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Pharmacological Therapy for Ischemic Stroke Patients Accordance to Clinical Practice Guidelines

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ABSTRACT

Stroke ranks as the second most common cause of mortality and the third most significant cause of disability globally. The frequency of stroke remains elevated in low- and middle-income countries, affecting 70% of the population. Additionally, stroke-related deaths and disability-adjusted life years might reach as high as 87%. This study aims to evaluate the suitability of a pharmacological treatment approach for stroke patients in Malaysia, specifically in a public hospital setting. The evaluation will be based on the Clinical Practice Guidelines (CPG) 2012. A four-year retrospective, cross-sectional study was undertaken using medical records conducted among (n=682) hospitalized patients at Sungai Buloh Hospital; only (n=126) conforms with inclusion criteria and confirmed ischemic stroke diagnoses. Data was gathered utilizing a self-created data-collecting form that included demographic information, comorbidity, and pharmacological treatment. The mean age of the reported cases was 66.66 years, with the majority (58%) males and only (42%) females. The compliance to the Clinical Practice Guideline Malaysia 2012 for ischemic stroke inpatient setting in a public hospital is (>72%) (p=0.001). A significant proportion of patients had pharmacological therapeutic management in adherence to stroke recommendations, which is considered a critical factor in reducing stroke-related disability and mortality.

Keywords: Ischemic Stroke, Clinical Practice Guideline (CPG) Malaysia, Pharmacotherapy Management, Cerebrovascular Diseases, Cardiovascular Diseases.

INTRODUCTION

Based on the World Health Organization (WHO) Report 2017, stroke is one of the top ten causes of death worldwide and has remained a significant cause of death globally in the past 15 years. The WHO statistical health profile for Malaysia indicated that stroke was also one of the leading causes of death in 2012. The mean age of stroke onset in Malaysia is between 54.5 and 62.6 years. (Kooi et al., 2016) Globally, stroke is a common health problem, contributing to death and disabilities. (Muñoz-Venturelli et al., 2019) 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 the growth of a thrombus that obstructs a cerebral artery. Although atherosclerosis is the most common source of thrombus development, 30% of ischemic strokes are cryptogenic, which means the origin is unknown. (Yaghi et al., 2017) Patients who survive an ischemic stroke or transient ischemic attack (TIA) have a higher risk of recurrent stroke, with TIA survivors having a 10-year risk of only 19%. (Benjamin et al., 2019) risk factor reduction, particularly blood pressure decrease, is critical for stroke prevention.

Stroke treatment requires immediate action since any delay can worsen and complicate the patient's condition. (Murphy & Werring, 2020)

Additionally, time is crucial in evaluating and diagnosing stroke due to the narrow therapeutic window for treating acute ischemic stroke. For example, tissue plasminogen activator (r-tPA) should ideally be administered to acute stroke patients within 4.5 h to achieve optimal results (Jauch et al., 2013). In most acute stroke cases, patients cannot receive r-tPA due to delays in the arrival time (Song et al., 2015).

Several studies attempted to determine the factors contributing to the delay. Most identified the lack of patient knowledge on stroke and visits to local practitioners leading to a delay in seeking treatment as contributing factors (Party, 2012). In a survey conducted on physicians, thrombolytic is unlikely to be used even when the situation to use thrombolytic therapy is ideal (Cheng & Kim, 2015). Co-morbidity, common in stroke patients, causes decreased health outcomes and is negatively correlated with an increased mortality rate (Singh et al., 2018). Studies previously conducted on comorbidities stated that co-occurring conditions contribute to more complex stroke treatment and recovery processes (Stinear et al., 2017).

Extensive research has been conducted on factors affecting delayed treatment and post-stroke management. However, there is a 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 medicine based on the type of drugs administered, dose, and route of administration to help reduce complications and death cases of stroke patients.

MATERIALS AND METHODS

A retrospective, cross-sectional study and the data were obtained from medical records of patients admitted from January 2014 to December 2017 with a confirmed diagnosis of ischemic stroke. The study was conducted at the Hospital Sungai Buloh, Selangor, Malaysia.

Inclusion/Exclusion criteria

All patients admitted to the medical ward with newly diagnosed ischemic stroke, aged above 50 years and with complete medical records during the study period, were recruited. Patients with recurrent or hemorrhagic 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 include: 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 and anti-hypertensive agents. Data for vital signs were collected when patients were admitted, while all other data were collected from the medical records. According to CPG (2012), Elevated blood glucose levels following an acute stroke are significantly linked to subsequent mortality and compromised neurological recuperation, a correlation that extends to both diabetic and non-diabetic patients. Furthermore, post-stroke hypertension represents a prevalent occurrence.

RESULTS AND DISCUSSION

Patient Demographic Profile

Males represented the vast majority of cases (57.9%). Until age 55, men had a higher frequency of stroke disease than women. It begins to alter with age because female sex hormones provide cardiovascular protection. Sex variations in pharmacokinetics and pharmacodynamics have been linked to serious clinical effects. The mean age for those above 55 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 Malaysia's mean age of stroke onset was between 54.5 and 62.6 years.

Table I. Socio-demographic characteristics

Characteristics		umber	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 Mean (66.66±2.01)	>55 years	126	100%

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 males in both the Malays and Chinese tend to have a higher

incidence of stroke. However, the situation is reversed in Indians, where females are more affected. The occurrence of ischemic stroke in Indian females 17 patients was higher compared to Indian males 12 patients. (Table I) display the distribution of the demographic data.

Correlation between Age, Gender, and Race in Ischemic Stroke

Those in the higher age group of 60-69 years had a higher tendency (39.7%) to suffer from ischemic stroke. The frequency is followed by those aged 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 an 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).

Ischemic Stroke Co-morbidity

Out of all the co-morbidities that were examined, 28 diseases were found to be commonly linked with all the patients. This includes hypertension, diabetes mellitus, dyslipidemia, 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, leukemia, 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 dyslipidemia (15.08%).

Hospital Arrival Time

Most patients (98%) arrived at the hospital more than 4.5 hours after a stroke attack, while only three (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 (Bluhmki et al., 2020; Cheng & Kim, 2015).

Medications Administration

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 was the highest proportion 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 mmHg (11.9%) and <120/80 mmHg (4.8%) (Table II).

Table II. Percentage of patient's BP classified according to the stages of BP.

Blood Pressure (mm Hg)	Percentage
<120/<80	4.8%
120-139/80-89	11.9%
140-159/90-99	30.2%
>160/>100	18.3%
>180/>110	34.9%

Necessary management was conducted at the ED for 16 ischemic patients immediately when their blood pressure was high with an antihypertensive agent where eight patients (6.35%) were administered 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 drastically. Alternatively, administration of labetalol (10-20 mg boluses) at 10-minute 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 inappropriate since the recommended dose was 6.25 mg or 12.5 mg orally (Church et al., 2022).

Captopril 25 mg STAT was administered to 7 patients who had BP higher than >180/110 mmHg and to a single patient who had blood pressure higher than > 160/100 mmHg. In comparison, IV Labetalol 5mg STAT was administered to only seven patients who had BP higher than > 180/110 mmHg.

Finally, IV Labetalol 20 mg STAT in ED was administered in 1 patient who had blood pressure higher than > 180/110 mmHg. There are better management strategies than this, according to blood pressure recommendations for ischemic stroke for eligible or not eligible for alteplase. The remaining ischemic stroke patients were treated and administered medications in the ward, as shown in (Table III).

Table III. Anti-hypertensive agents administered in the medical ward.

Anti-Hypertensive Medications	Count (N)
Withhold all anti-hypertensive meds	(124)
Amlodipine 10mg Tab. OD,	(16),
Amlodipine 2.7mg Tab. OD,	(1),
Amlodipine 5mg Tab. OD	(30)
Atenolol 50mg Tab. OD	(1)
Bisoprolol 1.25mg Tab. OD,	(3),
Bisoprolol 2.5mg Tab. OD,	(3),
Bisoprolol 5mg Tab. OD	(1)
Captopril 50mg Tab. TDS	(1)
Frusemide 40mg Tab. OD,	(1),
Furosemide 40mg I.V OD	(1)
Perindopril 2.5mg Tab. OD,	(1),
Perindopril 2mg Tab. OD,	(8),
Perindopril 4mg Tab. OD,	(22),
Perindopril 8mg Tab. OD	(8)
Prazocin HCl 1mg Tab. OD	(1)
Ticlopidine 250mg Tab. BD	(1)

It was found that 98.41% of the plan was to withhold all antihypertensive medications and monitor blood pressure. Blood pressure reduction in chronic hypertensive patients remains one of the most important elements in primary and secondary stroke prevention; nevertheless, the optimal management strategy for an acute hypertensive response within the first 72 hours of acute ischemic stroke has been contested. Clinical trials to find out whether antihypertensive agents are effective in the acute phase of stroke are recommended by recent guidelines (AlSibai & Qureshi, 2016). Ninety-nine patients were administered hypertension medication on the 2nd and 3rd days of admission to the hospital. 23.81% (30) were prescribed 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.

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. According to the data from the Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial, combining aspirin with Clopidogrel after a stroke may be advantageous for a limited duration in a specific patient classification (Kheiri et al., 2019). Collected patients in the CHANCE study 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. At 90 days, there was a statistically significant reduction in recurrent stroke in patients taking combination therapy, with no difference in bleeding (Kheiri et al., 2019). Nonetheless, because the CHANCE study was completed in China, its generalizability may be limited. If Clopidogrel and aspirin are used to treat a mild stroke or TIA, they should only be used for 21 days (Ye et al., 2020). Regarding 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 guidelines for treating 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. It is not more effective or superior to Clopidogrel or aspirin alone, although eight patients (6.35%) received dual therapy.

Anticoagulation Medication

In compliance with the guideline, only a few 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 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 mortality

in patients with acute ischemic stroke (Ye et al., 2020).

Thrombolytic Medication

Only three patients (2.0%) were eligible to receive thrombolysis medication; here, it depends on the inclusion and exclusion criteria for tPA use in acute ischemic stroke. Overall, the proportion is low compared to other studies in Malaysian 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 (Alper et al., 2020).

Lipid-lowering drugs (Statin)

All patients admitted to the ward received lipid-lowering statin medications. Statins are effective cholesterol-lowering medications that minimize the risks of cardiovascular disease mortality and morbidity. Increasing data suggests that statin use has a considerable protective effect in people with ischemic stroke (Zhao et al., 2019). Simvastatin (40 mg and 20mg ON) was the most administered drug (68.25%), followed by atorvastatin (40 mg and 20mg ON) (31.75%), respectively.

From 2000 to 2006, there was a marked escalation in statin utilization, rising from 25% to 70%. After this period, the rate experienced a modest increase, stabilizing around 75% until 2014. This upward trajectory in statin adoption can be attributed to two primary factors. Initially, pre-stroke statin administration had a concomitant rise, which was below 10% in 2000 but exceeded 40% by 2014. Notably, nearly 90% of these initial statin recipients persisted with the treatment post-stroke throughout the 2000-2014 timeframe. Additionally, among those not previously on statins before their stroke, the uptake surged from 20% to 60% within the 2000 to 2006 period. While the administration of high-intensity statins exhibited some variability, there was a discernible increment from 10% in 2008 to approximately 35% in 2014 (Yang et al., 2019).

Antidiabetic Medication

Both hyperglycemia and hypoglycemia are treated locally, 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% of 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 the administration of antidiabetic medications STAT as seen in the majority of the patients. Approximately 96.04% of patients received Actrapid (6 units) 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 (Table IV).

Table IV. Antidiabetic medications administered in the medical ward.

Antidiabetic Medications	(N) Percentage
Metformin 850mg Tab. BD,	(1) 0.79%,
Metformin 500mg Tab. BD,	(8) 6.35%,
Metformin 250mg Tab. BD,	(1) 0.79%,
Metformin 1g Tab. OD	(1) 0.79%
Glicazide 80mg Tab. OD,	(4) 3.17%,
Glicazide 40mg Tab. BD,	(2) 1.59%,
Gliclazide 30mg Tab. OD	(1) 0.79%
Novomix 20u SC. BD	(1) 0.79%
Mixtard 8u SC. BD,	(2) 1.59%,
Mixtard 32u SC. BD,	(1) 0.79%,
Mixtard 20u SC. BD	(1) 0.79%
Insulatard 20u SC. ON,	(1) 0.79%,
Insulatard 16u SC. ON,	(1) 0.79%,
Insulatard 14u SC. ON,	(1) 0.79%,
Insulatard 12u SC. ON,	(1) 0.79%,
Insulatard 10u SC. ON	(2) 1.59%
Actrapid 6u SC. TDS,	(1) 0.79%,
Actrapid 10u SC. TDS,	(1) 0.79%,
Actrapid 8u SC. TDS	(3) 2.38%

Laboratory Data

The coagulation profile is a crucial set of laboratory results used to assess the suitability of stroke patients for thrombolysis treatment. The conducted tests revealed that only 35.7% met the eligibility criterion, while the remaining 64.3% were deemed ineligible due to conditions that did not align with the inclusion criteria.

Evaluation of guideline compliance

The relationship between compliance with the CPG Malaysia Management of Ischemic Stroke 2nd Edition (2012) guidelines and therapy outcomes based on the collected date we can break down the information and follow a structured approach, as shown in (Table V).

Table V. Compliance with the Malaysian CPG Management of Ischemic Stroke

Guideline Aspect	Guideline Recommendation	Compliance Measure	Comments
Thrombolysis Eligibility	Evaluate eligibility based on the onset of symptoms and contraindications.	Patients were evaluated based on eligibility, but specific compliance data is not provided.	Detailed data on thrombolysis compliance is needed for further analysis.
Blood Pressure Management	Do not treat hypertensive patients if SBP < 220 mmHg or DBP < 120 mmHg. Mild hypertension (SBP: 160-180 mmHg / DBP: 90-100 mmHg) is desirable. Labetalol or captopril is necessary.	Specific recommendations for labetalol and captopril usage are given.	Highlights the importance of specific drug compliance in hypertension management.
Blood Glucose Management	Treat if random blood glucose > 11 mmol/L or < 3 mmol/L.	Recommendations for treating high and low blood glucose levels are provided.	Blood glucose management is well-defined; compliance assessment focuses on adherence to treatment.
Coagulation Profile Testing	Perform coagulation or clotting profile tests.	36% (45 patients) had coagulation lab data performed; 64% (81 patients) did not.	Indicates significant non-compliance in conducting coagulation profile testing.

Each patient was evaluated based on their eligibility for thrombolysis, including the onset of symptom time and contraindications. The medications administered and their doses were also evaluated, as discussed above. The next was based on the 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 should be instilled at 10-minute intervals (up to 150-300 mg). Alternatively, labetalol 1 mg/ml infusion, infusion rate 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 treatment if random blood glucose >11 mmol/l or <3 mmol/L. Another is the investigation of coagulation or clotting profiles 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 include a coagulation profile upon admission if thrombolysis is considered. A blood coagulation test was performed for the 2% who received thrombolysis. The guideline suggests that the use of heparin is only sometimes recommended. However, in this study, nine patients received anticoagulation and antiplatelet. The coagulation test should be performed in those patients as there is an increased risk of bleeding. (Meinel et al., 2020; Purrucker et al., 2017) 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; if any of the above criteria were not fulfilled, they were given a score of 0. Thus, based on the calculation above, the compliance rate with the guideline was 72.2%, and the non-compliance rate was 27.8%.

Thus, due to the lack of studies regarding this matter, we encourage future research to 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.

Limitations of study

There is still a considerable lack of information in the existing literature about how to effectively treat ischemic stroke with medication.

The current study primarily assessed the understanding and application of medication for ischemic stroke. It is crucial to acknowledge that stroke care is complex, involving several elements such as lifestyle intervention screening, medication, and ongoing follow-up. The data given here are obtained from a single tertiary hospital. To have a more thorough knowledge, it is advisable to conduct prospective and retrospective validation using a wide range of patient cohorts. Due to the fact that this study was carried out at a solitary facility, its results may not be applicable to other areas of Malaysia, as compliance with and implementation of the Malaysian clinical practice guidelines CPG 2012 might vary among institutions.

CONCLUSION

The pharmacological management method for hospitalised ischemic stroke is considered a contributing factor to morbidity and mortality, as stated in the recommendations. Once these indicators are recognised, more investigations may be conducted, and methods can be devised to enhance the pharmacological treatment of stroke patients in hospitals. The research findings regarding the application of stroke pharmacotherapy strategy have significant effects on clinical practice. This impact factor enhances the knowledge and awareness of clinical chemists and clinicians, leading to improved management of ischemic stroke patients and reduced mortality and morbidity rates.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL 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 and Ethics Committee's (MREC) Ministry of Health Malaysia since this study involves secondary data under ethical requirements and does not involve direct contact with patients as it is a retrospective study.

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