ABSTRACT
 Stroke is abrupt onset of neurologic deficit, referable to a focal vascular cause. The study was undertaken to analyse treatment strategies adopted for patients with ischemic/haemorrhagic stroke, and associated short-term and long-term outcomes of management protocols. Single-centre, observational study, conducted in 200 stroke patients admitted in medicine department at tertiary care hospital with diagnosis of haemorrhagic/ischemic stroke. Data was collected over 18 months. Patient related information was documented into Case Report Form and analysed for a) Descriptive statistics regarding drugs used in patients b) Descriptive analysis of outcome in patients in form of death/survival as also improvement in the stroke specific scores i.e., NIH, Modified Rankin, Barthel c) Odds ratio for studying association between use of various drugs and outcome. Among ischemic stroke patients, most commonly prescribed drug was hypolipidemic agent atorvastatin and anti-platelet drug aspirin, followed by anti-hypertensive amlodipine and anti-coagulant enoxaparin sodium. Among hemorrhagic stroke patients, most commonly prescribed drug was atorvastatin, followed by amlodipine. 94% of ischemic stroke patients survived, 6% died while 88% of hemorrhagic stroke patients survived and 12% died. On the basis of stroke-specific scores, prognostic outcome among ischemic stroke patients showed improvement with use of atorvastatin, aspirin and clopidogrel whereas the hemorrhagic stroke patients showed improvement with use of atorvastatin and amlodipine primarily. In Ischemic stroke patient’s hypolipidemic and anti-platelets were apparently associated with better prognostic outcomes. In Hemorrhagic stroke patient’s better prognostic outcomes were seen in patients receiving hypolipidemic and anti-hypertensive primarily.

Keywords: Stroke patients, ischemic stroke, hemorrhagic stroke, outcome.

INTRODUCTION
 In adult life, one of the most common neurological disorders is Stroke. The incidence of strokes occurring every year worldwide is about 17 million and it is the second leading cause of death next to coronary artery disease. Myocardial infarction, a disease affecting the coronary arteries is almost always due to atherosclerosis of large vessels, while in stroke finding of risk factors is difficult as strokes come in many varieties.

Cerebrovascular diseases include, ischemic stroke and hemorrhagic stroke which are the most common and destructive disorders while cerebrovascular anomalies include arteriovenous malformations (AVMs) and intracranial aneurysms. A stroke, is characterized by the sudden onset of a neurologic deficit that is attributed to a focal vascular cause. Thus, by looking at the definition diagnosis of the stroke is clinical, and laboratory testing including brain imaging like Computed tomography (CT) scanning or magnetic resonance imaging (MRI) are used to support the diagnosis. Pharmacoepidemiology refers to the study of the utilization and effects/side-effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs in the population. It may be drug-oriented, emphasizing the safety and effectiveness of drugs as well as utilization-oriented aiming to improve the quality of drug therapy through educational interventions. So the drug utilization research or studies are the powerful exploratory tools to learn the role of drugs right from marketing, distribution, prescription to use of drugs in the well-defined population. So to determine the quality, pattern of use and outcomes of use it is important to do DUS which is an essential part of Pharmacoepidemiology. Hence it is necessity to investigate periodically drug utilization pattern for increasing the cost-effectiveness, therapeutic drug efficacy, and to minimizing the adverse effects of drugs. Rational use of medicines involves their proper and acceptable use so that drugs should be appropriate for
patients clinical needs and at the lowest cost to them and community. It also includes proper dispensing, dosing, right selection and duration of drugs.\(^6\) The primary aim of DUS is to promote the rational use of drugs in well-defined population and generate hypotheses which will be helpful for further investigations and thus avert prolonged irrational use of drugs.\(^7\)

Studies related to stroke management are usually based on inadequate assessments which are undertaken only over the first few months’ post-stroke. Also, little information is available with respect to short-term and long-term outcomes of the various management strategies adopted for stroke patients. Hence, we have taken up this study to assess the drug utilization and the respective outcomes in the stroke patients admitted in our hospital.

**MATERIALS AND METHODS**

Single-centre, prospective, observational study carried out in Stroke patients with or without co-morbidity. Data was collected and the patient related information was entered into the Case Report Form and later analysed for a) descriptive statistics regarding the drugs used in the patients b) Descriptive analysis of the outcome in the patients c) odds ratio for studying the associates between the use of anti-platelets or anti-coagulants, and the outcome. The Data was collected after getting approval from Institutional Ethics Committee. The data was collected from the case files of Stroke patients with or without comorbidities, admitted to the Medicine Ward in a tertiary healthcare hospital and was recorded in a self-designed case record form. Inclusion Criteria’s were Patients admitted in medicine ward with signs and symptoms and/or provisional diagnosis of stroke and Diagnosed cases of stroke with or without co-morbidity. While pregnant patients and Patients not willing to be a part of study or refusing to sign informed consent form were excluded.

Assessments were performed according to NIH score (on admission vs 48 hours), Modified Rankin Score (at discharge vs 3 months) and the Barthel Index (at discharge vs 3 months). Severity of stroke was assessed by NIH score as Mild (1-4); Moderate (5-15); Severe (=or >16). In case of Modified Rankin Score The scale runs from 0 to 6, running from perfect health without symptoms to death. The Barthel Index evaluate 10 functional tasks of activities of daily living (ADL). Scores range from minimum 0 to maximum 100, with a higher score indicating higher degree of independence.

Data was inserted into the Microsoft excel sheet and data was analyzed statistically with the help of Microsoft excel 2016 software. Fisher’s exact test and Wilcoxon rank sum test was used to analyse the categorical variables and continuous variables respectively. The Wilcoxon signed-rank test was applied to compare the stroke-specific scores, before and after treatment. Odds ratio was derived at, by using Binary logistic regression

**RESULTS AND DISCUSSION**

Total number of stroke patients included in the study was 200. Among the total of 122 patients admitted for ischemic stroke, 66 patients were females (54%) whereas 56 were males (46%). The median age of total patients enrolled for ischemic stroke was 65 (54 – 73). Among the total no. of patients admitted for hemorrhagic stroke (N=78), 40 were females (51%) whereas 38 were males (49%). The median age of total patients enrolled for hemorrhagic stroke was 57 (47-68). Out of 122 patients of ischemic stroke, 7 (6%) patients died, while 115 (94%) patients survived. Out of 78 patients of hemorrhagic stroke, 9 (12%) patients died, while 69 (88%) patients survived.

In case of ischemic stroke patients, the median score for NIH at the time of admission was 10 (8 - 14) and after 48 hours of treatment it changed to 9 (6 - 12), There was statistically significant difference in the score of NIH (p-value < 0.001) before and after treatment. The median score on the modified rankin scale was 3 (2 – 3) at the time of discharge and after the 3-month follow-up it changed to 2 (1 - 2). There was statistically significant difference in the score at time of discharge and that after 3 months of discharge. (p-value < 0.0001) Barthel Index showed a median value of 65(50-80) at discharge, whereas at 3-month follow-up, the median value improved to 80(65-90), which was statistically significant (p < 0.001).

Table 1. NIH Score, Modified Rankin Score and Barthel Index as seen in patients of ischemic stroke and haemorrhagic stroke initially vs. on follow-up

<table>
<thead>
<tr>
<th>Stroke</th>
<th>NIH score Median/ (Inter Quartile Range)</th>
<th>Modified Rankin Median/ (Inter Quartile Range)</th>
<th>Barthel Index Median/ (Inter Quartile Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Admission Discharged</td>
<td>discharge/discharged</td>
<td>discharge/discharged</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 month</td>
<td>3 month</td>
</tr>
<tr>
<td>IS (n=122)</td>
<td>10/8 – 14</td>
<td>9* /6 – 12</td>
<td>65/50 – 80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3/2 – 10</td>
<td>2* /1 – 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>63/40 – 75</td>
<td>78*/60 – 90</td>
</tr>
<tr>
<td>HS (n=78)</td>
<td>10/8 – 16</td>
<td>10*/6 – 16</td>
<td>63/40 – 75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3/2 – 10</td>
<td>2* /1 – 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75*/40 – 75</td>
<td>78*/60 – 90</td>
</tr>
</tbody>
</table>

*p value was statistically significant (p < 0.05) showing improvement in all three scores after treatment in both strokes. P value was calculated using Sign-Rank Test.

Among hemorrhagic stroke patients, the median score for NIH at the time of admission was 12 (10 – 16) and after 48 hours of treatment it changed to 10 (6 – 12), which was statistically significant (p < 0.001). Modified Rankin Score showed a median value of 3(2-4) at discharge, whereas at 3-month follow-up, the median value improved to 2(1-3), which was statistically significant (p < 0.001). Barthel Index showed a median value of 63(40-75) at discharge, whereas at 3-month follow-up, the median value improved to 78(60-90), which was statistically significant (p < 0.001).

Among the 122 patients diagnosed with ischemic stroke, Lipid-lowering drug Atorvastatin was prescribed to 85 patients. Among the anti-platelet class of drugs, Aspirin was prescribed to 85 patients, whereas Clopidogrel was prescribed to 20 patients.
Among the anti-coagulant class of drugs, Enoxaparin sodium was prescribed to 20 patients, whereas the thrombolytic drug Alteplase was prescribed to 4 patients. Anti-hypertensive prescribed were amlodipine (57), atenolol (8), labetalol (6), prazocin (4) and enalapril (10). The anti-diabetics prescribed were metformin (20) and insulin (14). The other drugs prescribed were Optineuron (36), Mannitol (61) and Dexamethasone (6).

Among the 78 patients diagnosed with hemorrhagic stroke, Lipid-lowering drug Atorvastatin was prescribed to 49 patients. Among the anti-coagulant class of drugs and Enoxaparin sodium was prescribed to 14 patients. Anti-hypertensives prescribed were amlodipine (44), nimodipine (2), atenolol (13), labetalol (5), prazocin (5) and enalapril (7). The anti-diabetics prescribed were metformin (7) and insulin (7). The other drugs prescribed were Optineuron (20) and Mannitol (61).

Figure 1 shows, among the ischemic stroke 77%, 71%, 85% and 85% of the patients on atorvastatin, aspirin, clopidogrel and enoxaparin sodium treatment were associated with NIH Score improvement at 48 hrs. (vs. On admission), while 32%, 46%, 60% and 60% of patients not on atorvastatin, aspirin, clopidogrel and enoxaparin sodium showed association with NIH Score improvement respectively. There was statistically significant difference seen in proportion of patients on atorvastatin, aspirin, clopidogrel and enoxaparin sodium showing association with improvement in NIH Score, as compared to patients not on atorvastatin, aspirin, clopidogrel and enoxaparin sodium treatment (p<0.05). While There was no statistically significant difference in the proportion of patients on alteplase showing association with improvement in NIH Score, as compared to patients not on alteplase treatment (p >0.95). In case of Modified Rankin score, there was statistically significant difference seen in proportion of patients on Atorvastatin showing association with improvement in Modified Rankin Score, as compared to patients not on atorvastatin, aspirin, clopidogrel and enoxaparin sodium treatment with improvement in NIH Score, Modified Rankin score and Barthel score. Proportion of patients showing association with improvement in Barthel Index Score is more with clopidogrel (p value 0.02) administration but it was insignificant in case of Atorvastatin, aspirin and enoxaparin sodium treatment.

Figure 2 shows, Among the 78 hemorrhagic stroke patients, Atorvastatin and amlodipine treatment showed association with improvement in NIH Score at 48 hours (vs. On admission), while There was no statistically significant difference in proportion of patients on enoxaparin sodium showing association with improvement in NIH Score, as compared to patients not on enoxaparin sodium treatment (p value 0.17). In case of Modified Rankin score, among Atorvastatin, amlodipine and enoxaparin sodium treatment only amlodipine showed association with improvement in Modified Rankin Score at 3-months (vs at discharge) (p value <0.001). Among the above three drugs none showed improvement in Barthel Index Score in hemorrhagic stroke patients.

As co-morbidities 80 out of 122 ischemic stroke patients were hypertensive, while the remaining 42 patients were not hypertensive. 54 (67%), 63 (78%), 67 (84%) patients of hypertension showed improvement in NIH score, Modified Rankin score, Barthel Index score whereas 24 (57%), 28 (66%), 34 (81%) patients who were not hypertensive showed improvement in NIH score at 48 hours, Modified Rankin score at 3 months and Barthel Index at 3 months (p value 0.25, 0.15, 0.69) respectively. while 33 out of 122 ischemic stroke patients were diabetic, while the remaining 89 patients were not diabetic. 20(60%), 26 (78%), 27 (81%) patients of diabetes showed improvement in NIH score, Modified Rankin score, Barthel Index score whereas 24 (57%), 28 (66%), 34 (81%) patients who were not diabetic showed improvement in NIH score at 48 hours, Modified Rankin score at 3 months and Barthel Index at 3 months (p value 0.64, 0.52, 0.86) respectively. In hemorrhagic stroke patients 50 were hypertensive and 14 were diabetic out of 78. In both,
hypertensive and diabetic patient p value was not significant when compared between patients showed improvement in scores among hypertensive and non-hypertensive as well as diabetic and non-diabetics.

**DISCUSSION**

**Demography**

In this study conducted on a sample size of 200, it was found out that the prevalence of ischemic stroke was greater (122), compared to the prevalence of hemorrhagic stroke (78), which is in consonance with the study of Chachu Kuriakose et al. In contrast to a study by Vurumadla et al, where there was male sex predominance while our study showed female sex predominance in both stroke.

Variation in the sex predominance could be associated to the regional differences of study, consent of the study subjects, and duration of study leading to seasonal variations in admission patterns. Median age of patients admitted for ischemic stroke was 65 years, whereas for hemorrhagic stroke patients the median age was found to be 57 years, comparable to the study of Chachu Kuriakose et al.

According to Mo-Yeol Kang et al propose that involuntary job loss as well as voluntary retirement increase the risk of stroke or cardiovascular disease right from middle-aged to older populations.

**Drug Utilization Pattern**

Among the patients of ischemic stroke in the study, most frequently prescribed drug was hypolipidemic agent atorvastatin (69.67%) and anti-platelet drug aspirin (69.67%), followed by anti-hypertensive drug amlodipine (46.72%), and the anti-coagulant enoxaparin sodium (16.39%). Among the patients of haemorrhagic stroke in the study, most frequently used drug was hypolipidemic agent atorvastatin (62.82%), followed by anti-hypertensive drug amlodipine (56.41%). In the study conducted by Subhransu et al, most frequently prescribed drug in hospitalized stroke patients was anti-hypertensives (69.9%), followed by the lipid-lowering agents (66.9%) and the anti-platelet drugs (65.7%). In the study of Spurthi et al, most common drug prescribed were the anti-platelet agents (91.16%), although the study did not clearly state drug utilization pattern in each type of stroke.

The major and most familiar risk factor associated with stroke patients in the study conducted was found to be hypertension (65%) followed by Diabetes (23.5%), comparable with the study of Subhransu et al, wherein the most frequent risk factors attributed with the stroke was hypertension (65.7%) followed by dyslipidaemia (52.6%), diabetes (50.1%). The reasons for the progression with these risk factors to the stroke might be due to change in capillary tone and advanced glycation product formation. Proper risk factor management as well as following the guidelines in the treatment reduces the severity, hence the prognosis will be good. Early identification of risk factors and pattern of therapy plays a vital role in qualitative patient care.

**Outcome**

Out of the patients managed for haemorrhagic stroke and ischemic stroke, 69(88%) survived, while 9(12%) patients died and 115(94%) survived, while 7(6%) patients died respectively. Haemorrhagic stroke patients showed greater morbidity and mortality due to more extensive brain injury as a result of a) the accumulation of blood and b) brain ischemia following the haemorrhage. In the study conducted by Ehsan et al, Case-fatality rate of haemorrhagic and ischemic strokes were 49.2% and 21.7%, respectively.

Ischemic Stroke patients treated with Atorvastatin (20 mg) showed statistically significant reduction in the mean NIH score at 48 hours (p < 0.001) as well as showed significant improvement in the mean score on Modified Rankin Scale at 3 months (p value 0.04) which is in accordance with the study of Tuttolomondo et al, wherein 80 mg atorvastatin treatment was seen to be associated with significant improvement in the mean NIH score at 72 hours as well as improvement in the median modified rankin score at 7 days of treatment initiation. Thus showing better outcome of disability grade and acute neurological deficit. Ischemic stroke patients treated with aspirin showed significant reduction in NIH score (p value 0.008), which is in accordance with the study conducted by Wilterdink et al, Grilli et al found that both aspirin and its metabolite sodium salicylate appear to reduce glutamate-mediated excitotoxicity, thereby supporting a neuro-protective role of aspirin independent of its antiplatelet effect. Similarly use of clopidogrel showed significant improvement in both the score, in accordance with the CAPRIE Trial, wherein the study showed that Clopidogrel is as safe as medium-dose aspirin.

Among the anti-coagulants, ischemic stroke patients on enoxaparin sodium showed significant reduction in the mean NIH score (p value 0.04), similar results were seen in PREVAIL study which stated that enoxaparin a Low-molecular-weight heparin compared to unfractionated heparin is significantly more effective for prevention of VTE i.e venous thromboembolism in patients diagnosed with acute ischemic stroke. While, Patients on Alteplase treatment did not show any significant improvement in the scores and/or outcome. Muir KW, et al demonstrated that alteplase treatment is of benefit for patients diagnosed with acute ischemic stroke when treated within 3 hours. The reason for this variation in the current study could be the small no of patients on Alteplase treatment in the study.

Hemorrhagic stroke patients on atorvastatin and anti-hypertensive drug amlodipine showed statistically significant decreased in NIH score at 48 hours (p value 0.03). while amlodipine also showed statistically significant increase in Modified Rankin Score (p value <0.001). In the study of Nishiyama et al, intravenous
nicardipine infusion decreased intracranial pressure with no evidence of rebreeding or exacerbation of edema.\(^{(21)}\)

**CONCLUSION**

We found that Atorvastatin was the most commonly prescribed drug in ischemic as well as hemorrhagic stroke patients. Use of Anti-platelet drugs aspirin and clopidogrel showed significant improvement in the stroke-specific scores. Use of amlodipine in hemorrhagic stroke have an association with improvement in the stroke-specific scores. So the prescribing pattern of drugs should preferably be based on the specificity of the condition and the severity of stroke so as to facilitate rational use of drugs and thereby provide optimal care. Therefore, Standard Stroke Prescribing Guidelines should be adopted in India to provide rational drug therapy.

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