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RESEARCH ARTICLE

A COMPREHENSIVE STUDY ON SYNERGISTIC EFFECT OF ANTIHYPERTENSIVE DRUGS WITH STATIN DERIVATIVES AND SUPPORTIVE THERAPY IN MANAGING STROKE PATIENTS: A PROSPECTIVE OBSERVATIONAL STUDY

***Dr. Mukesh Kumar Saphi[1], Dr. Yalla Sai Vijaya Durga[1], Dr. Shiv Shankar Shah[2], Dr. S. Sreenivas[3], Dr. Penugonda Vineela[4]**

[1] PHARM-D, Department of Pharmacy Practice, Aditya College of Pharmacy, Surampalem, 533437, Andhra Pradesh, India; [2] Research Scholar, AU College of Pharmaceutical Science, Andhra University Andhra Pradesh; [3] MD, DM (Neuro-Physician), Department of General Medicine (Neurology), GSL General Hospital & Medical College, 533294, Rajahmundry; [4] PHARM-D, Associate professor of Aditya college of Pharmacy, surempalem Andhra Pradesh.

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***Corresponding author:**
Dr. Mukesh Kumar Saphi

ABSTRACT

Background: Stroke remains a significant cause of morbidity and mortality around the world, necessitating comprehensive strategies for effective management. This prospective observational study aimed to investigate the synergistic effects of hypertensive agents and supportive therapy in the management of stroke patients. As Hypertension is the major significant modifiable risk factor for causing stroke, its control is paramount in preventing recurrent events of stroke. **Methods:** This prospective observational study included 213 stroke patients admitted to the tertiary care hospital in south India. The patients received hypertensive agents and concurrent supportive therapy followed over a specified period when admitted to the hospital. Also, data collected through clinical assessments, patient-reported outcomes, and medical records review over a predetermined follow-up during a period of admission were analyzed. Statistical methods, including multivariate regression analysis, Descriptive Statics analysis, and Hypothetical test Z-test assessed the synergistic effect of hypertensive agents and supportive therapy in stroke management outcomes. **Result:** The study found the combined antihypertensive agent with stain shows a synergistic effect when compared to without statins. The combined hypertensive agent and supportive therapy brought a significant improvement in functional recovery. These outcomes are accessed including the rate of stroke reoccurrence, functional recovery, overall mortality rate, and quality of life improved. **Conclusions:** Preliminary findings suggest that the combined use of hypertensive agents with statin derivatives shows a synergistic effect as compared to those without statin. Also, multiple hypertensive therapy shows a higher synergistic effect as compared to double and single hypertensive therapy. This study also concludes that Supportive therapy is significantly associated with improved blood pressure control, functional recovery, and reduced incidence of complications in stroke patients. These findings underscore the multidisciplinary approach in stroke rehabilitation and suggest further research is required to optimize treatment patterns and improve patient quality of life outcomes.

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INTRODUCTION

A stroke is the second leading cause of mortality and morbidity around the world. It is also called a neurological disorder characterized by the blockage of blood vessels or blood capillaries. It occurs when a blood vessel in the brain becomes blocked or narrowed, or when a blood vessel bursts and spills blood into the brain (1). or when a blood vessel bursts and spills blood into the brain (1). It is a major global cause of death and disability that places a heavy financial and social strain on people, families, and the healthcare system (2). It is also called a CVA (Cerebrovascular Accident) that carries a high risk of death and can cause loss of vision, slurring of speech, paralysis, and confusion (3). Strokes are defined by the World Health Organization (WHO) as "rapidly developing clinical signs of focal disturbance of cerebral function, with which the

symptoms lasting for 24 hours or longer or leading to death, with no apparent cause other than vascular origin (4,5). The stroke is of 5 types according to the American Stroke Association, Ischemic stroke (clot) 87%, Hemorrhagic Stroke (bleed), TIA (Transient Ischemic Attack), Cryptogenic stroke, and Brain Steam stroke (6). A multimodal strategy is used to address types of strokes with the goals of limiting neuronal damage, restoring blood flow, and averting secondary problems (7). According to the World Stroke Organization, over 13.7 million stroke attacks are reported each year, of those cases, 60% are under age 70, and in India, the stroke case is reported to be 152/100,000 persons per year. These values were higher than those of high-income countries (8,9,10). Hypertension is the major modifiable risk factor for causing stroke which majorly affects cerebral perfusion and neurological consequences. Contributing to approximately 50-60% of all cases.

Pharmaceutical treatments are a key component of the many therapeutic methods used in the treatment of stroke. So, Effective blood pressure management plays an important role in both primary as well as secondary stroke prevention (7). Antihypertensive agents, such as ACE-Inhibitor, ARBs, CCBs, and Thiazide Diuretics play a cornerstone in the pharmacological management of Hypertension. The prior choice of antihypertensive therapy and its synergistic effect with supportive therapies such as Neuroprotective agents, antiepileptic therapy, statin therapy (11,12,13) and also, physiotherapy, electro-stimulation therapy, lifestyle modification, and rehabilitation in stroke management is so effective and requires furthermore exploration. When compared to normal medical therapy alone, reperfusion techniques such as mechanical thrombectomy and intra-arterial thrombolysis have improved functional outcomes and increased rates of successful recanalization in the management of major artery occlusion strokes (14,15).

In light of these considerations of all parameters, this prospective observational study aims to conduct a comprehensive analysis of the synergistic effects of hypertensive agents and supportive therapy in the management of stroke patients. By elucidating the complex interactions between pharmacological and non-pharmacological interventions, this study seeks to refine our understanding of optimal treatment strategies for hypertensive stroke patients.

OBJECTIVES

- To analyze the impact of different classes of hypertensive agents on stroke outcomes, including mortality, functional recovery, and recurrent vascular injury.
- To evaluate the effectiveness of supportive therapies, such as physical rehabilitation, psychosocial interventions, and neuroprotective agents in improving functional outcomes and quality of life among stroke patients.
- To evaluate the potential synergistic effects of hypertensive agents with statin and other supportive therapies in enhancing clinical outcomes and reducing the burden of stroke-related morbidity, mortality, and disability.
- To identify and predict the treatment response and prognosis among hypertensive stroke patients, considering both pharmacological and non-pharmacological factors in the management of stroke patients.

MATERIALS AND METHODS

The current Prospective Observational study (Cohort study) of over 12 months duration was performed in the Department of General Medicine (Neurology) of a tertiary care teaching hospital in south India. A structured process was followed for obtaining permission from hospital authority by submitting a detailed proforma of the study which included the protocol of the study, evidence of critically evaluated biomedical literature, special design data collection form, patient informed consent form. After initial acceptance from the hospital, the study was registered with the institutional review board (IRB) of the institution for ethical approval. A total of 213 patients diagnosed with Stroke of both genders admitted to the Department of General Medicine (neurology) showing willingness toward study were included and others were excluded (patients who showed unwillingness and with other organ failure). A documentation form was designed to collect the patient's information only after explaining the study and taking a valid signature on the consent form.

After enrolling a patient into the study the Data was collected through clinical assessments, patient-reported outcomes, laboratory and medical records review over a predetermined follow-up during admission and were analyzed. Descriptive data was presented as mean, median, mode, standard deviation, standard error, and percentage. Also, Data was tabulated and graphically represented and All statistical analyses were performed using SPSS software version 20.0 and MS EXCEL 2019. For association among categorical variables, Z-Test, the correlation was done by SPSS software 20.0.

RESULTS

This study includes 213 patients out of which 134 (62.1%) are male and 79 (37.9%) are female. According to this data (Table no.1), Males are more susceptible to stroke. Based on social history (Table no.2) among stroke patients 100 are smokers and 113 are non-smokers, taking to alcohol history 88 are alcoholics and 125 are non-alcoholics. When compared to types of strokes (Table no.3), the majority are ischemic stroke 64.3%, hemorrhagic stroke 24.4%, and transient ischemic stroke 11.2%. Taking into consideration of pattern of symptoms(Table no.4) in stroke patients, weakness of upper limbs (67.6%), weakness of lower limbs (64.7%), facial palsy (62.9%), and dysarthria (56.3%). While comparing the pattern of co-morbidities (Table no.5) in stroke patients, hypertension (61.9%), Diabetes (42.2%), and epilepsy (14.5%) were mainly risk conditions for stroke.

Compared to the treatment(Table no.6) given for hypertension in a stroke patient, ARBs were the main drug given along with thiazide diuretic (72.3%) followed by 8.9% of stroke patients given inj labetalol in IV form for the intensive decrease in blood pressure with continuous monitoring until the desired level is achieved. Supportive therapy like Antiplatelet agents (63.7%), neuroprotective agents (81.9%), antiepileptic drugs (60.56%), and physiotherapy (76.7%) were commonly utilized for stroke management. For statistical tests, a descriptive study (Table no.9) along with matched pair Z test and correlation(Table no .10) was done.

Gender Wise Distribution Among Stroke patients

Table 1. Gender

	No. of Patients	%
Male	134	62.1
Female	79	37.9

Social History Wise Distribution Among Stroke Patients

Table 02. Social Habits

	Male	Female
Smoker	80	20
Non-Smoker	54	59
Alcoholic	61	27
Non- Alcoholic	73	52

Types of Strokes Among Stroke Patients

Table 03. Types of Strokes

	No of Patients
TIA	24
Ischemic Stroke	137
Hemorrhagic Stroke	52

Pattern of Symptoms Among Stroke Patients

Table 4. Symptoms

	No. of Patients
Weakness of upper limbs	144
Weakness of the lower limb	138
Facial palsy	134
Dysarthria	120
Left hemiparesis	92
Right hemiparesis	63
Giddiness	46
Tingling sensation	23
Altered sensorium	21
Headache	19
Vomiting	7
Blurred vision	8
Hearing loss	2

Patterns of Comorbidities Among Stroke Patients

Table 05. Comorbidities

	No. of Patients
Hypertension	132
Diabetes	90
Recurrent Stroke History	43
Epilepsy	31
No Any	25
CAD	16
Accidental Head Injury	13
CKD	6
LVD	4

Patterns of Anti-Hypertensive Therapy Among Stroke Patients.

Table 06. Anti-Hypertensive Drugs

	No. of Patients
inj-Mannitol	92
tab-Telma-h	93
tab-Telma-CT	24
tab-Telma	31
Inj- Labetalol	19
tab-Metoprolol	8
tab-Losartan	24
tab-Cilnidipine	35
tab-Nicardipine	5
tab-Amlodipine	2
tab-Enalapril	1
tab-Dytor plus	6

Supportive Therapy Among Stroke Patients

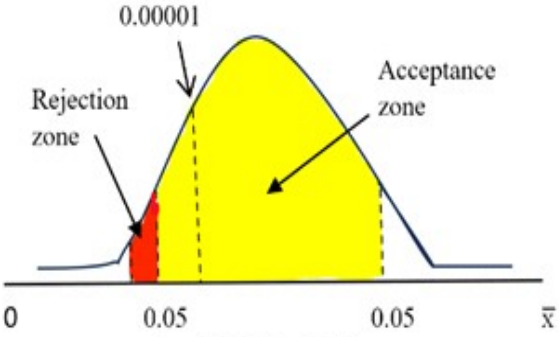
	No of Patients
Antiplatelet	137
Anticoagulant	34
Neuroprotective agent	176
Anti-epileptic agent	129
Statin Derivatives	114
Physiotherapy	165
Physiotherapy with Electrostimulation therapy	35

Types of Anti-Hypertensive Therapy Among Stroke Patients

Table 08. Types of Therapy

Multiple Therapy	104
Double Therapy	90
Single Therapy	19

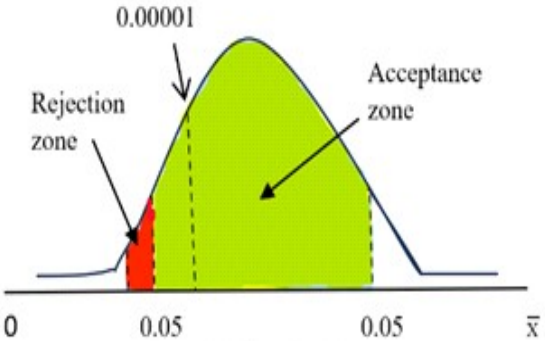
A



P = 0.00001 < 0.05

∴ The alternative hypothesis was accepted and the Null hypothesis rejected which means there was a highly a significant difference between systolic blood pressure before medication and after medication.

B



P = 0.00001 < 0.05

∴ The alternative hypothesis was accepted and the Null hypothesis rejected which means there was a highly a significant difference between Diastolic blood pressure before medication and after medication.

Synergistic Effect of Anti-Hypertensive drugs with or without statin Derivatives Drugs in Stroke Patients

Table 09. Descriptive Statics

	No. of sample	Mean	Median	Mode	SD	SE	Confidence Level (95%)	Correlation
SBP level for a patient taking Antihypertensive medication without statin	99	133.2	130	130	9.25	0.93	1.855	0.3010
SBP level for a patient taking antihypertensive medication with Statin	114	126.26	130	130	8.27	0.77	1.54	
DBP level for a patient taking Antihypertensive medication without Statin	99	84.07	80	80	6.13	0.61	1.22	0.5175
DBP level for a patient taking Antihypertensive medication with statin	114	78.45	80	80	4.71	0.44	0.87	

Matched pair Z-Test was conducted on Blood Pressure at 0.05 significance level and correlation, the following results were observed

Table 10. Sample characteristics and results from Matched Pair Z-Test on blood pressure at 0.05 significance level and Correlation between before and after treatmentN=213

	Observation	Mean	Z - Value	P(Z<=z) ONE-TAIL	Z CRITICSL ONE-TAIL	P(Z<=z) TWO-TAIL	Z CRITICAL TWO-TAIL
A.							
Systolic Blood Pressure before medication	213	158.8	8.53	0.00001	1.6440	0.00001	1.9599
Systolic Blood Pressure after medication	213	129.7					
Correlation between before and after medication of systolic blood pressure	0.5986 » systolic before medication and after medication correlation are found to be positive so it concludes that the higher positive value indicates a higher correlation						
B.							
Diastolic blood pressure before medication	213	98.31	10.26	0.00001	1.6448	0.00001	1.9599
Diastolic blood pressure after medication	213	81.26					
Correlation Between before and after medication of diastolic blood pressure	0.4878 » diastolic before medication and diastolic after medication correlation are found to be positive so it concludes that the higher positive value indicates a higher correlation						

DISCUSSION

The outcomes of this prospective observational study provide valuable insights into different aspects of stroke care and how various treatment methods work together. The study included 134 males (62.1%) and 79 females (37.9%) out of 213 stroke patients (Table no.01, Graph no.01), indicating a higher prevalence among males. This trend is consistent with existing research that suggests males are more susceptible to stroke due to risk factors like smoking and heavy alcohol use as compared to females and Further investigation is necessary to uncover the underlying reasons behind this gender difference. This study based on social history-wise distribution (Table no.02, Graph no. 02)revealed no Table distinctions between male and female stroke patients regarding smoking and alcohol use. Male patients exhibited higher rates of smoking (59.7%) and alcohol consumption (45.5%) compared to females, highlighting a potential need for targeted interventions to address these risk factors and reduce stroke incidence in this demographic. This study includes Ischemic stroke (64.3%) which was the most common type, followed by hemorrhagic stroke (24.4%) and transient ischemic attack (11.2%) (Table no.03 , Graph no. 03). This pattern aligns with broader epidemiological trends and underscores the necessity for tailored treatment approaches tailored to each stroke subtype. Pattern of Symptom analysis (Table no. 04, Graph no. 04) showcased a wide array of clinical presentations among stroke patients. Common symptoms included weakness of upper limbs (67.6%), weakness of lower limbs (64.7%), facial palsy (62.9%), and dysarthria (56.3%). Understanding these symptom patterns is crucial for early detection and intervention, ultimately leading to improved patient outcomes. Among the identified comorbidities (Table no. 05, Graph no. 05), hypertension emerged as the most prevalent, affecting 132 (61.97%) individuals. This high prevalence underscores hypertension's pivotal role as a leading risk factor for stroke onset and recurrence.

Additionally, diabetes mellitus was notably prevalent, impacting 90 (42.25%) stroke patients. The occurrence of recurrent stroke history in 43 (20.18%) patients signals the heightened risk of subsequent cerebrovascular events within this subset. The presence of epilepsy among 31 (14.55%) stroke patients underscores the intricate relationship between cerebrovascular pathology and seizure disorders, necessitating vigilant surveillance and tailored antiepileptic management to optimize seizure control and mitigate adverse neurological outcomes post-stroke. Remarkably, a subset of 25 (11.73%) stroke patients did not exhibit any documented comorbidities. While suggestive of a relatively healthier cohort, this finding prompts further exploration into potential underdiagnosed or subclinical risk factors and underscores the importance of comprehensive risk factor assessment to preempt future cerebrovascular events. Less prevalent comorbidities, including coronary artery disease (CAD), accidental head injury, chronic kidney disease (CKD), and left ventricular

dysfunction (LVD), warrant attention for their potential impact on stroke prognosis and treatment strategies, despite their lower frequency in our cohort. By addressing the complex interplay of vascular risk factors and associated health conditions, healthcare providers can optimize therapeutic interventions, enhance secondary prevention efforts, and ultimately improve patient outcomes in the continuum of stroke care. Based on types of antihypertensive therapy (Table no. 08, graph no. 08), Multiple therapies (48.82%), double therapy (44.25%), and single therapy (6.93%) regimens were preferred and showed that depending upon the severity of the patient the types of therapy given to the patient for anti-hypertensive treatment, and emphasizing the complexity of managing hypertension in stroke patients and the significance of controlling blood pressure to prevent further damage to the strokes patients. Therefore, the treatment of hypertension became crucial in the study and the pattern of antihypertensive therapy (Table no. 06, Graph no. 06)has been found that almost all the patient was prescribed Telmisartan, Hydrochlorothiazide followed by Labetalol, Cilnidipine, Amlodipine, Metoprolol, Torsemide. For an intensive decrease in BP Labetalol has been given in IV form until the BP reaches to desired level, and an Osmotic diuretic inj Mannitol was given to decrease ICP to prevent further damage to the brain. This study suggests that an angiotensin receptor blocker combination with a thiazide diuretic will be more effective in reducing blood pressure at the desired level and reducing the risk of recurrent stroke. Labetalol was given in IV form when the patient was unable to take medication orally until the blood pressure goal was achieved and continuous monitoring was required. Supportive therapy (Table no. 07, graph no. 07) like Antiplatelet agents (63.7%), neuroprotective agents (81.9%), antiepileptic agents (60.56%), and physiotherapy (76.7%) were commonly utilized for stroke management aimed at minimizing disability and improving long-term prognosis.

A Descriptive study (Table no 09) was done to show a synergistic effect of the antihypertensive drug with the station and showed the mean blood pressure value was less in patients taking antihypertensive with statin derivatives than those without statin derivatives. Varies Clinical studies have shown that combining statins with antihypertensive medications, such as ACE inhibitors, ARBs, calcium channel blockers, or beta-blockers, can lead to better control of cardiovascular risk factors and a reduced incidence of heart attacks and strokes. The synergistic effect between these drug classes has made this combination a popular approach in managing patients with multiple cardiovascular risks, such as high blood pressure, high cholesterol, and other related conditions. For the hypothetical test, Matched pair Z-test analysis (Table no. 10, graphs no A and B) was done at the level of significance 0.05 and found that the result value was much less than of significance value which concludes that acceptance of the alternative hypothesis and rejection of the Null Hypothesis showed high significance between systolic blood pressure before – systolic blood pressure after medication and diastolic blood pressure before – diastolic blood pressure after medication. Also, the correlation was done between before-therapy and after-therapy of systolic blood pressure and diastolic blood pressure and was found to be 0.5986 and 0.4878 which showed a high correlation and concluded that antihypertensive therapy is effective in managing stroke patients. Also the descriptive study was made to understand the synesrgistic effect of antihypertensive drugs with statin derivatives shown in Table no. 09. The mean of blood pressure is less in antihypertensive therapy with statin as compared without station. This findings suggest a potential synergistic effect of antihypertensive medication with statin derivatives in effectively reducing blood pressure levels among stroke patients. The higher prevalence of stroke among males and the association with smoking and alcohol consumption emphasize the need for targeted interventions to address modifiable risk factors. Understanding the diverse symptom presentations and common comorbidities underscores the importance of comprehensive risk factor management. The preference for multiple or double therapy regimens for hypertension and the widespread utilization of supportive therapies highlight the holistic approach to stroke management aimed at minimizing disability and improving long-term prognosis.

CONCLUSION

The results of our study highlight significant findings regarding the synergistic effect of antihypertensive drugs with or without statin derivatives in stroke patients. Descriptive statistics revealed that patients receiving antihypertensive medication with statin derivatives demonstrated slightly lower mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels compared to those without statin derivatives. Furthermore, the matched pair Z-test indicated significant reductions in both SBP and DBP levels following medication administration, with positive correlations between pre- and post-medication blood pressure measurements. Specifically, the mean SBP decreased from 158.8 mmHg to 129.7 mmHg after medication administration, with a correlation of 0.5986, while the mean DBP decreased from 98.31 mmHg to 81.26 mmHg, with a correlation of 0.4878. These findings suggest a potential synergistic effect of antihypertensive medication with statin derivatives in effectively reducing blood pressure levels among stroke patients. Further research is warranted to elucidate the underlying mechanisms and assess the long-term clinical implications of this synergistic effect, ultimately informing evidence-based treatment strategies for stroke management.

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ABBREVIATIONS

CVA- Cerebro Vascular Accident
WHO- World Health Organisation
TIA- Transient Ischemic Stroke
ACE- Angiotensin Converting Enzyme
ARB- Angiotensin Receptor Blocker
CCB- Calcium Channel Blocker
IRB- Institutional Review Board
SPSS- Statistical Package for the Social Sciences
IV- Intra Venous
CAD- Coronary Artery Disease
CKD- Chronic Kidney Disease
LVD- Left Ventricular Dysfunction
ICP- Intra Cranial Pressure
SBP- Systolic Blood Pressure
DBP-Diastolic Blood Pressure

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INFORMED CONSENT: Informed consent was taken from all the patient

AUTHOR CONTRIBUTION: All authors contributed equally

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