved by the Malaysian Medical Research and Ethics Committee (MREC).

[NMRR ID: NMRR-16-2691-32571]

Methods:

1. Patients, not randomised were diagnosed with hypertensive haemorrhage based on CT scan on admission who fulfilled the inclusion and exclusion criteria were recruited. Patients underwent treatment in accordance to standard protocol for hypertensive hemorrhagic stroke.

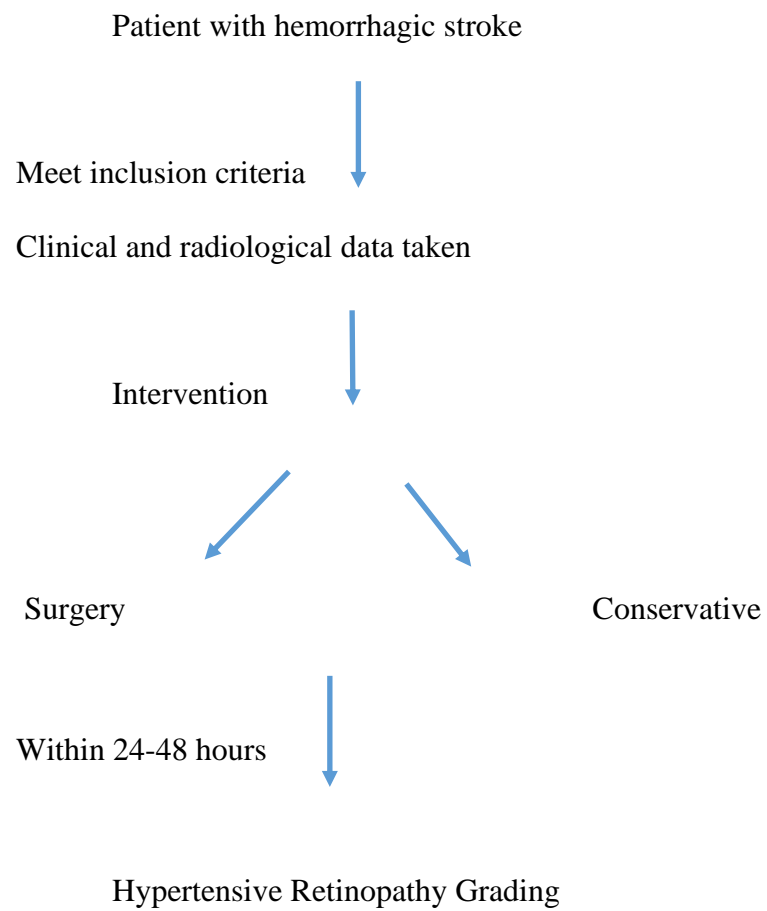
2. Clinical and radiological parameter, were collected in a standard collection data entry form, the parameter include Glasgow Coma Scale (GCS), clot volume, site of haemorrhage, Intracerebral Haemorrhage (ICH) score, and Glasgow Outcome Score (GOS).
3. Retinal examination picture was taken with a digital fundoscopic camera apparatus using Pan-Optic Ophthalmoscope WELCH ALLYN, USA, that was recorded and stored as photo or image, within the first 24-48 hours, after the patients were clinically stabilised.
4. The severity was graded on both the fundi, based on *Wong and Mitchell classification of Hypertensive Retinopathy*,^[35] The retinal picture were accessed by two independent ophthalmologist that were blinded to the patient clinical condition.

Control group

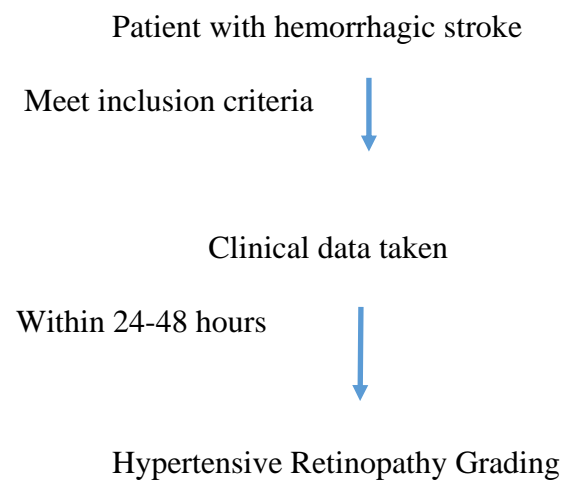
1. Control group, consisting of patients having hypertension without hemorrhagic stroke and not randomised who fulfilled the inclusion and exclusion criteria were recruited during their follow up hypertension visit in the community clinic.
2. The clinical parameter were taken, like blood pressure, during the visit to the clinic, after matching statistically with the hemorrhagic stroke patients, and retinal examination picture of the fundi were carried out and accessed by two independent ophthalmologist that were blinded to the patient clinical condition based on *Wong and Mitchell classification of Hypertensive Retinopathy*.^[35]

Study Flow Chart

Hemorrhagic Stroke Group



Non Hemorrhagic Stroke / Control Group



Statistical Analysis

The sample size was calculated using PS sample size software, with a power of 0.8, α of 0.05, P_0 of 0.14 and P_1 of 0.4, the sample was 45 patients, with a drop out rate of 10 percent, the total sample size for each group is 50 patients. For the hemorrhagic stroke patients the 50 patients were analysed as there were no prior studies to determine the sample size. Statistical analysis would be performed with the use of commercially available software SPSS Inc., version 20. Numerical variables will be presented in mean and standard deviation whereas categorical variables will be presented in frequency and percentage. Association between HR and HS will be assessed by Pearson's chi-square test.

Results

101 patients were recruited in the study, 51 patients with hypertension and HS, as the investigated arm and 50 patients with hypertensive disorder but no event of hemorrhagic stroke taken as a control group that satisfy the inclusion criteria of the study. The age group include from 35 years old till 70 years old, Mean(SD) age of the patients 54.0(9.2). The demographic distribution, 58.4% subjects were male and 41.6% were female, with majority of patient Chinese (n=31), followed by the ethnic group of Sabah, Dusun (n=20) and Kadazan (n=19), other ethnic group of Sabah accounting for 28 patients and Malay patients being the least with 3 patients, as in Table 2.

The blood pressure (BP) for the entire population, ranges from 122-268 mmHg for systolic, with mean (SD) 166.36(31.734), and for diastolic 64-148 mmHg with mean (SD) 94.53(16.05). As for the HS group, the systolic BP, Mean (SD) 187.95(29.66) and diastolic BP Mean (SD) 99.24(20.68) that was taken during the acute stage, which was higher than the non-HS (control group) systolic BP Mean (SD) 144.34(13.34) and diastolic BP mean (SD) 89.74(6.55). The data collected in the HS group, with GCS of 3-8 accounting for 17(33.3%), 19(37.3%) having

GCS 9-12, and GCS of 13-15 having 15(29.4%). 2 main grouping was done for GCS, a score of 3-8 having 17 patients considered poor conscious level on admission and GCS of 9-15 with 34 patients, considered good conscious level on admission. The distribution for site of clot are putamen 30(58.8%), thalamus 13(25.5%), followed by cerebellar, brain stem and lobar, 4, 3 and 1 patients respectively. The results for clot volume less 30 ml by computed tomography (CT), accounts for 30 (58.8%) of the patients and clot volume more than 30 ml having 21 (41.2%) patients. ICH score were calculated on admission for all the hemorrhagic stroke, ICH score from 0-2 had 42 patients, and ICH score of 3-6 had 9 patients. The GOS score were taken with favourable outcome (GOS score 4-5) in 24 (47.1%) patients , and unfavourable outcome in 27 (52.9%) patients. 21 patients in the study were treated conservatively and another 21 patients were treated surgically, another 9 patients had only cerebrospinal fluid diversion, all these are depicted in Table 3.

The fundoscopic examination was reviewed and classified according to the Mitchell and Wong hypertensive retinopathy, we then grouped normal and mild retinopathy as low severity and moderate and severe retinopathy as high severity. In the hypertensive with hemorrhagic stroke 49 patients has low severity and only 1 presented with high severity. Whereas in the hemorrhagic stroke group, 21 had low severity accounting for 41.2% and 30 patients had high severity as depicted in Table 4, this comparison was significant with a p value of 0.001. Fundoscopic examination for both the eyes were recorded and interpreted by 2 independent accessor, and a inter-rater bias analysis was done using Cohen Kappa test with a value of $k=0.94$ for the right eye, and $k=0.985$ for the left eye, giving almost perfect agreement between accessors as depicted in Table 9 and 10.

We analyse the association of hypertensive retinopathy severity with GCS on admission, clot volume, ICH group and GOS score using Pearson chi square test. When analysed with GCS on admission, low severity had a total of 21 patients of which 19 patients had GCS between 9-

15, and only 2 patients had GCS 3-8. For high severity, a total of 30 patients with 15 patients in each GCS of 3-8 and 9-15, that was statistically significant with a p-value of 0.003, as depicted in Table 5.

Low severity also showed a clot volume less than 30 ml in 19 patients with only 2 patients having a clot volume more than 30 ml. In high severity, 11 patients had clot volume less than 30 ml, and 19 patients had clot volume more than 30 ml, the chi square test reveal a p value of 0.001, also statically significant, as depicted in Table 6. ICH score was group into ICH 0-2 and ICH 3-6, when analysed low severity only had ICH score between 0-2 accounting for 21 patients, as for high severity 21 had ICH score 0-2, while another 9 patients had ICH score of 3-6, the p value calculated was 0.006, as depicted in Table 7. Lastly we compared with the GOS score of the patient, we found favourable outcome of GOS score 4-5, low severity of retinopathy accounted for 17 patients, with only 4 having unfavourable outcome (GOS score 1-3). As for high severity, 23 patients had unfavourable outcome with 7 having favourable outcome, this was statistically significant having a p value of 0.001, as depicted in Table 8. The estimated risk for patient of high severity retinopathy in hemorrhagic stroke is 0.588, whereas for low severity retinopathy is 0.412. The relative risk for patient with high severity having hemorrhagic stroke is 29.4, while for low severity is 0.42, as shown in Table 11. McNemar's test could not be performed as the fundoscopy examination was done only during admission, and not repeated during the duration of the study.

Discussion

There has been studies done to correlate hypertension retinal study with renal disease, even prospective one, but were not conclusive, as seen in the ARIC study, Beaver Dam Eye Study and Cardiovascular health study.³³⁻³⁵ A similar study was also conducted for retinopathy

association with cardiovascular disease (CVD), to predict the mortality, the Blue Mountain Eye Study, showed association of CVD with mortality in patients with retinopathy.³⁶ Ibaraki Prefectural Study, describe patients with mild retinopathy changes regardless of hypertensive status, were at risk of CVD mortality, giving a prognostic value of retinopathy changes in CVD.⁵ Based on the study Hypertensive Retinopathy and Risk of Stroke⁷, it was established that the moderate retinopathy had higher risk of developing stroke, but it was mainly cerebral infarct seen, with the hazard ratio (HR) 1.39 for mild retinopathy, and HR of 2.20 for moderate retinopathy.⁷ Unfortunately there is a lack of study to compare hypertensive retinopathy with its association with hemorrhagic stroke, as the number of affected patients are relatively lower, therefore, we decided to take a approach to capture the data of admitting patient within our neurosurgical centre with hemorrhagic stroke, and to detect severity of retinopathy, for the possibility to shed some light on the association between hypertension and hemorrhagic stroke. Firstly, the blood pressure for the HS group was higher on admission to hospital within the first 24 hours as compared to the non HS group, the blood pressure was taken during the first day of presentation, with mean systolic BP, 187.95mmHg and, mean diastolic BP 99.24mmHg. It reveals chronic hypertension within these group, but these changes may be attributed to elevation of intracranial pressure resulting in physiological response of the BP to compensate. The non-HS group had a mean systolic of 144.34mmHg and mean diastolic of 89.74mmHg. Patient within the HS group definitely suffer from some form of retinopathy be it mild or moderate, this may reveal that the retinal vasculature does reveals some similarities between the cerebral vasculature and retinal vasculature, the elevation of blood pressure and that hemorrhagic stroke may be an inevitable consequence. This makes it a valuable indicator for HS, hence retinopathy screening for hypertensive patients should be routinely performed and retinopathy changes warrants closer follow up and an increase prevalence of HS. Postulating that the hemorrhagic stroke may have an association with the formation of hemorrhages within