RESEARCH ARTICLE

Effective Application of Pharmacotherapy Strategy for Hospitalized Ischemic Stroke Patients in Malaysia

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Abstract

Background: Worldwide, cerebrovascular accident (stroke) is the second leading cause of death and is the third leading cause of disability. Sadly, stroke prevalence in the low- and middle-income countries remains high (70%) with both stroke-related deaths and disability-adjusted life years reported to be as high as 87%.

Aim: The objective of this study is to evaluate the success of pharmacotherapy management strategy for Malaysian stroke patients in a public hospital based on the Clinical Practice Guidelines (CPG), 2012.

Methods: A retrospective, cross-sectional study based on medical records of patients (n=682) with confirmed diagnoses of ischemic stroke admitted to Sungai Buloh Hospital for four years was conducted. Data was collected using self-developed data collection forms consisting of demographic profiles, comorbidity and pharmacotherapy treatment.

Results: The mean age of reported cases was 66.66 years with the majority (58%) being males while only 42% were females. The majority (>72%) adhered to the pharmacotherapy management of Clinical Practice Guideline Malaysia 2012 for ischemic stroke inpatients setting in a public hospital (p=0.001).

Conclusion: Most patients complied to the pharmacotherapy management of ischemic stroke guideline which is important to avoid disability and mortality caused by stroke.

Keywords: Pharmacotherapy management, Ischemic Stroke, In-patient, Clinical Practice Guideline Malaysia.

1 | BACKGROUND:

Based on World's Health Organization (WHO) report, 2017, stroke is one of the top ten causes of death worldwide and remains a major cause of death globally in the past 15 years. The WHO statistical health profile for Malaysia indicated that stroke is also one of the top leading causes of death in 2012.

The mean age of stroke onset in Malaysia is between 54.5 and 62.6 years. (1) Globally, stroke is a common health problem, contributing to death and disabilities. (2) WHO, 2018.

A stroke occurs due to the blockage of blood flow or rupture of the artery in the brain leading to the death of brain cells. Ischemic stroke is caused by thrombus formation that occludes a cerebral artery.

Although atherosclerosis is usually the cause of thrombus formation, 30% of ischemic strokes are cryptogenic, meaning there is no known cause. (3) Patients who survive an ischemic stroke or transient ischemic attack (TIA) are at increased risk of recurrent stroke, with survivors of TIA having a 10-year risk of only 19%. (4) Therefore, risk factor reduction, particularly blood pressure lowering, is essential for stroke prevention.

Stroke treatment requires an immediate action since any delay can worsen and complicate the patient's condition. (5) Additionally, time is crucial in the evaluation and diagnosis of stroke due to the narrow therapeutic window for the treatment of acute ischemic stroke. For example, tissue plasminogen activator (t-PA) should ideally be administered to acute stroke patients within 4.5 hours to achieve optimal results. (6) In most acute stroke cases, patients are unable to receive t-PA due to delay in the time of arrival. (7)

Several studies attempted to determine the factors contributing to the delay and in most identified the lack of patient's knowledge on stroke and visit to local practitioner leading to a delay in seeking treatment as contributing factors. (8) In a survey conducted on physicians, thrombolytic is unlikely to be used even when the situation to use thrombolytic therapy is ideal. (9) Co-morbidity, which is common in stroke patients, causes decreased health outcomes and is negatively correlated with an increased rate of mortality. (10) Studies previously conducted on comorbidities stated that co-occurring conditions contribute to more complex stroke treatment and recovery process. (11)

Extensive research has been conducted on factors affecting delayed treatment and the management of post-stroke. However, there is lack of local data to determine pharmacotherapy success among stroke

patients in Malaysian hospitals which can be used as a baseline to reduce the time gap (if any) for instituting treatments. Our study aims to evaluate if patients are given appropriate treatment based on the type of drugs administered, dose, and route of administration to help reduce complications and death cases of stroke patients.

Ethics Approval

Ethical clearance was obtained from the Clinical Research Centre (CRC) of Sungai Buloh Hospital. National Medical Research Registry was approved (NMRR-17-2412-38218 (IIR)). A waiver of consent was also obtained from the Medical Research & Ethics Committee's (MREC), Ministry of Health Malaysia since this study involves secondary data under ethical requirement and this study does not involve direct contact with patients as it is a retrospective study.

2 | METHODS AND MATERIAL:

This is a retrospective, cross-sectional study where data collection was obtained from medical records of patients with confirmed diagnosis of ischemic stroke admitted from January 2014 until December 2017. The study site is Hospital Sungai Buloh, which is a tertiary hospital.

Inclusion/Exclusion criteria

All patients admitted to the medical ward newly-diagnosed ischemic stroke, aged 55 years and with complete medical record during the study period, were recruited. Patients with recurrent or haemorrhagic stroke will be excluded.

Research Tools

In this research, a self-developed patient data collection form was used. The collection form consisted of six sections which includes: A. Patient's Demographic Profile, B. Vital Signs- Blood Pressure and Random Blood Glucose C. Laboratory Data (Coagulation Profile), D. Past Medical History, E. Recent Medication History and F. Detailed medications given for treatment including treatment given for the management of ischemic stroke and medication started due to patients' condition including insulin

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Pharmacotherapy management for hospitalized ischemic stroke patients

and anti-hypertensive agents. Data for vital signs were collected at the time of patients' admission while all other data were collected from the medical records. According to CPG (2012), hyperglycaemia following acute stroke is strongly associated with subsequent mortality and impaired neurological recovery which is applicable to diabetics and non-diabetics patients. Besides that, hypertension following stroke is also common.

3 | RESULTS AND DISCUSSION:

Patient Demographic Profile

Males accounted for the majority of the cases (57.9%). The prevalence of stroke disease is more common in men compared to women until the age of 55 years. With aging, it begins to shift, that's because female sex hormones offer cardiovascular protection. Sex-specific differences in pharmacokinetics & pharmacodynamics have been reported to have important clinical consequences. The mean age for those above 55 years old was 66.66 years old, the median was 65.00 and the mode of age was 55. Patients aged 55 years and above. This is because the mean age of stroke onset in Malaysia was between 54.5 and 62.6 years.

As for ethnicities, the Malays accounted for 67 (53.2%), while Chinese (23.0%) and Indians (23.0%) had similar prevalence. However, the proportion may reflect the local demographic structure. When ethnicity and gender were combined, it was noteworthy to see that in both the Malays and Chinese, males tend to have a higher incidence of stroke. However, the situation is reverse in Indians where females tend to be more affected. The occurrence of ischemic stroke in Indian females 17 patients was higher compared to Indian males 12 patients. (Table 1) shows the distribution of the demographic data.

Relationship of Age, Gender, Race with Ischemic Stroke

Those in the higher age group of 60-69 years had a higher tendency (39.7%) of suffering from ischemic stroke. The frequency is followed by those in the age group 55-59 years (27.8%) and 70-79 years old (23.8%). To be more specific with individual age,

those aged 55 years old had the highest frequency of patients who had ischemic stroke (12 patients), followed by those aged 59 years old (9 patients), and those aged 58 years, 61, years, 62 years and 64 years respectively (7 patients).

Comorbidity of Ischemic Stroke

Among the investigated comorbidities, 28 diseases seemed to be commonly associated. This includes hypertension, diabetes mellitus, dyslipidaemia, ischemic heart disease, atrial fibrillation, coronary artery disease, unstable angina, transient ischemic attack, chronic kidney disease, gout, osteoarthritis, chronic obstructive pulmonary disease, bronchial asthma, neuropathy, retinopathy, hyperthyroidism, human immunodeficiency virus, breast cyst, cervical spondylosis, schizophrenia, lung emphysema, liver cirrhosis, breast cancer, leukaemia, ovarian cancer, benign prostatic hyperplasia, colon cancer, Parkinson's and no known medical illness). Among the various diseases, hypertension was the most commonly associated with ischemic stroke (78.57%), followed by diabetes mellitus (52.38%) and dyslipidaemia (15.08%).

Arrival time assessment of patients

The majority (98%) of patients arrived after more than 4.5 hours of stroke attack while only three patients (2%) arrived within 4.5 hours. The latter group who arrived within time were eligible for thrombolysis and were then accessed to determine if they had any contraindications in receiving alteplase based on a checklist. It was then determined that they had no contraindications in receiving alteplase and were subsequently administered with alteplase. (9, 20)

Medications administered

i) Antihypertensive Medication

Patients were admitted to the emergency department (ED) showing a wide range of blood pressure including low, normal, slightly high, high and some even in hypertensive crisis. The percentage of patient's blood pressure classified according to the stages of blood pressure were the highest proportion are recorded with very high BP >180/110 mmHg (34.9%), followed by 140-159/90-99 mmHg (30.2%), >160/100 mmHg (18.3%), 120-139/80-89

Table 1: Socio-demographic characteristics

Characteristics		Number	Percentage %
Gender	Male	73	57.9
	Female	53	42.1
Race	Malay	67	53.2
	Chinese	29	23.0
	Indian	29	23.0
	Others	1	0.8
Age	>55 years	126	100%
Mean (66.66±2.01)			

mmHg (11.9%) and <120/80 mmHg (4.8%) respectively as shown in figure 1.

FIGURE 1: Percentage of patient's blood pressure classified according to the stages of blood pressure

Necessary management has been conducted at the ED to 16 ischemic patients immediately when their blood pressure was high with an antihypertensive agent where eight patients (6.35%) was administered with Captopril 25 mg STAT, followed by seven patients (5.56%) with labetalol intravenously (IV) (5 mg STAT) and a single patient (0.79%) received labetalol (IV) (20 mg STAT).

The CPG guideline states that hypertension should not be treated if blood pressure is < 220 mmHg (systolic) or < 120 mmHg (diastolic). Additionally, it is suggested that mild hypertension (160-180/90-100 mmHg) is desirable and blood pressure reduction should not be done in a drastic manner. Alternatively, administration of labetalol (10-20 mg boluses) at 10

minutes' intervals (up to 150-300 mg) or labetalol 1 mg/ml infusion with the rate of infusion as 1-3 mg/min or captopril (6.25 mg or 12.5 mg orally) can also be done. Captopril administered at 25 mg is not appropriate since the recommended dose was 6.25 mg or 12.5 mg orally. (12)

Captopril 25 mg STAT was administered to 7 patients who had BP higher than >180/110 mmHg and in a single patient who had a blood pressure higher than > 160/100 mmHg while IV Labetalol 5mg STAT was administered to 7 patients only who had BP higher than > 180/110 mmHg, and finally IV Labetalol 20 mg STAT in ED was administered in 1 patient who had a blood pressure higher than > 180/110 mmHg. Here is not ideal management strategy according to blood pressure recommendations for ischemic stroke for those who are eligible or not eligible for alteplase. The remaining ischemic stroke patients was treated and administered with medications in the ward as shown in Figure 2.

It was found that 98.41% of the plan was to withhold all antihypertensive medications and monitor blood pressure. Blood pressure reduction in patients with chronic hypertension remains one of the most important factors in primary and secondary stroke prevention, the proper management strategy for acute hypertensive response within the first 72 hours of acute ischemic stroke has been a matter of debate. Recent guidelines recommend clinical trials to ascertain whether antihypertensive therapy in the acute phase of stroke is beneficial. (13)

99 patients were administered with hypertension medication on the 2nd and 3rd day of admission

Pharmacotherapy management for hospitalized ischemic stroke patients

FIGURE 2: Type of anti-hypertensive agents administered in ward

in the hospital. 23.81% (30) were prescribed with Amlodipine 5 mg OD followed by 17.46% with Perindopril 4 mg OD and 12.70% (16 patients) with Amlodipine 10 mg OD and 6.35% (8 patients) with Perindopril 8 mg OD.

ii) Antiplatelet Medication

In this study, the antiplatelet of choice was aspirin 150 mg STAT (84.92%), followed by a high dose of aspirin 300 mg STAT (13.49%) on the first day of admission to the ward. Subsequently, 90.48% received aspirin (150 mg OD only) while three patients received aspirin 75 mg OD only. The combination of aspirin with Clopidogrel after a stroke may be beneficial for a finite time, in a very specific patient population based on the data from Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial. (14) In CHANCE, patients were enrolled within 24 hours of the onset of a minor stroke or TIA and were randomized to receive a loading dose of Clopidogrel on day 1, followed by Clopidogrel 75 mg daily for 90 days plus aspirin 75 mg for 21 days, or aspirin 75 mg daily and placebo for 90 days. There was a statistically significant decrease in recurrent stroke in patients receiving combination therapy, with no difference in bleeding, at 90 days. (14) Nevertheless, the CHANCE trial was completed in China, which may limit its generalizability. If the combination of Clopidogrel and aspirin is used for minor stroke or TIA, it should be continued for only 21 days. (15) With regards to the current study, dual therapy of Aspirin 150 mg OD and Clopidogrel 75 mg OD

was administered in 8 patients (6.35%). The recommended dose of aspirin according to CPG guideline for the treatment ischemic stroke is 75mg to 325 mg daily. The recommended dose for Clopidogrel is 75 mg daily. Patients receiving Clopidogrel and aspirin were administered with the appropriate dose. However, based on the guideline, combination therapy of Clopidogrel and aspirin has a higher life threatening bleeding risk and it is not more effective or superior than Clopidogrel or aspirin alone although eight patients (6.35%) received dual therapy.

iii) Anticoagulation Medication

In compliance with the guideline, not many patients received anticoagulants. For example, fondaparinux (2.5 mg OD) was administered subcutaneously (SC) to six patients (4.76%), while SC. Heparin 5000 I.U BD was administered to only three patients (2.38%). The guideline states that the use of heparins such as unfractionated heparin, low molecular weight heparin or heparinoids are not routinely recommended. LMWHs reduce venous thromboembolic events in patients with acute ischemic stroke and increase the risk of extracranial bleeding. LMWH should not be used in the routine management of patients with ischemic stroke. This is because it does not reduce the mortality in patients with acute ischemic stroke. (16)

iv) Thrombolytic Medication

Only three patients (2.0%) were eligible to receive thrombolysis medication, here's depends on the inclusion and exclusion criteria for tPA use in acute ischemic stroke. In overall the proportion is low compared to other studies in Malaysia territory. The recommended dose for intravenous rt-PA is 0.9 mg/kg, for a maximum of 90 mg. Only 10% of the dose should be given as a bolus followed by a 60-minute infusion and should be administered within 4.5 hours of the onset of ischemic stroke. (17)

v) Lipid-Lowering Drugs (Statin)

All patients admitted to the ward were treated with lipid-lowering statin drugs. statins are effective cholesterol-lowering drugs for reducing the risks of mortality and morbidity of cardiovascular diseases. Increasing evidence has shown that statin use is associated with a significant beneficial effect in patients with ischemic stroke. (18) Simvastatin (40 mg

and 20mg ON) was the highest administered drug (68.25%), followed by atorvastatin (40 mg and 20mg ON) (31.75%) respectively.

Overall, the percentage of statin use increased steadily between 2000 and 2006, from 25% to 70%. While the percentage continued to grow slightly afterward, it became stable at about 75% through 2014. Two factors accounted for the trend in increasing statin use. First, the general trend ran parallel to an increasing trend in statin use prior to stroke, which accounted for less than 10% of patients in 2000 and over 40% in 2014, and these prior users of statins continued to use them after stroke in almost 90% of cases throughout 2000–2014. Second, the use of statins among pre-stroke non-users increased from 20% to 60% between 2000 and 2006. Use of high-intensity statins has fluctuated over time, but there is evidence of an increase from 10% since 2008, to about 35% in 2014. (19)

vi) Antidiabetic Medication

Random Blood Glucose

Locally, both hyperglycaemia and hypoglycaemia are treated according to CPG Malaysia Ischemic Stroke 2012. The guideline states that random blood glucose of > 11 mmol/l (hyperglycemia) requires insulin while a random blood glucose level of < 3 mmol/l (hypoglycemia) requires a glucose infusion. Statistics have shown that up to 73.8% patients have normal random blood glucose with 26.2% at more than > 11 mmol/l (hyperglycemia). The mean blood glucose level for the patients upon arrival to the emergency was 4.0–20.9 mmol/l which necessitated administration of antidiabetic medications STAT as seen in the majority of the patients. Approximately 96.04% patients received Actrapid (6 unit) SC if their dextrose levels were more than 12 mmol/L while only five patients (3.96%) received Actrapid (8 units) SC STAT upon admission. In the ward, most patients received antidiabetic medication on the second or third day as shown in figure 3

Laboratory Data

Coagulation profile is one of the most important laboratory data to determine stroke patients' eligibility for thrombolysis. The tests performed indicated that only 35.7% were eligible, while the remaining

(64.3%) were not eligible for some circumstances not machining with the inclusion criteria.

Compliance to guideline evaluation

Compliance to the guideline was estimated based on the pharmacotherapy management of ischemic stroke according to CPG Malaysia-Management of Ischemic Stroke 2nd Edition (2012). Each patient was evaluated based on their eligibility for thrombolysis which included the onset of symptom time and contraindications. The medications administered and their doses were also evaluated as discussed above. The next was based on treatment of blood pressure whereby CPG Malaysia-Management of Ischemic Stroke 2nd Edition recommends not to treat hypertensive patients if systolic blood pressure (SBP) < 220 mmHg or diastolic blood pressure (DBP) < 120 mmHg since mild hypertension (SBP:160-180 mmHg/ DBP: 90-100 mmHg) is desirable.

If labetalol is used, 10-20 mg boluses at 10 minutes' intervals (up to 150-300 mg) should be instilled. Alternatively, labetalol 1 mg/ml infusion, rate of infusion for 1-3 mg/min or Captopril 6.25-12.50 mg orally can also be administered. The criterion was the treatment of high blood glucose whereby the guideline recommends to treat if random blood glucose > 11 mmol/l or < 3 mmol/L. Others is the investigation of coagulation or clotting profile in patients. In this study, 36% (45 patients) coagulation laboratory data was performed and in 64% (81 patients) the coagulation laboratory test was not performed. The CPG guideline suggests performing blood investigations which includes coagulation profile upon admission if thrombolysis is considered. For the 2% who received thrombolysis, blood coagulation test was performed. The guideline suggests that the use of heparin is not routinely recommended. However, in this study, nine patients received anticoagulation and antiplatelet. In those patients, the coagulation test should be performed as there is an increased risk of bleeding. (21,22) A score of 0=non-compliance and 1= compliance was given to these patients. If all the criteria were fulfilled they were given a score of 1 and if any of the criteria above were not fulfilled, they were given a score of 0. Thus, based on the calculation above, the compliance rate to the guideline was 72.2% and the non-compliance rate was 27.8%.

Pharmacotherapy management for hospitalized ischemic stroke patients

FIGURE 3: Percentage and type of antidiabetic medication administered in ward

Thus, due to lack of studies regarding this matter, we encourage future research can be carried out on the practice for management strategy or assess the adherence of physicians in the treatment of ischemic stroke as this will be able to capture the wide range as to the reason why full compliance is not achieved.

4 | LIMITATIONS OF STUDY:

In fact, ischemic stroke pharmacotherapy management is still not addressed widely in previous studies. Both the knowledge and practice evaluation sections of the current study focused on ischemic stroke pharmacotherapy, while stroke management consists of several components including screening lifestyle interventions, pharmacotherapy and follow up. Finally,

our findings are based on a single general hospital, a retrospective validation of different patient populations should be conducted. This study was single centre study and may not represent other parts of Malaysia, since the practice and adherence to clinical practice guidelines may vary from one institution to another.

5 | CONCLUSION:

The strategy of pharmacotherapy management for hospitalized ischemic stroke according to the guideline is one of the contributing factors to morbidity and mortality. If these factors are identified, further studies can be carried out and strategies can be planned to improve the pharmacotherapy manage-

ment of stroke patients in hospitals. The impact of research findings on clinical practice that will increase the knowledge and awareness for the clinical pharmacists and clinicians about stroke pharmacotherapy strategy, were considered as a significant impact factor in the management of ischemic stroke patients and reduce the mortality and morbidity.

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Conflicts Of Interest

The authors declare that they have no conflicts of interest.

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Pharmacotherapy management for hospitalized ischemic stroke patients

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