



To Study the Medicine Use Evaluation in Stroke Patients in Hospital

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Abstract

Stroke is a big problem of mortality worldwide and commonly occurs in old patients. First prevention of stroke should include antiplatelet therapy with aspirin, statin therapy and blood pressure management. The current Observational prospective study of six months duration was performed to consider the sign ,symptoms and risk factors, prescribing pattern , appropriateness of medication, Drug related problems occur in the stroke patients in neurology multispecialty healthcare setting of India. Ischemic stroke (78.57%) was more prevalent in our study, hyperlipidemia (47.05%) and hypertension (28.05%) were the most predominant diagnoses observed in majority of population. In our study majorly patients 19(27.14%) suffer from stroke was in 41-50 years age group male gender (79%) was more prone to stroke attacks, that too within age group of 51-60 years ,headache was more common symptom in stroke patients 57(12.6%),majority no. of symptoms 123(27.4%) was the cofound contributing risk factor. Anti-atherogenics and statins were commonly utilized in study population found rationale which is the value addition in stroke management. Drug related problems was assessed in 52 patients majorly identified drug related problem were drug interaction 37(69.8%), followed by medication error 13(24.52%), overdose 2(3.77%), sub therapeutic dose 1(1.8%).

Introduction

A Medicine Use Evaluation is a performance improvement method that focuses on evaluating and improving medicine-use processes with the goal of improving patient health outcomes^[1]. The term Drug Use Evaluation (DUE) has been used to indicate a prospective review, while the term Drug Utilization Review (DUR) has been used to indicate a retrospective review. In contrast, the nomenclature espoused by the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) and the American Society of Health-System Pharmacists (ASHP) is Medicine Use Evaluation (MUE). MUE may be applied to a medicine or therapeutic class, disease state or

condition, or a medicine-use process (ordering and transcribing, preparing and dispensing, administration, and monitoring). Stroke is clinically characterized by the World Health Organization (WHO) as 'the fast developed of clinical signs and symptoms of a focal neurological aggravation enduring over 24 hours or prompting to death with no evident reason other than a vascular origin'.^[3] **Types of Stroke** In light of the pathophysiology of brain harm, stroke is comprehensively characterized into Ischemic stroke and Hemorrhagic stroke. Ischemic strokes happen when artery providing blood to the brain is blocked. The blockage can be either because of a thrombus at the site of

occlusion or shaped in another piece of the dissemination (embolus)^[5]. Ischemic strokes represent almost 80% of all strokes around the worldwide^[6]. The hemorrhagic stroke happens when a vein breaks or ruptures and bleed into the encompassing brain. The bleeding can happen inside the brain tissue (intracerebral) or then again can be happen in the space between the meninges (sub-arachnoid)^[7]. Hemorrhagic strokes represent around 20% of all strokes around the world^[6]. Brain harm in hemorrhagic stroke is normally significantly more serious and more prone to be lethally contrasted with an ischemic stroke^[4]. The Global Burden of Disease think about evaluated that 29.6% of death around the world (15616.1 million passing's) were caused by CVD in 2010, more than all transmittable, maternal, neonatal and wholesome clutters consolidated, and twofold the quantity of passing's caused by cancers^[15].

Methodology

Plan of Work

The study of six months duration was perform in the multispecialty healthcare setting and is Distributed into three phases.

Phase I

- Site of practice
- Design of study
- Criteria's of study
- Literatures survey
- Followed and selection of Performa
- Designing data collection form
- Approval and permission from hospital authority
- Approval and registering the study in the Institutional board

Phase II

- Data collection

Phase III

- Analysis and then evaluation of collected data Interpretate of results
- Deriving conclusion
- Limitations if any
- Recommendations.

➤ Sources of Data

All the relevant and necessary data was collected from the following sources-patients consent form, Patients data collection form, Patient record file/prescription Treatment chart. Patient interview, Laboratory reports. Also, Data was obtained from every patient at the first and subsequent out patient's visits, also from past medical records as well as family members.

➤ Development of the Tool

An extensive study and review helped in the preparation of the tool. A self -prepared questionnaire were used as the tool for this study. These include questions. It include drug prescribed, name of drug type of drug therapy, frequency of medication, develop any side effect, drug related problems. In the present study, the rationality assessment of data had done with the help of standard clinical guidelines for stroke therapy and management.

➤ **Sample Size:** The study was conducted on a patient pool of 70 people.

➤ **Sampling Technique:** Purposive sampling

➤ **Study Duration:** This study was conducted for a period of 6month.

➤ **Study Criteria:** Prospective observational study.

➤ **Study Site:** This study was conducted in both in and outpatient setting of the neurology department at Teerthanker Mahaveer Hospital, Moradabad, Uttar Pradesh. It is a near out 800 bedded multispecialty tertiary care teaching hospital.

➤ Pilot study

Pilot study was done before study. Ten patients were taken for the pilot study. The pilot study was conducted to find out the feasibility of the study.

➤ Inclusion Criteria

- Patients suffering from stroke, both the genders with different age groups.
- Those are willing to participate in the study.
- First or recurrent stroke within a month of assessment.

- Those patients who had radio logically confirmed diagnosis of Stroke using CT/MRI scan were included.

➤ **Exclusion Criteria**

- Patients who do not fulfill inclusion criteria.
- Patients with incomplete information.
- Comatose patients.
- Patients in whom CT/MRI could not be obtained were excluded from the study.

➤ **Method of Data Collection**

Patients data such as the type of stroke and its risk factors, sign and symptoms ,number of drug prescribed, dose ,prescribing pattern of drug and drug-related problems if any during the therapy and whether drug monitoring was carried out or not was collected from various data sources case sheets, out-patient cards, laboratory reports etc. The follow-up was done based on the next appointment given by treating clinician .The follow-up was done for a period of 6 months.

Statistical Methods: The data were subjected to descriptive statistical analysis using Microsoft Excel. Microsoft word, the collected data were cleared, categorized and analyzed using Microsoft Excel and the results were presented in excel have been used to generate bar graph, pie chart, histogram, and tables.

Biostatic: Frequencies, percentage were obtained.

Results and Discussion

Demographic particular of study participants

Age Group Categorization of Stroke Patients

(In the table)The incidence of stroke is maximum in the age group around 41-50 years which comprised of 27.14% of the patients followed by the age group 51-60, and 61-70 which comprised of 25.71% and 22.85% respectively, age group 31-40 and 71-80 comprised of (7.1 %) age group 21-30 comprised of 5.71%, age group 81-90 comprised of 2.85% and age group 13-20 comprised of 1.428% of an entire study population.

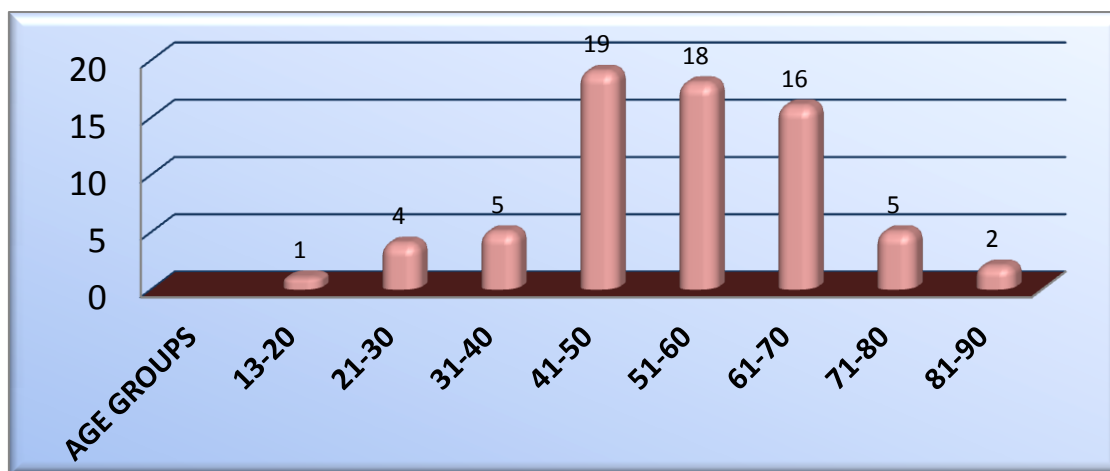


Figure: Column diagram Age group categorization of stroke participants

Gender Categorization of Stroke Patients

(In the table) the incidence of stroke was high in Males 55(79%) than in females 15(21%) which can be attributed to-

- Estradiol has terribly potent effects on endothelia that promote dilation of blood vessels and blood flow, whereas testosterone has opposite

effects. This indicates women are protected by endogenous estrogens.

b. Males are more prone to HTN and DM than females.

c. Smoking.

Table: Gender categorization of stroke patients`

Gender	Male	Female	Total
No. of Patients	55	15	70
Percentage	79%	21%	100%

Study Participants with Family Histories of Stroke

Table shows Out of 70 study population bases on histories (family) 56 (80%) found to have positive family history for stroke and 14(20%) patients were with negative family histories of stroke reported (Study participants with family histories of stroke).

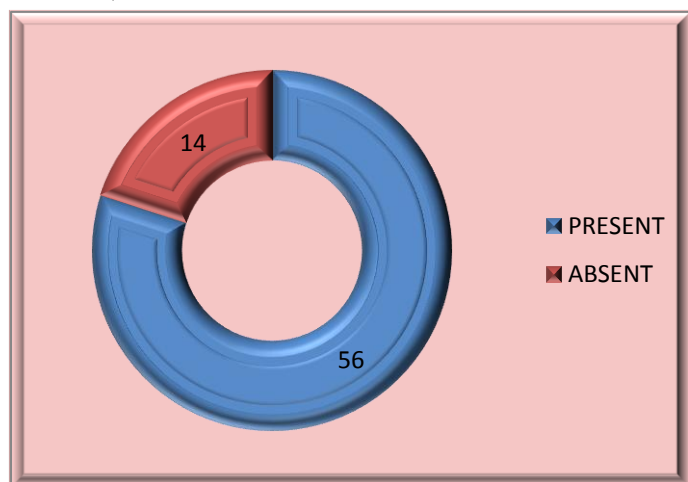


Figure: Pie Diagram Study participants with family histories of stroke.

Pattern of Symptoms among Stroke Patients

Table shows symptoms wise distribution of stroke was assessed in which headache 57(12.6), weakness of upper limbs, weakness of lower limbs 54(12%), and other symptoms shown in study population illustrated (Symptoms of stroke).

Table: Pattern of Symptoms among Stroke patients

SYMPTOMS	No. of Patients	Percentage
WEAKNESS OF UPPER LIMBS	54	12%
WEAKNESS OF LOWER LIMBS	54	12%
DYSARTHRIA	20	4.4%
TINGLING SENSATION	28	6.2%
LEFT HEMI PARESIS	19	4.2%
RIGHT HEMI PARESIS	20	4.4%
DEVIATION OF MOUTH	1	0.2%
HEADACHE	57	12.6%
FACIAL PALSY	1	0.2%
DYSKINESIA	14	3.1%
GIDINESS	34	7.5%
ALTERED SENSORIUM	25	5.5%
APHASIA	24	5.3%
ATAXIA	48	10.6%
VOMITING	31	6.8%
SLURRED SPEECH	20	4.4%
TOTAL	450	100%

Pattern of Risk Factors among Stroke Patients

The table 9 shows the most common risk factors found in the stroke patients were smoking (27%), hypertension (27%), hyperlipidemia (22.2%), recurrent stroke (8.14%), alcohol (5.8%), diabetes (4.4%), seizure (2.96%), headinjury (1.48%). in contrast to the study conducted reported by (Md. Obaidur Rahman et al, 2012). in which hyperlipidemia (47.05%), hypertension (28.05%), heart failure (27.25%), myocardial infarction (23.78%), ischemic heart disease (21.55%), diabetes mellitus (15.6%) and angina (12.47%)

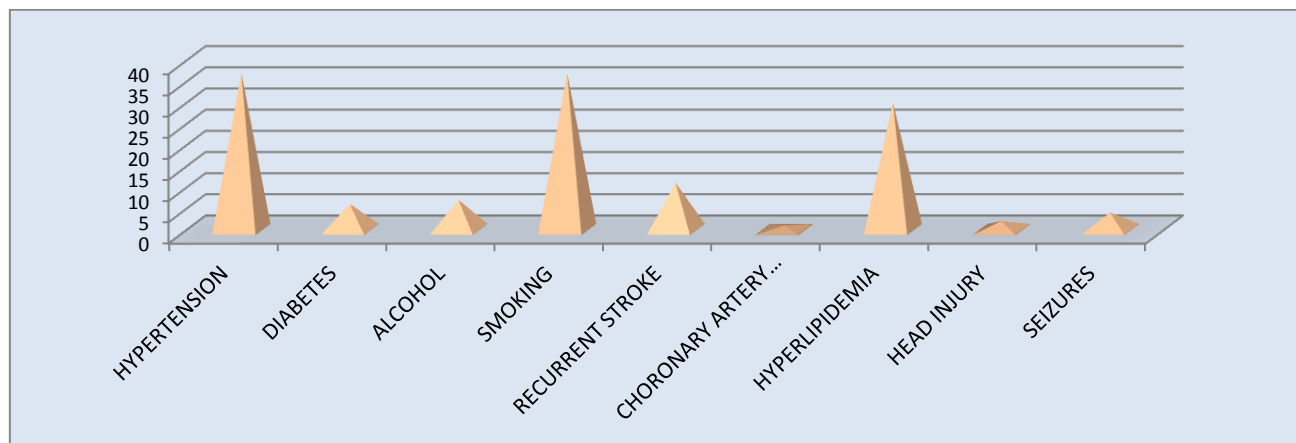


Figure: Column Diagram Pattern of Risk factors among Stroke patient

Incidence of Stroke in Different age Groups and No. of Risk Factors

In table the incidence of stroke in different age group with the risk factor of stroke in majorly present in the age group of 61-70 year, the no. of risk factor 38(28%) followed by in the age group of 41-50 year age group ,no. of risk factor 37(27%) and other incidence of stroke in different age group and no. of stroke patients assessed.

Table: Incidence of stroke in different age groups and no. risk factors

AGE GROUP`	No.of risk factors present	Percentage
13-20	1	0.7%
21-30	6	4.4%
31-40	7	5.1%
41-50	37	27.40%
51-60	32	23.7%
61-70	38	28.4%
71-80	9	6.6%
81-90	5	3.7%
Total	135	100%

Type Wise Categorization of stroke according to their Frequency

The table shows In our study out of 70 patients (78.57%) patients experienced Infract or Ischemic stroke, 2(2.85%) patients experienced hemorrhagic stroke and 13(18.57%) patients with transient ischemic attack stroke results of which are thoroughly assesses in Table (Types of stroke).

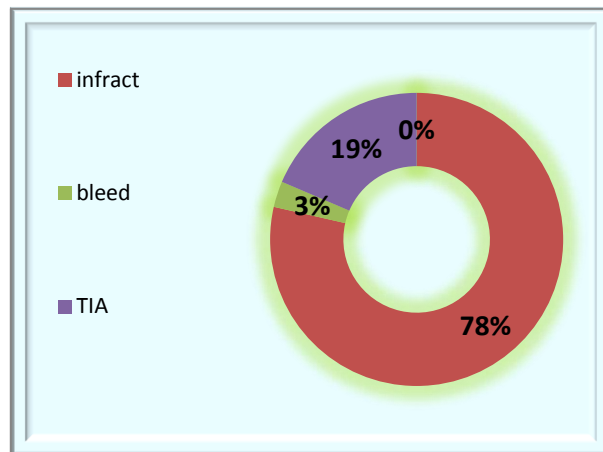


Figure: Pie diagram Type wise categorization of stroke according to their frequency.

Incidence the Type of Stroke in Different Age

This table shows that the incidence of types of stroke in different age group is shows that in the ischemic or infract stroke majorly patients are present the age group of 41-50 year 16 patients followed by 15 patients present in the age group of 51-60 year,12 patients present in the age group of 61-70 year. And in hemorrhagic stroke 1patients present in age group 10-20 year and 1 patient present in 21-30 year .In TIA majorly 5 patients present in age group 71-80 year followed by 3 patient present in 61-70 year and 81-90 year, 2 patient present in 51-60 year age group.

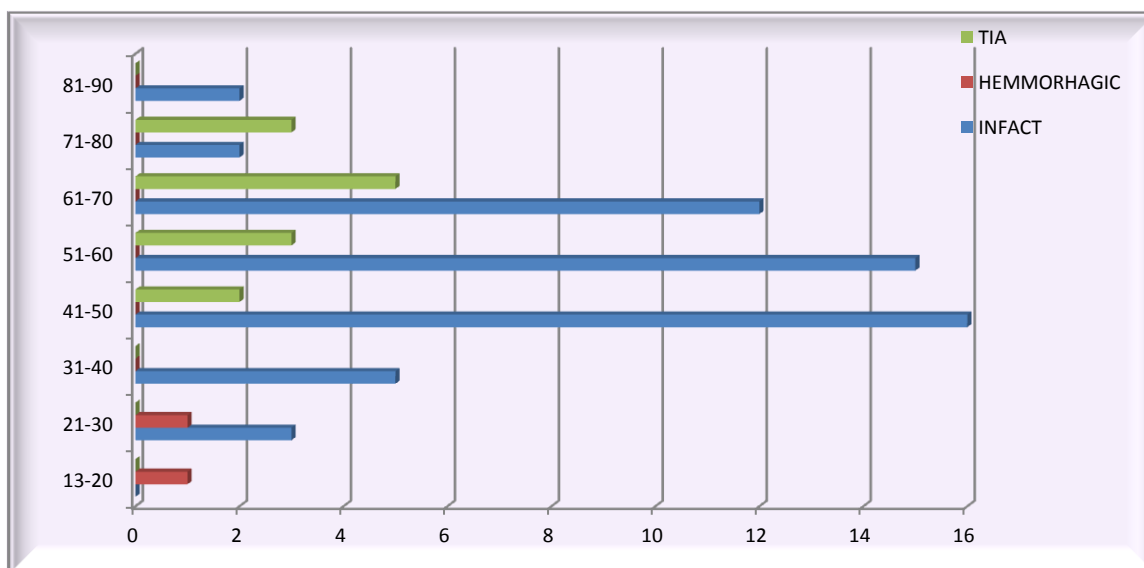


Figure: Bar diagram Incidence the type of stroke in different age

Drug Prescribed in Types of Stroke Patients

This table shows that the extent of drug prescribing pattern in different type of stroke the majorly aspirin prescribes 38 patients in infract/ischemic stroke and 7 patients in patients in TIA patient. Followed by the Atorvastatin prescribed 30 patients in ischemic stroke and 7

patients in TIA, Ranitidine prescribed 17 patients in ischemic stroke, 2 patients in hemorrhagic stroke and 1 patient in TIA, amlodipine prescribed 17 patients in ischemic stroke ,and 1 patient in TIA .And other drug prescribed in types of stroke assessed by this table.

Table: Drug prescribed in types of stroke patients

PRESCRIBING PATTERN OF DRUGS	INFRACT/ISCHEMIC	HEMORRHAGIC/BLEED	TIA
ASPIRIN	38	0	7
CLONAZEPAM	9	0	0
CLOPIDOGREL	8	0	1
GABAPENTIN	2	2	0
LABETOLOL	2	0	0
AMLODIPINE	17	0	1
TELMISARTAN	1	0	2
PHENYTOIN	16	2	3
CARABAMAZEPINE	2	2	0
ATORVASTATINS	30	0	10
MULTIVITAMINS	2	0	1
MANNITOL	12	2	4
CEFTRIAZONE	8	0	5
AMIKACIN	4	2	1
SODIUM VALPROATE	1	0	0
TAZOBACTAM	3	0	1
ONDANSETRON	13	2	5
INSULIN	6	0	2
RANITIDINE	17	2	1
RABEPRAZOLE	11	0	1
QUETIAPINE	2	0	2
AZITHROMYCIN	7	2	0
PANTAPRAZOLE	10	0	3
LEVODOPA	5	0	2
LEVOTHYROXINE	3	0	0
BIASCODYL	2	0	0
OLMESARTAN	2	0	2
BIOSPROLOL	1	0	0
CEFOTAXIME	2	0	0
LACTIOL	3	0	0
CITICOLINE	7	0	0
PIRACETAM	2	0	0
CLOBAZAM	0	0	1
BENFOTIAMINE	0	0	1
BIOTIN	0	0	1
LORAZEPAM	5	0	0
MICOBALAMINE	2	0	0
ACITRETIN	0	0	1
TELPERISONE	1	0	0
CYPROHEPTADINE	1	0	0
TRAMADOL	3	0	0
AMITRYPTINE	2	0	0
PARACETAMOL	5	0	0
ATROPINE	2	0	0
LIDOCAINE	2	0	0
GLIMEPIRIDE	1	0	0
METFORMIN	1	0	0
OMEPRAZOLE	1	0	0
LEVOFLOXACIN	2	0	0
CELECOXIB	1	0	1
PROPANOLOL	10	0	3
DICLOFENAC	1	0	0
TORSIMIDE	1	0	0
NITROFURANTOIN	1	0	0
ETODOLAC	1	0	0

Drug Related Problems

This table show In 70 patients Majorly identified drug related problems were drug interactions 37(69.8%%) followed by Medication error 13(24.52%), overdose 2(3.77%), sub therapeutic dose 1(1.8%). Studies have shown that the clinical pharmacy activities decrease drug related issues, probability of readmission and total cost of health care.

The total numbers of DRPs were predominant in males than in females. Average number of medications received per patient in our study was 5.2. This indicates that the main responsible factors for developing DRPs in stroke patients are multiple medicines in single patient.

As drug-drug interactions can affect patient's clinical outcomes, quality of life and contribute to unnecessary health care costs, the high prevalence rate of drug interactions (69.8%) in this study would make this as an important area requiring further investigation and the future pharmacist should focus on reviewing patients' medication charts and checking for potential drug interactions regularly.

Table: Drug related problems

DRUG RELATED PROBLEMS	NO.OF PATIENTS	PERCENTAGE%
ADVERESE DRUG REACTION	0	0%
DRUG –DRUG INTERACTION	37	69.8%
SUB-THERAPEUTIC DOSE	1	1.8%
MEDICATION ERROAR	13	24.52%
IMPROPER DRUG SELECTION	0	0%
OVERDOSE	2	3.77%
TOTAL	53	100%

Distribution of Sample according to Drug-Drug Interaction

This table shows that the drug–drug interaction in 70 patients in their prescription .155 drug interaction was found in 70 patients. Major drug interaction was found between involving aspirin and Insulin moderate resulted in hypoglycemia in 13 (8.38%) patients in hemorrhagic stroke patients. Followed by drug interaction telmisartan and insulin in 9(5.8%) patients, Phenyntoin+ Pantoprazole in (5.1%).other drug interaction shows in the table.

Table: Distribution of sample according to drug-drug interaction

DRUG - DRUG INTERACTION	FREQUENCY	PERCENTAGE(%)
INSULIN+ASPIRIN	13	8.38%
RABEPRAZOLE+CLOPIDOGREL	6	3.8%
ASPIRIN+AMIKACIN	7	4.5%
TELMISARTAN+ATORVASTATIN	4	2.5%
ASPIRIN+CLPIDOGREL	3	1.9%
GABAPENTIN+BIOTIN	1	0.645%
PHENYNTOIN+RABEPRAZOLE	6	3.8%
CLONAZEPAM+LORAZEPAM	1	0.67%
PHENYNTOIN+CLOPIDOGREL	3	1.9%
PHENYNTOIN+AZITHROMYCIN	7	4.51%
PHENYNTOIN+ATORVASTATIN	7	4.51%
PIRACETAN+CLOPIDOGREL	1	0.6%
ATORVASTATIN+AZITHROMYCIN	3	1.9%
ASPIRIN+CLOPIDOGREL	4	2.5%
RANITIDINE+PHENYNTOIN	8	5.1%
PHENYNTOIN+PANTOPRAZOLE	8	5.16%
PHENYNTOIN+ONDANSETRON	5	3.22%
TELMISARTAN+ASPIRIN	9	5.8%
QUETIAPINE+LEVODOPA	1	0.64%
LEVODOPA+AMLODIPINE	6	3.8%
PHENYNTOIN+AMIAKACIN	3	1.9%
TRAMADOL+AMITRYPTINE	2	1.29%
CLONAZEPAM+TRAMADOL	2	1.29%
CLONAZEPAM+AMITRYPTINE	2	1.29%
ATORVASTATIN+AMITRYPTINE	1	0.67%
ACECLOFENAC+ASPIRIN	2	1.29%
ASPIRIN+GLIMPRIDE	1	0.67%
ASPIRIN+LABETOLOL	3	1.9%

CARBAMAZEPINE+ONDANSETRON	2	1.29%
CARBAMAZEPINE+PHENYNTONIN	3	1.29%
OMEPRAZOLE+CARBAMAZEPINE	1	0.67%
LEVOFLOXACIN+ONDANSETRON	1	0.67%
OMEPRAZOLE+PHENYNTONIN	1	0.67%
TELMISARTAN+METOPROLOL	1	0.67%
TELMISARTAN+INSULIN	2	1.29%
ASPIRIN+METOPROLOL	2	1.29%
PHENYNTONIN+TELMISARTAN	1	0.67%
RABEPRAZOLE+LEVOTHYROXINE	2	1.29%
PHENYNTONIN+LEVOTHYROXINE	2	1.29%
CELECOXIB+AMIKACIN	1	0.67%
PHENYNTONIN+INSULIN	1	0.67%
LEVODOPA+PROPRANOLOL	1	0.67%
QUETIAPINE+INSULIN	1	0.67%
OXCARBAZEPINE+PHENYNTONIN	1	0.67%
OXCARBAZEPINE+ATORVASTATIN	2	1.29%
OXCARBAZEPINE+ONDANSETRON	1	0.67%
OXCARBAZEPINE+PANTOPRAZOLE	1	0.67%
CARBAMAZEPINE+ATORVASTATIN	1	0.67%
AZITHROMYCIN+ONDANSETRON	1	0.67%
DICLOFENAC+AMIKACIN	1	0.67%
CARBAMAZEPINE+DICLOFENAC	1	0.67%
LEVOTHYROXIN+PHENYNTONIN	1	0.67%
AZITHROMYCIN+LEVOFLOXACIN	1	0.67%
METOPROLOL+TORSEMIDE	1	0.67%
METPROLOL+AMLODIPINE	1	0.67%
ASPIRIN+TORSEMIDE	1	0.67%
PHENYNTONIN+AMLODIPINE	1	0.67%
ASPIRIN+CELECOXIB	1	0.67%
CLOPIDOGREL+ETODOLAC	4	2.5%
Total	155	100%

Severity of Drug–Drug Interaction

Type of drug–drug interaction in the prescription for the treatment of stroke .majorly of drug –drug intraction72.9% are moderate followed 17.4% are mild and 9.6% are sever showed in table.

Table: Severity of drug–drug interaction

Drug-drug interaction	No.of patients	Percentage
Mild	27	17.4%
Moderate	113	72.9%
Severe	15	9.6%
Total	155	100%

Conclusion

Based on the results we would like to conclude that In our study a total of DRPs were found in 53 patients during the study period, in which prevalence of DRPs was found to be more males than in females. Predominant DRPs identified in the study patients were drug interactions in 37(69.8%) patients followed by medication error 13 (24.52%), overdose 2(3.77%), sub therapeutic dose 1(1.8%). Potential drug interactions, co-morbidities and polypharmacy were the most

common factors found in this study Ischemic stroke was more prevalent than Hemorrhagic and TIA. The most commonly seen symptom was headache followed by weakness of upper limbs and weakness of lower limbs in our study. hyperlipidemia and hypertension are the most predominant diagnoses observed in majority of population. Hypertension and Smoking were the most common risk factors and the frequently prescribed class of drugs were Antiplatelet followed by Atorvastatin. In our study male gender was more prone to stroke attacks, that too within age group of 51–60 years. Early identification and prevention of DRPs and rational use of drugs in stroke are necessary to prevent complications and unnecessary hospitalization, high cost of treatment and deaths among stroke patients.

Future Direction

- ❖ The similar study could be carried out in and out-patients separately.
- ❖ The pharmacoeconomic study can be done.

Bibliography

1. WHO MONICA Project Investigators. The World Health Organization MONICA Project (Monitoring trends and determinants in cardiovascular disease). *J Clin Epidemiol*. 1988; (41): 105-114.
2. Sims NR, Muyderman H. Mitochondria, oxidative metabolism and cell death in stroke. *Biochimica Et Biophysica Acta*. 2009; 1802 (1): 80 -91.
3. Adams HP Jr, Birgitte H, Bendixen BH, Kappelle LJ, J Biller, et al. Classification of subtype of acute ischemic stroke. Definitions for used in a multicenter clinical trial. TOAST. Trial of Org10172 in Acute Stroke Treatment. *Stroke*. 1993; 24 (1):35-41.
4. Feigin VL. Stroke in developing countries: can the epidemic be stopped and outcomes improved? *Lancet Neurology*. 2007; 6 (2): 94-97.
5. Smith SD, Eskey CJ. Hemorrhagic stroke. *Radiol Clin North Am*. 2011; 49: 27-45.
6. Sacco RL, Benjamin EJ, Broderick JP, Dyken M, Easton JD, et al. Risk factors. *Stroke*. 1997;28:1507-1517.
7. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, et al. Risk factors for ischemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*. 2010; 376 (9735): 112-123.
8. Hewer RL, Tennant A. The epidemiology of disabling neurological disorders. *Handbook of neurological rehabilitation*. Edited by Greenwood RJ, Barnes MP, McMillan TM, Ward CD. Psychology Press. 2003: 5-14.
9. Rothwell PM, Warlow CP. Timing of TIAs preceding stroke: Time window for prevention is very short. *Neurology*.2005; 64:817-820.
10. Caplan, LR, van Gijn J, eds. *Stroke Syndromes*, 3rd ed. Cambridge: Cambridge University Press,2012.
11. Heros R. Stroke: Early patho-physiology and treatment. *Stroke*.1994; 25:1877-1878.
12. Department of Health and Human Services. The National Institute of Neurological Disorders and Stroke (NINDS). NIH Stroke Scale Training, Part 2. Basic Instruction. 2010.
13. Ver Hage A. The NIH stroke scale: a window into neurological status. *Nurse.Com; Nursing Spectrum (Greater Chicago)*. 2011; 24 (15):44-49.
14. Davenport RJ, Dennis MS, Wellwood I, Warlow CP. Complications after acute stroke. *Stroke*.1996; 27:415-420.
15. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study. *Lancet*, 2010; 380: 2095-128.
16. Muhit MA, Rahman MO, Raihan SZ, Asaduzzaman M, Akbar MA, Sharmin N, et al. Cardiovascular disease prevalence and prescription patterns at a tertiary level hospital in Bangladesh. *J Appl Pharm Sci.*, 2012; 2: 80-4.
17. Manjula Devi AS, Sriram S, Rajalingam B, Alfet Raju A, Varghese RS, VenkataPhani A. Evaluation of the rationality of fixed dose combinations of cardiovascular drugs in a multispecialty tertiary care hospital in Coimbatore, Tamil Nadu, India. *Hygeia: J Drugs Med.*, 2012; 4: 51-8.
18. Khonputsa P, Veerman LJ, Bertram M, Lim SS, Chaiyakunnaphruk N, Vos T. Generalized cost-effectiveness analysis of pharmaceutical interventions for primary prevention of cardiovascular disease in Thailand. *The values in Health Regional Issues*, 2012; 1: 15-22.