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Original Article

A PROSPECTIVE OBSERVATIONAL STUDY ON PRESCRIBING TRENDS AND ADVERSE DRUG REACTIONS IN STROKE PATIENTS

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ABSTRACT

Objective: To evaluate medication use pattern and adverse drug reactions (ADRs) among stroke patients admitted in Neurology department of a multi-speciality hospital.

Methods: A prospective observational study was carried out for a period of 6 mo, in a 750 bedded multi-speciality hospital in Bangalore. The clinical pharmacist analysed the medication use pattern and occurrence of ADRs in stroke patients.

Results: Out of 100 patients, 75% had an ischemic stroke and 25% had a hemorrhagic stroke. The incidence of stroke was found to be higher in males (66%) compared to females (34%). Most of the patients were of the age group>60 y (52%). The common risk factors for stroke were hypertension (31%), diabetes (24%), and dyslipidemia (21%). The average number of drugs prescribed per patient was 7.67±3.1. The most common class of drugs prescribed were antihypertensives (14.3%), neuroprotectors (14.1%), antiplatelets (11.5%) and antihyperlipidemic (10.4%). Aspirin monotherapy was more prevalent in this study. Only 4 patients received thrombolytics. During the study, a total of 18 ADRs were reported from 14 patients (18%). Amlodipine (16.6%) and fondaparinux (11%) were the more frequent to cause ADRs. The most common reactions were bleeding (33.3%), pedal edema (16.6%) and headache (11.1%).

Conclusion: The study helps to identify drug utilization pattern and in addition to monitor adverse drug reactions among stroke patients. The study also emphasises the need for creating awareness regarding early recognition of stroke symptoms, which helps to prevent the occurrence of stroke.

Keywords: Ischemic stroke, Hemorrhagic stroke, Adverse drug reactions, Prescribing trends, Medication use pattern

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INTRODUCTION

According to World Health Organization (WHO), "stroke is a clinical syndrome characterized by rapidly developing clinical symptoms and/or signs of focal, and at times global (applied to patients in deep coma and those with subarachnoid hemorrhage), loss of cerebral function, with symptoms lasting more than 24 h or leading to death, with no apparent cause other than that of vascular origin [Hatano, 1976].

Ischemic stroke is accountable for 85% of cases. It occurs due to blockage within the artery supplying blood to the brain. Whereas, 15 % of the stroke cases belongs to hemorrhagic stroke, which results due to rupture of a weakened blood vessel leading to compression of the surrounding brain tissue [1].

Stroke is the third most common cause of death, consuming the lives of 6 million people annually [2]. According to the Indian epidemiological data, the incidence rate of stroke is considered to be 102-152 per 100000 persons. Indians are having a higher risk of developing stroke, which may be due to the high prevalence of risks factors such as obesity, smoking, hypertension, high cholesterol, alcohol consumption and diabetes [3].

The primary treatment strategy for stroke patients is to optimize the cerebral perfusion. Acute management of ischemic stroke includes treatment with an intravenous (IV) tissue plasminogen activator (tPA), aspirin and antihypertensive [4]. The number of effective and feasible treatment is still limited regardless of the recent advances in the stroke therapy. Individual decisions in drug selection are often made by physicians in order to deliver an effective treatment. Not only the drug selection, even route of administration and dosage form has an impact in providing the desired effect [5]. Controversies still exist on the efficacy in combination antiplatelet; despite the demonstrated clinical trials [6]. Even the use of IV citicoline is questionable whether it can achieve an observable outcome. This underscores the need for further studies to assess the various prescribing strategies for the treatment of stroke.

According to WHO, adverse drug reaction (ADR) 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. ADR reporting is one of the major responsibilities of health professional and mainly emphasises patient's safety. In neurology setting, ADRs are not scarce and account for about 18.7% [7]. Drugs such as thrombolytic, antiplatelets and anticoagulants which are commonly used in stroke pose a high risk of causing serious hemorrhagic manifestations. ADR monitoring is highly warranted among stroke patients due to the existence of multiple risk factors like polypharmacy, prolonged therapy, medication errors and comorbidity. Monitoring and reporting of ADRs will help to identify and quantify the risks associated to the drug use. This helps in improving the prescriber's knowledge in identifying and minimising preventable ADRs.

The aim of the study was to describe the prescription pattern of drugs in stroke patients and in addition; we sought to identify the various adverse drug reactions (ADRs).

MATERIALS AND METHODS

The proposed work was a hospital based prospective observational study. It was carried out for a period of six months from January to June 2015 among 100 Stoke patients in a 750 bedded multi-speciality hospital in Bangalore. The institutional ethics committee of M. S. Ramaiah Medical College, Bangalore, approved the study. Patient consent was taken from the patients or caretakers. Stroke patients of either gender enrolled in the study. Unconscious patients and those who were not willing to give the consent where excluded from the study.

The case records of medication charts, lab reports and other relevant documents of all the stroke patients admitted to the neurology ward

and intensive care unit reviewed on a daily basis and the data entered in a suitably designed data collection form. Patients were also interviewed and monitored for the occurrence of ADRs and identified ADRs were documented in ADR reporting and documentation form. The medication use pattern in stroke patients was analysed using World Health Organization (WHO) prescribing indicators.

Statistical analysis

The datum uploaded in IBM SPSS Statistics 20 for easy accessibility, storage, retrieval and analysis. The data was analysed using basic descriptive statistic measures (e. g. mean).

RESULTS

A total of 100 patients were included in the study out of which 66% were males, and 34% were females. The mean age was 57.18±14.53 y. The relationship between stroke and age is shown in fig. 1.

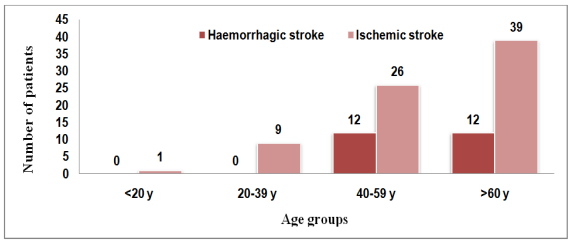

Fig. 1: Increase in stroke occurrence with age

It was observed that 75% (n=75) patients had an ischemic stroke and 25% (n=25) had a hemorrhagic stroke. Among the study population, 86% (n=86) experienced stroke for first time, 13% (n=13) for second time and 1% (n=1) for third time. Most of the patients were admitted after the window period of 3hr (n=72) (fig. 2).

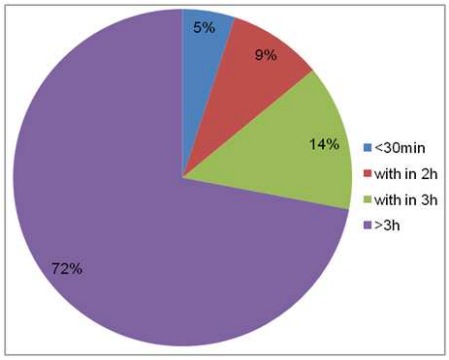

Fig. 2: Pattern of window period in stroke patients

The commonly identified risk factors among our study population were hypertension (31%), diabetes (24%) and dyslipidemia (21%) (fig. 3).

Drug use pattern was analysed by using WHO prescribing indicators. The drugs prescribed per patient were 7.67±3.1. The details are shown in table 1.

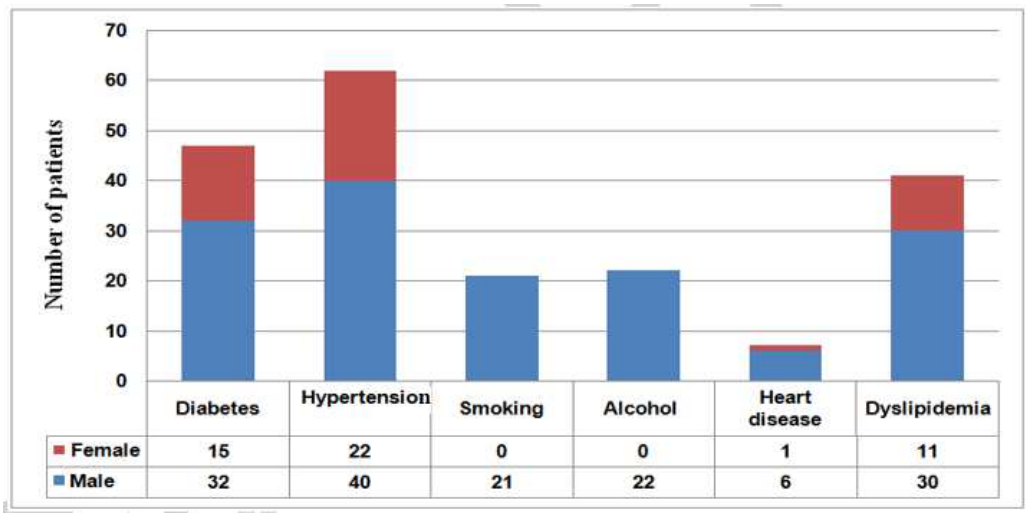

Fig. 3: Risk factors in stroke patients

Table 1: WHO prescription indicators

Prescribing indicators	Total drugs	Percentage
Total drugs prescribed	767	-
Prescription in combination	39	5.1 %
Prescribed by generic name	47	6.1%
Antibiotics prescribed	35	4.6%
IV drugs prescribed	272	35.5%

Most commonly used drug categories were antihypertensives (14.3%), neuroprotectors (14.0%), antiplatelets (11.5%), antihyperlipidemics (10.2%), anticoagulants (9.9%) and antidiabetic agents (8%).

Fig. 4 shows that the most frequently prescribed drugs were atorvastatin (10.45%), aspirin (8.9%) and citicoline (8.08%). Amlodipine 39% (n=43) was the most frequently used antihypertensive (table 2). The most common antihypertensive drug combinations were amlodipine+ metoprolol (n=3), metoprolol+ramipril (n=2) and metoprolol +telmisartan+amlodipine (n=2).

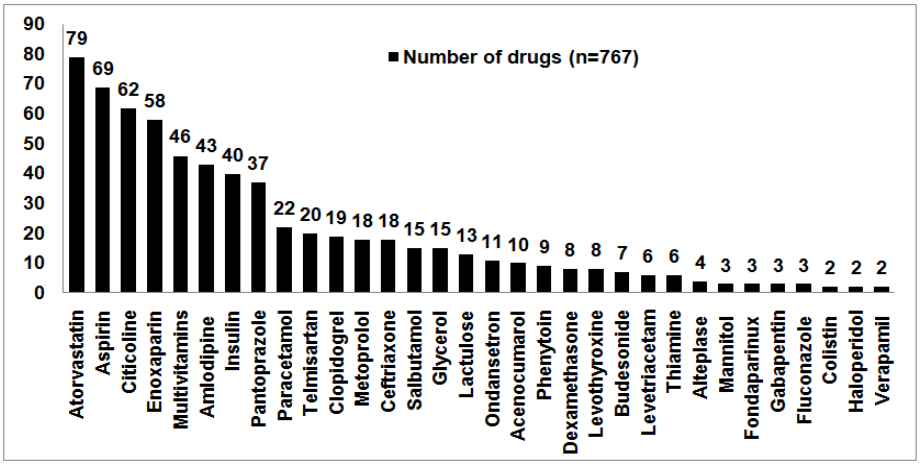

Fig. 4: Common drugs prescribed in stroke patients

Table 2: List of antihypertensive drugs used in stroke patients

Drug name	Number of drugs (n=110)
Amlodipine	43 (39%)
Telmisartan	19 (17%)
Metoprolol	18 (16%)
Furosemide	7 (6%)
Hydrochlorothiazide	5 (4.5%)
Torsemide	5 (4.5%)
Labetolol	3 (3%)
Ramipril	2 (2%)
Propranolol	2 (2%)
Cilinidipine	1(1%)
Enalapril	1 (1%)
Losartan	1 (1%)
Atenolol	1 (1%)
Carvedilol	1(1%)
Prazosin	1 (1%)

Aspirin (n=69) and clopidogrel (n=19) were the two antiplatelet drugs used. Aspirin-clopidogrel combination was given to 15 patients. Anticoagulants used in the study were mostly enoxaparin 76.3% (n=58) followed by acenocoumarol (13%), heparin (3.94%) and fondaparinux (2.6%). Only 4 patients (0.52%) were prescribed with tissue plasminogen activator (tPA)-alteplase.

Citicoline 57% (n=62) and multivitamins 43% (n=46) were the drugs used for neuroprotection. Atorvastatin (n=79) was the most used antihyperlipidemic. Insulin (78.33%) was the more frequently used in patients with diabetes, followed by metformin (13.3%). Antibiotic therapy was indicated for 28 patients. The most commonly prescribed classes of antibiotics were cephalosporins (table 3).

Table 3: Antibiotics prescribed in stroke patients

Antibiotic	Antibiotic class	Number of drugs (n=34)
Ceftriaxone, cefotaxime, cefoperazone	Cephalosporins	20
Meropenem	Carbapenems	4
Piperacillin+tazobactam	Penicillins	2
Colistin	Polymixins	2
Tigecycline, minocycline	Tetracyclines	2
Amikacin, gentamycin	Aminoglycosides	2
Ofloxacin	Flouroquinolones	1
Vancomycin	Glycopeptide antibiotic	1

A total of 21 patients received anticonvulsants in which phenytoin (50%) was found to be the most commonly prescribed drug, followed by levetiracetam (22.27%) and gabapentin (13.6%). Mannitol 17% (n=3) and glycerol 83% (n=15) were the anti-oedema agents used in this study.

During the six months of study, a total of 18 ADRs were reported from 14 stroke patients. The overall incidence of ADR was 18%, and most reactions occurred among males 67% (n=12). The common drugs involved were amlodipine (16.6%), clopidogrel (11%), fondaparinux (11%) and colistin (11%). The main adverse reactions were bleeding (33.3%), pedal edema (16.6%), fever (11.1%) and headache (11.1%) (table 4).

Details regarding classification and assessment of ADRs are in table 5. Type A and Type H reactions were predominant in our study. Blood and lymphatic system-related reactions were predominant comparing to other organ systems. Most of the reactions were probable (n=13) according to naranjo's scale.

Severity assessment indicated 50 % (n=9) of the reactions were found to be 'moderate', 44.4% (n=8) were 'mild' and 5.6% (n=1) were 'severe' reactions.

According to the preventability scale, 67% (n=12) were 'probably preventable' and 33% (n=6) were 'not preventable'.

Table 4: Drugs most commonly involved in ADRs and their reaction details

Drugs involved	ATC code*	Reaction details (n=18)	(%)
Amlodipine	C08CA01	Pedal edema (n=3)	16.6%
Clopidogrel	B01AC04	Allergic rhinitis (n=1), Epistaxis (n=1)	11%
Fondaparinux	B01AX05	Urethral bleeding (n=1), nasal and oral bleeding (n=1)	11%
Colistin	J01XB01	Fever (n=1), loose stools (n=1)	11%
Haloperidol	N05AD01	Drowsiness (n=1)	5.6%
Ceftriaxone	J01DD04	Skin rashes (n=1)	5.6%
Fluconazole	J02AC01	Fever (n=1)	5.6%
Alteplase	BB01AD02	Sub arachnoid haemorrhage (n=1)	5.6%
Aspirin	B01AC06	Bleeding through ear (n=1)	5.6%
Verapamil	C08DA01	Constipation (n=1)	5.6%
Enoxaparin	B01AB05	Bleeding through penis (n=1)	5.6%
Metoprolol	C08AB02	Headache (n=1)	5.6%
Citicoline	N06BX06	Headache (n=1)	5.6%

*ATC code-Anatomical and therapeutic classification code

Table 5: Classification and assessment of ADRs

Parameter	Number (%) (n=18)
Type of reaction▲	
Type A-Augmented reactions	11 (61.1%)
Type B-Bugs reactions	-
Type C-Chemical reactions	2 (11.1%)
Type D-Delivery reactions	-
Type E-Exit reactions	-
Type F-Familial reaction	-
Type G-Genotoxicity reactions	-
Type H-Hypersensitivity reactions	5 (27.8%)
Type U-Unclassified reactions	-
System organ classification (SOC)	
Gastro-intestinal disorders(SOC-14)	2 (11.1%)
Vascular disorders (SOC-12)	3 (16.7%)
Skin and sub-cutaneous disorders (SOC-16)	1 (5.5%)
Blood and lymphatic system (SOC-03)	5 (27.8%)
Immune system (SOC-04)	1 (5.5%)
Nervous system (SOC-08)	3 (16.8%)
Surgical and medical procedures (SOC-25)	1 (5.5%)
General disorders and administration site conditions (SOC-22)	2 (11.1%)
Causality*	
Definite	-
Probable	13 (72.2%)
Possible	5 (27.8%)
Unlikely	-
Onset of ADRs	
Acute (1h)	5 (27.8%)
Sub-acute (1-24h)	2 (11.1%)
Latent (>2 d)	10 (55.6 %)
Unknown Severity#	1 (5.5%)
Mild	
Level 1	6 (37.5%)
Level 2	3 (16.6%)
Moderate	
Level 3	3 (16.6 %)
Level 4a	5 (31.3%)
Level 4b	-
Severe	
Level 5	1 (6.3%)
Level 6	-
Level 7	-
Preventability†	
Preventable	1 (5.5%)
Probably Preventable	11 (61.1%)
Not Preventable	6 (33%)
Treatment	
Stopped the medication	7 (38.8%)
Reduced dose	1 (5.6%)
Added another drug	5 (27.8%)
Added substituent drug	1 (5.6%)
Required Intensive medical care	2 (11.1%)
No change	2 (11.1%)

▲Wills and Brown classification [8], *Classification based on Naranjo Scale *et al.* [9], # Classification according to Hartwig *et al.* [10], †Classification based on Shumock Thornton criteria [11].

DISCUSSION

The study focused on assessment of medication use patterns in stroke and its associated adverse reactions. The gender distribution in our study showed resemblance to the results from the study conducted by Pandian *et al.*, in Bangalore [12]. The occurrence of stroke among female patients was low. Vasodilator action of estrogen could be the protective mechanism for fewer incidences in females [13]. Risk factors were predominant in males which have increased their risk of developing stroke.

The incidence of ischemic stroke and hemorrhagic stroke and the risk factors involved in our study was similar to the findings of Pandian *et al.* [12]. The mean age of the stroke patients was concordant with the results of Eapen *et al.*, i.e. 57 y [14]. Depending on our study, with an increase in age, the incidence of stroke also increased (fig. 1) that resembled the study conducted by Mozafarrian *et al.* [15]. We also identified that 9% patients belonged to the age group of 20-39 y, which indicate that stroke rates are also increasing among the younger population. This warrants the need for controlling the risk factors such as smoking, alcohol use, obesity and also the necessity of lifestyle modifications in a younger population to prevent premature stroke attacks. Even these risk factors have the same impact in causing cardiovascular events.

The drug prescribed per patient was a higher value when compared with the results from the study conducted by Kuriakose *et al.* [16]. This might be due to additional drugs used for the supportive care and for the treatment of the comorbidity and complications. The trend of generic drug prescribing was very least seen through our study. Drug categories used in our study were similar to the study conducted by Abbasi *et al.* [17].

Hypertension was one of the main risk factors for both ischemic and hemorrhagic stroke [18]. The pattern of antihypertensive use in our study was similar to the findings of the study conducted by Jithin *et al.* [19]. Calcium channel blockers were preferred more because they could control the high blood pressure effectively with less adverse reactions.

Frequently used neuroprotectors in our study was citicoline. The neuroprotectors use pattern was similar to the study conducted by Abbasi *et al.* [17]. Preclinical animal studies and several small studies have shown positive results for neuroprotective action of citicoline. But recently, two large pivotal clinical trials have shown that there is no significant benefit in stroke patients. These results focuses on the need of demonstrating the rationality behind IV citicoline use [20].

In our study, aspirin monotherapy was more prevalent than the combination therapy. Combination therapy of aspirin and clopiogrel showed no greater effect in decreasing the risk of stroke reoccurrence [6]. So, the selection of an antiplatelet regimen should be carefully decided to ensure a rational therapy. Most commonly used anticoagulant was enoxaparin. Anticoagulant use reduces the risk for further stroke attacks, deep vein thrombosis and pulmonary embolism [21].

IV tPA (e. g. alteplase) is a very effective when administered within three hours of stroke occurrence. Alteplase can reduce death or dependence due to stroke by an odd's ratio of 0.66 without a significant increase in ADRs [22]. Currently, in India, only 15% of stroke patients are able to reach the hospital within three hours. In our study, at most 28 % could reach the hospital within three hours. The main factors that contribute to the delay in providing thrombolysis included patient's unawareness regarding the stroke symptoms, delayed transportation, heavy traffic, increased the cost of the drug and delayed diagnosis [3, 17]. The use of alteplase in our study was similar to the study performed by Padma *et al.* (5%). This ascertains that the use of tPA is very low in Indian settings [23]. The general public required the awareness about the disease, its symptoms, need of immediate hospital administration, which can reduce the death due to delayed admission.

Anticonvulsants had become an important component of stroke therapy in order to prevent post-stroke seizures. The study conducted by Vurumadla *et al.*, supported the repeated use of phenytoin for treating post-stroke seizures [13]. The introduction of antibiotic therapy in stroke patients was to prevent post-stroke infection. Most preferred antibiotic in our study was cephalosporin. The study results were comparable with findings of Kuriakose *et al.* [16].

The complexity of the disease and drug therapy in stroke can increase the occurrence of certain drug-related problems like adverse drug reactions, which lead to an increased health care cost and length of hospital stay. Apart from these, other factors like smoking, alcohol consumption, ethnicity, creatinine clearance and allergy can also predispose ADRs [24]. The incidence of ADRs in our study was same as the study conducted by Thuermannin *et al.*, where the incidence of ADRs was 18.7% [7].

Type A reactions were more common. Understanding on the mode of action and pharmacology of drug or the excipient could predict those reactions [25]. Pedal edema caused by amlodipine is an example of Type A reaction. Pedal edema mainly occurred in amlodipine users as it causes arteriolar dilation, which facilitates flooding of venules and leakage of fluids into perivenular space [26]. Amlodipine caused pedal edema in three patients. The drug was stopped in all three patients.

The reported ADRs were more latent in onset than acute. Fluconazole-induced fever was one of the latent reactions. The patient started developing fever spikes (101.4 °C, 103.8 °C, 104.2 °C) on 13th day of fluconazole 150 mg therapy. Fever was not reduced with IV paracetamol infusion. Fever was subsided only after stopping fluconazole. Acute reactions will include hypersensitivity reactions like ceftriaxone-induced rashes. Rashes developed over the right palm and chest region within 20 min after administration of IV ceftriaxone 1g. The drug was stopped, and the patient was treated with cetirizine 10 mg tablet.

Some of the probable reactions in our study include fluconazole induced fever; citicoline induced headache, and metoprolol induced headache. Out of all reported ADRs, only alteplase induced haemorrhage (n=1) was severe (Level 5). The patient required intensive care treatment and hospital stay prolonged by one week. Though alteplase is the first-line therapy, it carries a risk of causing intracranial haemorrhage. The survival rate will drop down to 20 to 50% once it causes bleed [27].

We have assessed the preventability of ADRs. Most of the reactions belong to type H category was not preventable. Fondaparinux induced urethral bleed (haematuria) was the only ADR that was preventable. The patient on fondaparinux 2.5 mg had an increased INR of 5.5 with no bleeding manifestations. The patient suffered a severe urethral bleed while inserting a urinary catheter. The reaction could have prevented if the insertion performed carefully, and INR maintained in the desired range.

The adverse reactions were managed by withdrawing the drug that caused a reaction or by providing symptomatic treatment. The dose of the drug was reduced in cases where the drug could not be removed. In haloperidol-induced drowsiness, the drug dose was reduced from 10 mg to 5 mg.

Monitoring ADRs in stroke patients is important. In the present study, the clinical pharmacist was involved in ADR monitoring by reporting, assessing and creating awareness of ADRs in the neurology unit. Globally, pharmacists are encouraged to participate in ADR monitoring program. This study showed that the inclusion of a clinical pharmacist in the health care system could help inadequate monitoring and prevention of ADRs.

CONCLUSION

The present study highlights the importance of assessing the medication use pattern in stroke patients. Further studies are warranted to confirm the practical outcomes of drugs like citicoline and combination use of antiplatelets in stroke. This could reduce the unnecessary medication cost and drug-related problems. The study also focuses upon the need of awareness about early recognition of stroke symptoms. This will help to cut down the treatment failure rates in stroke. The general public should be educated regarding the availability of best medicines for stroke. The use of tPA was considerably low and needed to be promoted as first-line therapy. In medical practice, ADR monitoring is an inevitable part. Standard

protocols are required for the usage of drugs that can cause serious adverse reactions. Pharmacovigilance programs should perform in every hospital in our country and the clinical pharmacist could play an important role in it.

ABBREVIATION

ADR-adverse drug reactions, WHO-world health organisation, IV-intravenous, tPA-tissue plasminogen activator, IBM-international business machine cooperation, SPSS-statistical package for social sciences, INR-international normalized ratio, ATC-anatomical and therapeutic classification

LIMITATION

The sample size of the study was relatively small due to the short duration of the study. Specifically, the number of hemorrhagic stroke cases was low. Details of laboratory investigation and brain imaging studies were limited. The current study was attributable only to a single hospital. More similar studies are required for a proper conclusion.

CONFLICT OF INTERESTS

Declared none

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