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Medication prescribing trends and its associated adverse drug reactions among hospitalized stroke patients from a main stroke center in Penang, Malaysia: A retrospective 5-year study

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Abstract

Adverse drug reactions (ADRs) are one of the major threats in our healthcare system, which profusely affects health, transience, and quality of life, especially among hospitalized patients. This 5-year study was conducted to determine the incidence and analyze the pattern of ADRs among stroke patients at Hospital Seberang Jaya (HSJ), Malaysia which is the main stroke center for all tertiary healthcare institutions in Penang, Malaysia. A total of 1,993 patients were hospitalized for stroke during the study period of 5 years out of which only 30 of them were reported to experience ADRs during hospitalization. The study patients had a mean (SD) of 61 (±11.8) years, Modified Rankin Score (mRS) score of 1.8 (±1.6), NIH Stroke Scale (NIHSS) score of 3.0 (4.0) with median (IQR) duration of adverse drug reaction of 3.0 (7.0) days. The majority of the patients were Malay (66.7%); female (50.0%); experienced ischemic stroke (90.0%); with first episode of stroke (93.3%); with comorbidity dyslipidemia (60.0%); and mostly recovered post ADRs (80.0%). The major drug classes that contributed to ADRs were vaccines, anti-infective, anti-epileptic, anti-platelets, and others. Evaluation of the causality of ADRs indicated majority were possible (50.0%) ADRs based on the Naranjo scale. The evaluated incidence of ADRs among stroke patients is low in this study. This low incidence rate could be possibly due to active clinical interventions by healthcare professionals during hospitalization. ADR monitoring is highly warranted among the sub-population of stroke patients due to the existence of multiple risk factors and their state of vulnerability.

Keywords: Adverse drug reactions, major drug classes, stroke, main stroke center, Malaysia

INTRODUCTION

In Malaysia, stroke or cerebrovascular disease is known to be the third leading cause of death, with approximately 32 deaths in a day.[1] Being a developing nation, the burden of stroke in Malaysia is hefty considering the amount of budget spent annually (USD 38 million) excluding thrombectomy.[2] The National Health and Morbidity Survey Malaysia from 2006 to date conducted by the Ministry of Health, Malaysia has shown a continuous upsurge in the prevalence of vascular risk factors among the population especially diabetes mellitus, hyperlipidemia, and obesity with a steady decline in the prevalence of hypertension.[3] Most of the time, these risk factors are not addressed judiciously from the beginning leading to unwanted consequences such as stroke. Acute stroke management involves treatment with an intravenous (IV) tissue plasminogen activator (tPA), antiplatelets such as high dose of aspirin or clopidogrel, and antihypertensives.[4] Additionally, other risk factors such as diabetes mellitus and hyperlipidemia are also optimized accordingly to prevent the occurrence of other complications leading to higher morbidity and even mortality. Only 3 out of 10 in Malaysia, are reported as stroke

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survivors, whereby able to live an independent life post-stroke.[2]

Many studies have reported significant adverse drug reactions (ADRs) related to the post-stroke diagnosis and management.[5-7] The drugs causing the ADRs are from various classes. Not forgetting, the recently developed vaccines to combat COVID-19 infection are reported to cause stroke as one of the ADRs.[8] ADRs opposes as one of the major threats in our healthcare system, which profusely affects the health and the quality of life especially among hospitalized patients.[9] According to WHO, ADRs is defined as a noxious and unintended response to a drug which occurs at doses normally used for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.[10] ADRs monitoring is highly warranted among stroke patients due to the existence of multiple risk factors like polypharmacy, prolonged therapies, medication errors and comorbidities.

Although there are various studies underlying the ADRs effects among stroke patients, but the data on the ADRs incidence and pattern have remained as neglected area especially in Malaysia. Thus, the purpose of this study, which was carried out at one of Malaysia's primary stroke centres, was to ascertain the incidence and analyse the pattern of ADRs among stroke patients. This study will help to gain insight on the number of patients that are affected with ADRs among stroke patients and provide the much-needed data to prevent reoccurrence of the ADRs among this subpopulation and further reduces the impact on the patients' quality of life.

METHODS

Study setting

This study was conducted at Hospital Seberang Jaya (HSJ), Malaysia, a government healthcare facility that serves as the main stroke center for all tertiary healthcare institutions on Penang, Malaysia.

Study design and data collection

Data of patients hospitalized for stroke at Hospital Seberang Jaya, Malaysia from 2018-2022 was collected for the purpose of this study. The hospitalized stroke patients were initially identified from the stroke database. The stroke database was established on the initiative of a consultant neurologist at HSJ, with the team from Clinical Research Centre Hospital Seberang Jaya (CRCHSJ) that actively collects clinical and epidemiological information on hospitalized stroke patients for the database on a daily basis.

Major drug classes caused ADRs and major symptom organ classes affected

Reported drugs that caused ADRs and the affected organs due to ADRs for the hospitalized stroke patients were recorded from the ADRs reporting form acquired from the Pharmacy Information system (PHIS) HSJ. The reported ADRs and the affected organs were cross-checked again for any discrepancies in the patients' medical report. Once, the no discrepancies observed in both documents, the drugs and the affected organs were classified into major drug classes and major symptom organ classes based on anatomical therapeutic chemical (ATC) classification system.

Statistical analysis

Continuously distributed variables were analyzed using either T-test or Mann-Whitney U test depending on skewness of data, whereas for categorical variables analysis was performed using the chi-square ($\chi 2$) test. Major symptom organ classes listed based on major drug classes were presented as frequency (n) and percentage (%). Statistical evaluation was performed by using IBM SPSS version 22 (SPSS Inc., Chicago, IL).

RESULTS

Demographic characteristics of included stroke patients from Hospital Seberang Jaya, Malaysia from 2018-2022

A total of 1,993 patients were hospitalized for stroke during the study period of 5 years and out of which only 30 of them were reported to experience ADRs during hospitalization. The included patients had experienced more than one ADRs events.

Table 1 illustrates the demographic characteristics of the included study patients. Variables that were described as mean (SD) were patients' age (years) 61 (±11.8) and Modified Rankin Score (mRS) score 1.8 (±1.6), whereas variables NIH Stroke Scale (NIHSS) score 3.0 (4.0) and duration of adverse drug reaction (days) 3.0 (7.0) were reported as median (IQR).

The study patients comprised of male [n=15 (50.0%)] and female [n=15 (50.0%)]; ethnicity Malay [n=20 (66.7%)], Chinese [n=6 (20.0%)] and Indian [n=4 (13.3%)]; smoking status yes

Table 1: Demographic characterization of patients experienced adverse drug reaction (ADR) who were admitted for stroke at Hospital Seberang Jaya (2018-2022) (n=30)

Characteristics	No. (%) of participants Composition
Demographics	
Age (years), mean (SD)	61 (11.8)
NIHSS score, median (IQR)	3.0 (4.0)
mRS score, mean (SD)	1.8 (1.6)
Gender	
Male	15 (50.0)
Female	15 (50.0)
Ethnicity	
Malay	20 (66.7)
Chinese	6 (20.0)
Indian	4 (13.3)
Smoking status	
Yes	4 (13.3)
No	26 (86.7)
Stroke category	
Ischemic stroke	27 (90.0)
Hemorrhagic stroke	3 (10.0)
Stroke episode	
First	28 (93.3)
Recurrent	2 (6.7)
Comorbid conditions	
Hypertension	14 (46.7)
Diabetes	10 (33.3)
Dyslipidemia	6 (20.0)
Vascular disease	3 (10.0)
Seriousness of adverse drug reaction	
Yes	10 (33.3)
No	20 (66.7)
Outcome post adverse drug reaction	
Recovered	24 (80.0)
Not recovered	6 (20.0)
Duration of adverse drug reaction (days), median (IQR)	3.0 (7.0)

[n=4 (13.3%)] and no [n=26 (86.7%)]; stroke category ischemic stroke [n=27 (90.0%)] and hemorrhagic stroke [n=3 (10.0%)]; stroke episode first [n=28 (93.3%)] and recurrent [n=2 (6.7%)]; with comorbid conditions hypertension [n=14 (46.7%)], diabetes [n=10 (33.3%)], dyslipidemia [n=6 (20.0%)] and vascular disease [n=3 (10.0%)]; seriousness of adverse drug reaction serious [n=10 (33.3%)] and not serious [n=20 (66.7%)] and outcome post ADRs recovered [n=24 (80.0%)] and not recovered [n= 6 (20.0%)].

Major drug classes related ADRs frequency and most common symptoms according to organ classes among study patients

The major drug classes contributed to ADRs among the study patients were vaccines, anti-infective, anti-epileptic, anti-platelets, anti-diabetic and others (Table 2). Major drug classes contributed to ADRs were vaccines [n=12 (40.0%)], anti-infectives [n=3 (10.0%)], anti-epileptic [n=2 (6.7%)], anti-platelets [n=2 (6.7%)], and anti-diabetic [n=2 (6.7%)] medications. Vaccine

Table 2: Major drug classes related adverse drug reactions (ADRs) frequency and most common symptoms according to organ classes among study patients

Major Drug Class	Patients, n (%)	Symptom Organ Class	Frequency of ADRs, n (%)
Vaccine	12 (40.0)	Neurological	15 (75.0)
		Gastrointestinal	2 (10.0)
		Skin	1 (5.0)
		Immunological	1 (5.0)
		Renal	1 (5.0)
Anti-infectives	3 (10.0)	Skin	6 (85.7)
		Renal	1 (14.3)
Anti-epileptic	2 (6.7)	Skin	6 (100.0)
Anti-platelets	2 (6.7)	Neurological	3 (100.0)
Anti-diabetic	2 (6.7)	Gastrointestinal	2 (100.0)
Others	9 (30.0)	Neurological	9 (42.9)
		Skin	8 (38.1)
		Gastrointestinal	2 (9.5)
		Others	2 (9.5)

caused neurological reactions [n=15 (75.0%)], gastrointestinal reactions [n=2 (10.0%)], skin reactions [n=1 (5.0%)], immunological reactions [n=1 (5.0%)] and renal reactions [n=1 (5.0%)]. Anti-infectives drug class primarily caused skin reactions [n=6 (85.7%)] and renal reactions [n=1 (14.3%)]. On the other hand, anti-epileptic, anti-platelets and anti-diabetic drug classes caused skin reactions, neurological reactions and gastrointestinal reactions respectively.

Causality assessment of ADRs of the study patients

Evaluation of causality of ADRs was performed for the 30 patients included in this study. There were 3 (10.0%) certain, 7 (23.3%) probable, 15 (50.0%) possible and 5 (16.7%) doubtful ADRs, respectively, based on the Naranjo scale (Figure 1).

DISCUSSION

As of today, there is no published studies focused on the spectrum of ADRs occurred among patients with underlying stroke condition especially in Malaysia. This study has given the much-needed data on the incidence rate of ADRs regardless on the type of medications administered among the sub-population of stroke patients in one of the many established stroke centers in Malaysia. It

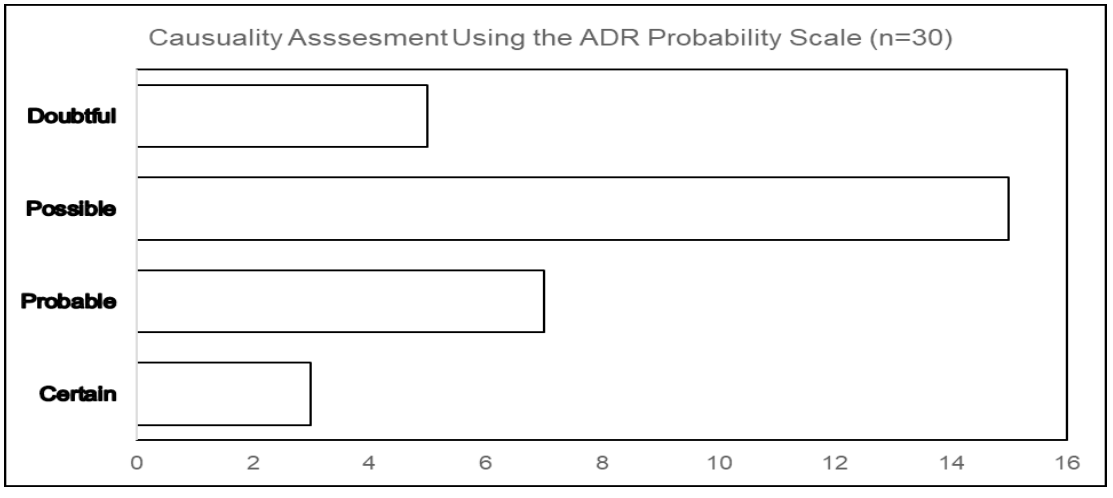

Figure 1. Causality assessment using adverse drug reaction (ADR) probability scale (n=30)

is utmost crucial to manage the ADRs diligently as patients with multiple comorbidities eventually prescribed with multiple medications are prone to untoward ADRs which consequently results in prolonged hospital stay and increased cost of hospitalization. Consequently, it might also increase the morbidity and mortality of the patients.

This study has revealed the incidence rate of ADRs occurrence among the stroke patients was as low as 1.5% (n=30) out of the total stroke population according to the stroke registry past 5 years. This low incidence rate could be possibly due to active clinical interventions by the healthcare professionals including doctors and pharmacists at the study site. These professionals are given constant updates from the neurologist, thus, keeping them updated on the latest drug safety events via their WhatsApp application. However, a study by Mathew *et al*. (2017) has shown the incidence rate of ADRs among stroke patients as high as 18% (n=18). It could be higher rate considering the smaller sub-population size of the study (n=100).[5]

Gender distribution in this study was unbiased with equal distribution of sample sizes between males and females. It is shown that most of the study participants were smokers. This is an evident that smoking is a resilient factor in amplifying the risk of stroke, in parallel with another study by Shah *et al*. (2010).[11]

Another prominent finding is vaccine has contributed as the major drug class contributing to the ADRs. All the 12 reported cases were vaccines combating COVID-19 infection. However, the specific details on the brand name were not retrievable. The most common initial manifestations reported were headache and giddiness. It is also found that patients who had experienced the ADRs post COVID-19 vaccination were mostly female and under 60 years of age. This finding is parallel to a study by Kakovan *et al*. (2022).[8] A study by Abrantes *et al*. (2021)[12] has reported similar results as our study indicating the incidence of ischemic stroke is higher than hemorrhagic stroke post COVID-19 vaccination.

On the other hand, penicillin-based antibiotics (amoxicillin and cloxacillin) and acyclovir also contributed to the ADRs among the stroke patients. A point to note is phenytoin, metformin and acetylsalicylic acid have also caused ADRs with the similar incidence rate respectively. Other drugs which had caused ADRs at least once among the stroke patients including allopurinol, isosorbide mononitrate, alteplase, pantoprazole and erenumab.

All the patients were treated accordingly with appropriate treatment (e.g. antihistamines, steroids and others). The offending drugs were discontinued and only 3 cases were re-challenged and the ADRs were reported as certain in view of similar outcome thereafter. The reported drugs causing certain ADRs among the patients were perindopril, bisoprolol and metformin and documented ADRs were dizziness, headache and diarrhea respectively. The symptoms of dizziness and headache developed half an hour post administration of the causative drugs whereas the onset of diarrhea was after four days later post metformin ingestion. Consequently, the causative drugs were substituted with another class having similar indication for better control of the disease. All the certain ADRs recovered completely and none were reported as serious ADRs.

Unfortunately, one fatality (within a day post ADRs establishment) was reported among this sub-population. The suspected causative drug was COVID-19 vaccine. However, no definite conclusion could be drawn from this fatality as the common manifestations reported by the 74-year-old affected female patient were dizziness and vomiting. Patient developed the symptoms within 24 hours post first dose vaccination. In fact, this subject had first episode of ischemic stroke with no known underlying comorbidities. Therefore, the causality assessment for this case was unlikely.

On a separate note, a total of 6 ADRs was reported as not recovered. This is possibly due to ongoing treatment and no follow up was made on the affected patients. None reported as recovered with sequelae and only one case was evidently not recovered as resulted in death.

In conclusion, our finding showed that the evaluated incidence of ADRs among stroke patients is low compared to other reported studies. This low incidence rate could be possibly due to active clinical interventions and rapid communication among the healthcare professionals ensure the maximal care of the hospitalized patients at HSJ. Continuous ADR monitoring is highly warranted among the sub-population of stroke patients due to the existence of multiple risk factors and their state of vulnerability.

This study improves the administration of commonly prescribed stroke medication. This study's data was obtained from the hospital-based stroke registry and medical records which makes the data reliable. In addition, the study was

conducted in the main stroke referral center for the state of Penang, Malaysia. The limitation of the study lies in the study being conducted in a single center as t there could be variation among centers due to differences in hospital specializations and community variables. Also, the ADRs of these patients was only assessed during hospitalization and not after discharge.

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DISCLOSURE

Ethics: The study was carried out after obtaining the approval from the Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia (MOH). Study approval number: NMRR-21-1851-61427. The need to obtain consent from study participants was waived as there is no direct interaction with the study participants in accordance with the Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia (MOH) regulations.

Data availability: The datasets generated and analysed during the current study are not publicly available due to data confidentiality policy as dictated in the study approval letter by the Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia (MOH) but are available from the corresponding author on reasonable request.

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Conflict of interest: None

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