

A RANDOMIZED CONTROL TRIAL ON CEREBROVASCULAR ACCIDENT PATIENTS WITH REFERENCE TO ETIOLOGY AND MANAGEMENT: A 24-WEEK, SINGLE-CENTER, PROSPECTIVE OBSERVATIONAL PILOT STUDY

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ABSTRACT

Objectives: Stroke is one of the leading causes of death and long-term disability in world. Stroke is an important cause of premature death and disability in low-income and middle-income countries like India, largely driven by demographic changes and enhanced by the increasing prevalence of key modifiable risk factors. The main aim of our study was to assess the clinical profile with special reference to the etiology of the condition, the management, and drug utilization review.

Methods: This is a hospital-based prospective observational randomized control trial which was conducted for a period of 6 months at Government General Hospital, Rajiv Gandhi Institute of Medical Sciences, Kadapa. Seventy-five patients were recruited based on study criteria. The data were analyzed and summarized as frequency and percentage by GraphPad Prism software using Microsoft Excel.

Results: In a total of 75 patients, it was found that 45 and 30 patients were female. Maximum number of patients (i.e. 36 patients) belonged to 51–60 years age group. We observed that 52 patients were suffering from ischemic stroke, 21 patients were suffering from transient ischemic stroke, and only 2 patients were suffering from ischemic stroke and transient ischemic stroke. Among 75 patients studied, hypertension (62%), diabetes mellitus (28%), smoking (33%), and alcohol (33%) were the risk factors.

Conclusion: In this study, ischemic stroke was most prevalent. Hypertension, that is, increase of blood pressure considered as one of the important and major risk factors for stroke occurrence and recurrence. Proper management includes non-pharmacological (physiotherapy) along with pharmacological treatment that included cardiovascular system drugs such as hypolipidemics, cognition enhancers, anticoagulants, and antihypertensive therapy.

Keywords: Cerebrovascular accident patients, Risk factors, Neuronal death, Multidisciplinary treatment.

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INTRODUCTION

A stroke occurs when a blood vessel in the brain ruptures and bleeds, or when there is a blockage in the blood supply to the brain. The rupture or blockage prevents blood and oxygen from reaching the brain's tissue. This loss of blood flow to the brain results to damage of tissues within the brain [1]. Symptoms of a stroke will be experienced in almost all the body parts in which brain plays a significant role for monitoring. The five warning signs of stroke are sudden onset of weakness or numbness on one side of the body, sudden speech difficulty or confusion, sudden difficulty seeing in one or both eyes, sudden onset of dizziness, trouble walking or loss of balance and sudden, severe headache with no known cause [2,3]. Three types of stroke, that is, transient ischemic attack, ischemic stroke, and hemorrhagic stroke are experienced by majority of the patients suffering from cerebrovascular accident (CVA) [4]. Risk factors of stroke include an unhealthy diet, inactivity, or lack of exercise, alcohol consumption, tobacco use, family history, sex, age, race, and ethnicity [5,6]. High blood pressure is the leading cause of stroke and is the main cause for increased risk of stroke among people with diabetes. Lifestyle factors that increase your risk of stroke include high blood pressure, smoking, diabetes, high blood cholesterol levels, heavy drinking, high salt and high fat diet and lack of exercise [7]. Proposed pathophysiology is etiological factors presses on nearby cranial nerves or brain tissue causing subarachnoid hemorrhage leads to increases in ICP resulting from the sudden entry of blood into the subarachnoid space that results to injuries brain tissue or by secondary ischemia of the brain resulting from the reduced perfusion pressure [8].

Diagnosis of stroke is taking medical history, physical examination, blood test, magnetic resonance imaging and computed tomography scan, EKG, cerebral angiogram, carotid ultrasound, and echocardiogram [9]. The most common stroke medications include tissue plasminogen activator is the only medication currently available and it must be given within 3–4.5 h after symptoms of a stroke begin [10,11]. Anticoagulant drugs reduce blood's ability to clot. The most common anticoagulant is warfarin [12]. Antiplatelet drugs prevent blood clot by making it more difficult for the blood platelets to stick together. Common drugs are aspirin and clopidogrel [13]. Statins helps in lowering high blood cholesterol levels. The most common statins include rosuvastatin, simvastatin, and atorvastatin [14,15]. Blood pressure lowering drugs cause break off pieces of plaque that buildup in arteries [16,17]. Mechanical thrombectomy is the procedure in which the doctor inserts a catheter into a large blood vessel inside head. Then, they use a device to pull the clot out of the vessel [18]. Stents may be performed to inflate the narrowed artery and support the walls of the artery with a stent. It is done when an artery wall gets weakened. In the rare instances, if other treatments do not work, doctor may perform surgery to remove a blood clot and plaques from arteries [19]. Stroke recovery focuses on four main areas such as speech therapy, cognitive therapy, relearning sensory skills, and physical therapy [20-22].

METHODS

Study design and ethical considerations

A hospital-based prospective observational pilot study on cerebrovascular accident patients with reference to etiology and

management was carried out in General Medicine Department patients at Rajiv Gandhi Institute of Medical Sciences (RIMS), Kadapa, for a period of 6 months, that is, from December 2019 to May 2020. RIMS Hospital is a 750 bedded, multidisciplinary tertiary care teaching hospital. Ethical approval was taken from respective ethical committee.

Inclusion criteria

Patient who are willing to participate, patients of age >30 years, patients suffering from transient ischemic stroke and ischemic stroke, and patients with comorbid pathological conditions were included in our study.

Exclusion criteria

Patients who are not willing to participate in, patients of age <30 years, patients suffering from hemorrhagic stroke, pregnant women, outpatients, and patients admitted for surgical procedures were excluded from the study.

Sample size

A total of 75 patients diagnosed with CVA were taken as sample size and examined as per study guidelines.

Method of collection of data

After taking consent from the patient, a self-designed patient data collection form was used to collect entire patient's data with special reference to CVA cases in which drug regimen was prescribed. Whole data were documented in proper format. Patients were also provided with information leaflets at time of discharge.

Statistical analysis

Results were represented as frequencies, percentages, mean, and medians. Percentage method was used for analyzing the data. For analyzing data, GraphPad Prism software was taken as considered statistical requirement. In some cases, inferential statistics like analysis of variance (ANOVA) followed by Student's t-test (at 95% confidence interval and $p < 0.05$ considered as significant) using SPSS 21.0 software were also applied.

RESULTS

A prospective observational pilot study was conducted in government general hospital (RIMS), Kadapa, for period of 6 months. A total of 75 patients were recruited under inclusion criteria on receive of International Classification of Diseases.

Patients distribution based on gender

Out of 75 patients being recruited, it was found that 45 (60%) were male and 30 (40%) were female; results are shown in Fig. 1:

Patients distribution based on age groups

Out of 75 patients, 4 (5%) patients were found to be in 31-40 years, 12 (16%) were found to be in 41-50 years, 36 (48%) were found to be in 51-60 years, 20 (27%) were found to be in 61-70 years, and 3 (4%) were found to be in 71-80 years; and results are represented in Fig. 2.

Patient distribution based on type of stroke

In our study, 52 (69.4%) patients had ischemic stroke among which 34 were male and 18 were female and 21 (28.0%) had transient ischemic stroke among which 13 were male and 8 were female and 2 (2.6%) were having both ischemic and transient ischemic strokes which were seen only in males, as shown in Fig. 3.

Risk factors based on sex-wise distribution

In our study of 75 stroke patients, based on sex-wise distribution, the frequency of the risk factors was observed as 34 males and 13 females were hypertensive, 15 males and 6 females were diabetic, excluding females, the frequency of both smoking and alcoholics was same, that is, 24, 4 males and 3 females presented with cardiac diseases, 1 male and 2 females had recurrent attacks, and only one male was presented with drug non-compliance, as shown in Fig. 4.

Percentages of the risk factors

In this study of 75 stroke patients, the major etiology was found to be hypertension (62%) followed by smoking (33%), alcohol (33%),

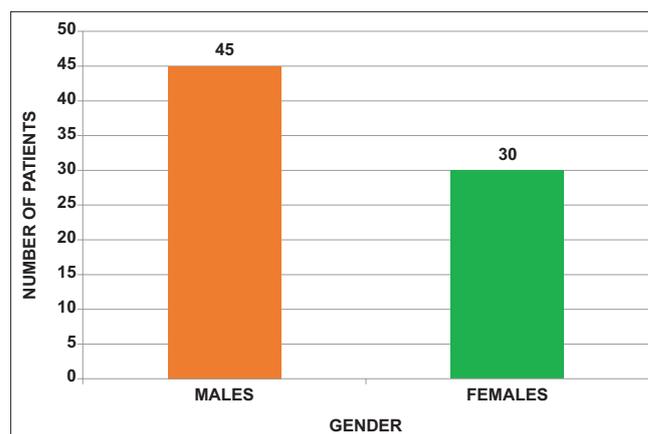


Fig. 1: Graphical representation of male patients and female patients

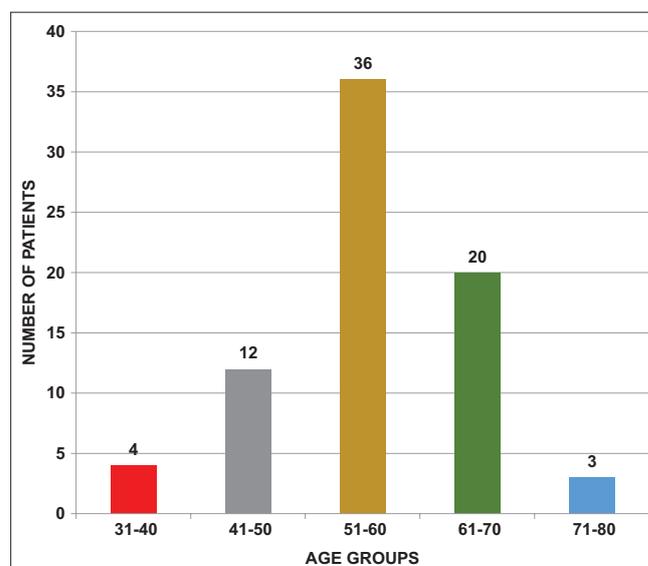


Fig. 2: Graphical representation of different age groups patients

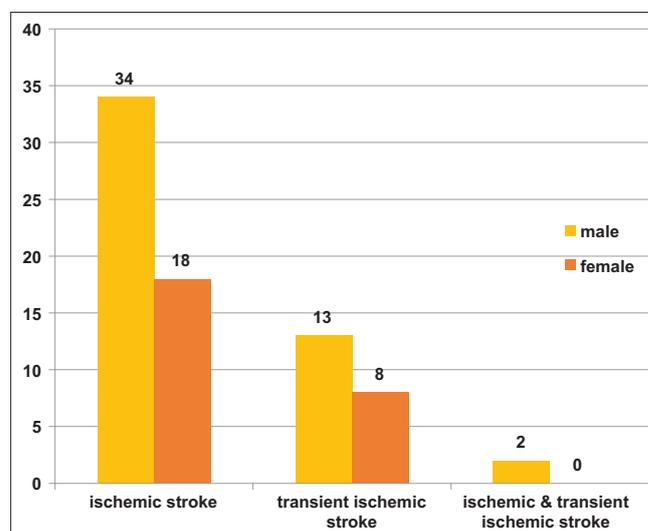


Fig. 3: Graphical representation of types of stroke

diabetes mellitus (28%), cardiac diseases (9%), recurrent attacks (4%), and drug noncompliance (1%), respectively, as shown in Fig. 5.

Utilization pattern of drugs: Classification

The utilization of various drugs and its classification in both ischemic and transient ischemic strokes was presented. In this study, a total of 22 different drug categories were utilized with the inclusion of various drugs present in these 22 drug categories. Eleven different classes, that is, only half of the classes that were utilized had been accounted for 95% of drugs that are shown in Table 1.

Utilization pattern of drugs: Nature and extent of drug use

Seventy-three different drugs were utilized in both ischemic and transient ischemic strokes of total 75 patients which are as shown in Table 2.

Drug utilization: Drug-drug interactions

It is defined as a reaction between the drugs or between a drug and a food, between a drug and a beverage, or between a drug and a supplement. Drug interaction will also occur if patients suffer from

the past medical conditions. For instance, nasal decongestant interacts with blood pressure lowering drugs, are represented in Table 3.

DISCUSSION

Stroke was considered as an emergency medical condition which is to be treated as early as possible. Other than ischemic and transient ischemic stroke, there are other conditions such as hemorrhagic stroke and silent ischemic stroke. Our study observed that stroke is being a major burden to neurological illness. In our hospital, the CVA was a most common diagnosis of stroke but it can vary from region to region and hospitals.

Most people with stroke were between 51 and 60 years and 61 and 70 years in age group. In this study, male patients have more chances of occurrence of stroke when compared to female patients. One reason may be due to different sex steroid hormones, notably estrogens and testosterone. We already knew that as the number of risk factors increases, the progression and complications of the disease increase. Even in the present study, we found that there were more patients

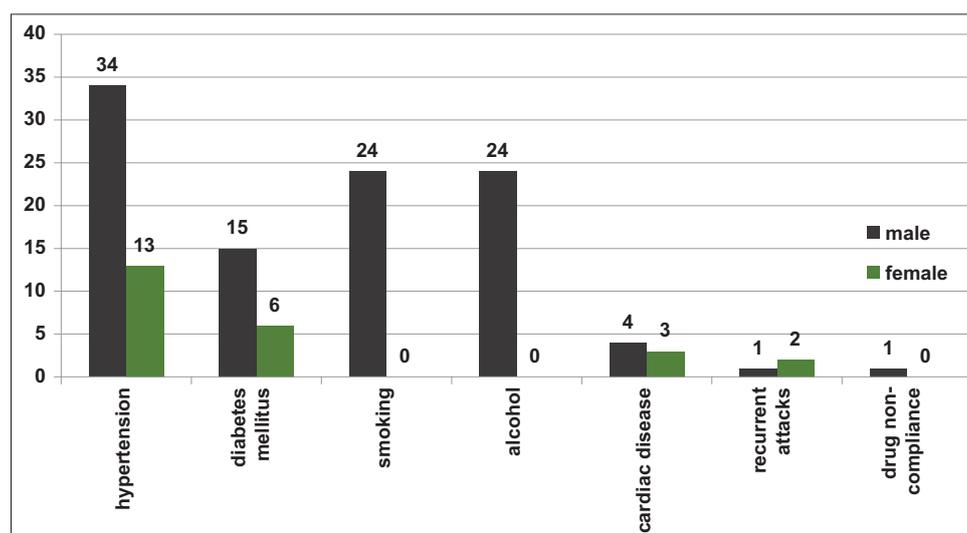


Fig. 4: Graphical representation of risk factors based on gender wise

Table 1: Drug utilization evaluation in stroke patients

S. No.	Class of drug	Ischemic stroke	Transient ischemic stroke	Frequency	Percentage
1.	Antiplatelets	29	23	52	8.88
2.	Antihypertensive	40	32	72	12.30
3.	Anticoagulants	4	4	8	1.36
4.	Supplements	52	21	73	12.47
5.	Antiepileptics	19	12	31	5.29
6.	Gastrointestinal agents	48	30	78	13.33
7.	Antibiotics	29	23	52	8.88
8.	Nootropics	12	9	21	3.58
9.	Hypolipidemics	41	34	75	12.82
10.	Antipyretics and analgesics	10	8	18	3.07
11.	Antidiabetic	9	8	17	2.90
12.	Diuretics	35	27	62	10.60
13.	Laxatives	1	0	1	0.17
14.	Bronchodilators	4	2	6	1.02
15.	Skeletal muscle relaxants	1	0	1	0.17
16.	Corticosteroids	2	1	3	0.51
17.	Ionotropic	1	0	1	0.17
18.	Antiviral	1	0	1	0.17
19.	Antidiarrheal	5	4	9	1.53
20.	Mucolytics	0	0	0	0
21.	Antiemetics	2	1	3	0.51
22.	Hepatoprotective	1	0	1	0.17
	Total	346	239	585	100

Table 2: Utilization pattern of drugs: Nature and extent of drug use

S. No.	Number of utilized drugs	Ischemic stroke	Transient ischemic stroke	Frequency	Percentage
1.	Mannitol	39	23	62	10.60
2.	Aspirin	25	22	47	8.03
3.	Atorvastatin	45	30	75	12.82
4.	Pantoprazole	28	21	49	8.40
5.	Amlodipine	19	16	35	5.98
6.	Calcium + Vitamin D3	14	14	28	4.80
7.	Thiamine	4	3	7	1.20
8.	Librium	1	1	2	0.34
9.	B complex	14	16	30	5.12
10.	Telmisartan	8	5	13	2.22
11.	Human insulin	5	7	12	2.05
12.	Phenytoin	9	5	14	2.40
13.	Iron supplement	6	5	11	1.90
14.	P+G+M	0	1	1	0.17
15.	Ranitidine	14	14	28	4.80
16.	Acetaminophen	11	7	18	3.07
17.	Gabapentin	1	0	1	0.17
18.	Citicoline	9	6	15	2.56
19.	Labetalol	7	2	9	1.53
20.	Prazosin	1	0	1	0.17
21.	Clopidogrel	2	1	3	0.51
22.	Ceftriaxone	22	14	36	6.15
23.	Theophylline	1	1	2	0.34
24.	Atenolol + Amlodipine	1	1	2	0.34
25.	Acenocoumarol	1	0	1	0.17
26.	Cefotaxime	2	1	3	0.51
27.	Atenolol	2	1	3	0.51
28.	Metformin+glibenclamide	1	0	1	0.17
29.	Cefixime	2	1	3	0.51
30.	Duolin+budecort	2	2	4	0.70
31.	Amoxicillin+clavulanate	1	1	2	0.34
32.	Nootropil	2	1	3	0.51
33.	Lorazepam	4	3	7	1.19
34.	Nifedipine	1	0	1	0.17
35.	Losartan	0	1	1	0.17
36.	Escitalopram+clonazepam	1	0	1	0.17
37.	Divalproex sodium+valproic acid	1	0	1	0.17
38.	Multivitamins	2	2	4	0.70
39.	Metformin+glimepiride	1	1	2	0.34
40.	Metoprolol	1	0	1	0.17
41.	Ursodeoxycholic acid	0	1	1	0.17
42.	Metformin	1	0	1	0.17
43.	Salbutamol	1	0	1	0.17
44.	Sandostatin	1	0	1	0.17
45.	Enalapril	1	0	1	0.17
46.	Giblenclamide	1	0	1	0.17
47.	Baclofen	1	0	1	0.17
48.	R+I+P+E	0	1	1	0.17
49.	Pyridoxine+hydrochloride	1	0	1	0.17
50.	Dexamethasone	0	1	1	0.17
51.	Piperacillin+tazobactam	1	0	1	0.17
52.	Streptomycin	0	1	1	0.17
53.	Hydrocortisone	1	0	1	0.17
54.	Levetiracetam	0	1	1	0.17
55.	Ondansetron	1	1	2	0.34
56.	Dopamine	0	1	1	0.17
57.	Artesunate	1	0	1	0.17
58.	Doxycycline	1	1	2	0.34
59.	Acyclovir	1	1	2	0.34
60.	Racecadotril	1	1	2	0.34
61.	Nimodipine	1	0	1	0.17
62.	Vitamin-c	1	0	1	0.17
63.	Potassium chloride	1	0	1	0.17
64.	Tramadol	1	0	1	0.17
65.	Methylprednisolone	0	1	1	0.17
66.	Ambroxol	1	1	2	0.34
67.	Pregabalin	1	0	1	0.17
68.	Midazolam	1	0	1	0.17
69.	Spiro lactone+torse mide	1	0	1	0.17
70.	Lactulose	1	0	1	0.17
	Total	340	245	585	100

Table 3: Drug-drug interactions

S. No.	Name of the drugs	Description of effect	Severity
1.	Phenytoin + nifedipine	Coadministration of drugs may decrease the effect of nifedipine	Serious
2.	Aspirin + enalapril	Combination of these drugs may need to monitor kidney function tests	Serious
3.	Aspirin + insulin aspartate	Using aspirin together with insulin may increase the risk of hypoglycemia	Moderate
4.	Aspirin + telmisartan	Combination of these drugs may reduce the effect of telmisartan in lowering blood pressure	Moderate
5.	Telmisartan + atorvastatin	Pharmacokinetic change was found except time of peak of telmisartan when administered with atorvastatin	Moderate
6.	Aspirin + clopidogrel	This combination may cause unusual bleeding and severe abdominal pain	Moderate
7.	Amlodipine + atenolol	This drugs may have additive effects in lowering blood pressure and heart rate	Moderate
8.	Pantoprazole + clopidogrel	Combination of these drugs may reduce the effectiveness of clopidogrel in preventing heart attack	Moderate
9.	Phenytoin + atorvastatin	Phenytoin may reduce the blood levels of atorvastatin which may make drug less effect for the treatment of high cholesterol	Moderate
10.	Calcium + amlodipine	Amlodipine together with calcium can decrease the effects of amlodipine	Moderate
11.	Metformin + amlodipine	This combination could cause blood sugar levels to get too low	Moderate
12.	Metronidazole + atorvastatin	Metronidazole together with atorvastatin may increase the risk of nerve damage	Moderate

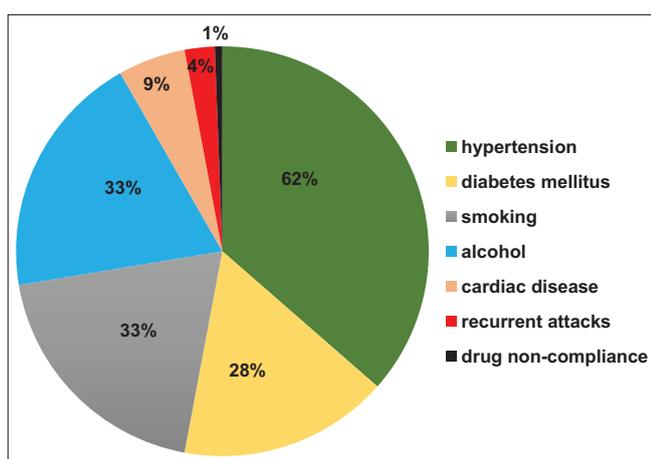


Fig. 5: Percentages of the risk factors

who have involvement of multiple risk factors than single or no risk factors. Proper intervention is to be done assessing risk factors. The major risk factor in stroke patients in the present study was found to be hypertension (62%) followed by diabetes (28%) and age and the least risk was seen with a history of coronary artery disease (4%). The reasons for the progression with these risk factors to the stroke might be due to the change in capillary tone and advances glycation product formation.

Drug utilization pattern provides the rationality in drug prescribing and analysis. We observed prescription which can theoretically cause effects of serious drug interactions such as Ceftriaxone + Enoxaparin, Phenytoin + Nifedipine, and Aspirin + Enalapril. Some products that may interact with this drug include: daptomycin, gemfibrozil. Other medications can affect the removal of atorvastatin from your body, which may affect how atorvastatin works. Examples include cyclosporine, glecaprevir plus pibrentasvir, telaprevir, telithromycin, ritonavir. Close and careful monitoring was done to these patients to optimize therapy. We observed utilization of drugs such as mannitol, aspirin, atorvastatin, multivitamins, amlodipine, ceftriaxone, pantoprazole, phenytoin, citicoline, clopidogrel, acetaminophen, and metronidazole. Apart from these drugs, we also observed the use of a combination of drugs such as Atenolol + Amlodipine, Metformin + Glibenclamide, Metformin + Glimepiride, Calcium+ Vitamin D3, Spironolactone + Torsamide, and Clopidogrel + Aspirin.

Antihypertensives such as β -blockers, diuretics, calcium channel blockers, α + β blockers, and angiotensin II receptor blockers were used to reduce target BP for these patients. It shows the fact that

antihypertensives were frequently used agents for stroke patients, along with antiplatelets, anticoagulants, dyslipidemics, nootropics, multivitamins, and antidiabetics, these categories of drugs were also prescribed.

Primary management of stroke includes antiplatelet therapy with aspirin, together with clopidogrel used in the management of stroke and in patients with a history of cardiac disorders and clopidogrel, statin therapy, and blood pressure management. Secondary prevention is through pharmacological therapy. Tertiary prevention is attributed to maintaining their ability to carry out daily activities if they receive rehabilitation services at home.

Treatment pattern of illness other than stroke involved specific pharmacological agents such as antiepileptics such as levetiracetam, gabapentin, phenytoin, and lorazepam and antipsychotics such as escitalopram and clonazepam for seizures related to stroke or epilepsy. Steroids such as dexamethasone and methyl prednisolone were used primarily. Other agents were used for symptomatic treatment such as antibiotics, alkalisers, supplements, antipyretics, laxatives, sedative-hypnotics, antidepressants, and antidiabetics. Stroke rehabilitation is expected to begin as soon as possible after the person has a stroke and continue for as long as it is clinically appropriate.

CONCLUSION

The present study has focused on risk factors and management of stroke. Ischemic stroke was found to be more prevalent. The risk factors play an important role in the development and progression of the disease. Among non-modifiable risk factors, majority of patients were male patients accounted for 60%, while female patients accounted for 40%. Most of the patients attending the department of general medicine with clinical diagnosis of stroke were above the age of 50 years and geriatric patients. Among the modifiable risk factors, hypertension accounted for 62% of the cases clearly indicating strong evidence of elevated BP levels with stroke occurrence and recurrence. Other risk factors include diabetes mellitus (28%), smoking (33%), and alcohol (33%). In all the recruited cases, drug utilization review was done effectively.

It is also observed that prescribed drugs for stroke cases are generic drugs, dependent on socioeconomic status of the patient. Various types of drugs were also prescribed depending on the diseased condition and illness of the patient. In this study, categories of antiplatelets, statins, diuretics, aspirin, atorvastatin, and mannitol were utilized at higher rates. Proper management includes non-pharmacological treatment along with pharmacological treatment. A primary prevention strategy to reduce highly prevalent neurological cases like stroke is highly needed. Finally, it has been concluded that proper risk factor management and

following the guidelines in the treatment reduce the severity and hence prognostic factors will be good.

CONTRIBUTION OF AUTHORS'

Dr. K. Leela Prasad sir contributed in study design and helped in data collection, that is, for attaining required sample size. Dr. Shaik Kareemulla sir conceptualized the idea, worked on making fruitful discussions, conclusions, and reviewed manuscript. K. Aliya Firdose worked on literature review, collected the data, performed analysis, and prepared dissertation book. S. Yasmeen conceived the data and drafted the final manuscript.

CONFLICTS OF INTEREST

No any conflicts of interest to disclose.

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