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ORIGINAL ARTICLE

Prevalence of Ischemic Versus Hemorrhagic Stroke in Patients Taking Anti-Coagulation Therapy

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ABSTRACT

Objective: To evaluate the prevalence of ischemic versus hemorrhagic stroke in patients taking anti-coagulation therapy.

Methodology: This cross-sectional prospective study was conducted at medicine Departments of Peoples University of Medical & Health Sciences (PUMHS), for a period of 18 months from September 2021 to January 2023. All the patients taking anti-thrombotic therapy (warfarin, rivaroxaban, dabigatran, or apixaban) were included in this study and their baseline and clinical data were collected. Statistical package for the social sciences version (SPSS v. 26) was used for data entry and data analysis. Chi-square test/fisher's exact and independent t-test test was used for determination of risk factors associated with hemorrhagic or ischemic strokes. A p value of <0.05 was considered as statistically significant.

Results: A total of 296 patients were enrolled for final analysis. The overall mean age, BMI, and duration of anticoagulation therapy was 62.14±8.44 years, 25.38±3.19 kg/m2, and 8.34±12.51 months. Among all study participants, 57.43% (n = 170) were taking NOACs while 42.56% (n = 126) were taking warfarin. The overall prevalence of stroke was 14.18% (n = 42) and among them hemorrhagic stroke was more common (57.14%, n = 27) than ischemic stroke (35.71%, n = 15). Patients taking NOACs were more likely to have hemorrhagic stroke as compared to ischemic stroke, 74.07% (n = 20/27) and 40.0% (n = 7), respectively, p value <0.001.

Conclusion: The risk of stroke is quite high in patients receiving anti-thrombotic therapies. Hemorrhagic stroke is higher in patients receiving NOACs

Keywords: Anti-thrombotic therapy, ischemic stroke, hemorrhagic stroke, Pakistan

Authors' Contribution:
[1,2]Conception; Literature research; manuscript design and drafting; [3,4] Critical analysis and manuscript review; [5,6]Data analysis; Manuscript Editing.

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Introduction

Anti-platelets such as aspirin, clopidogrel, and Anticoagulation therapy like warfarin, and novel oral anticoagulants (NOACs) are the drugs usually recommended in patients with atherosclerotic diseases such as coronary artery and cerebrovascular diseases, peripheral arterial disease (PAD), cardiac arrhythmias, valvular heart disease, and in patients underwent cardiac valve replacement[1,2]. Use of anticoagulants is not risk free and is associated with certain side effects which may vary from mild to life threatening (3). In a study conducted by Eek AK and colleagues have observed prevalence of adverse reaction after the use of oral

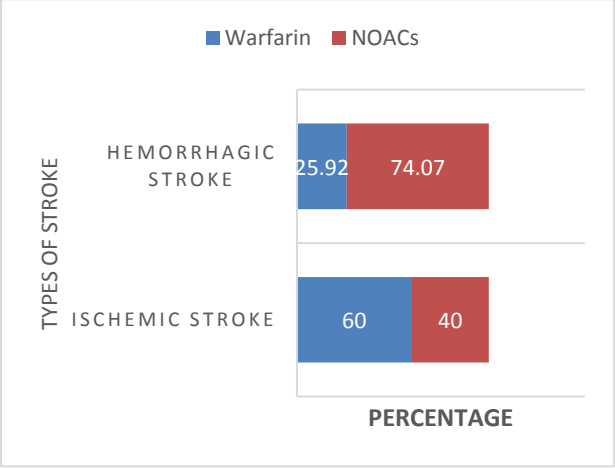
anticoagulants was 0.62% (n = 409/65,000) (4). The side effects include, drug hypersensitivity, therapeutic failure, headache, hair loss, cognitive function decline, ischemic or hemorrhagic cerebral vascular accidents, or even death[5]. The most common site of bleeding is gastrointestinal tract while intracranial bleeding is least common but devastating and even lead to disability and death[6]. The overall risk of bleeding among anticoagulant users depends upon multiple factors such as dose of anticoagulant, underlying pathology, age, gender, duration of therapy, type of anticoagulation therapy, and comorbid conditions. In a previously published study, the risk of bleeding was observed around 7.2%[7]. It is observed that 10 times higher risk of bleeding among warfarin users during the first month of therapy[8]. While another study conducted by Noseworthy PA and colleagues[9] have observed that patients using NOACs (Rivaroxaban, Apixaban, and Dabigatran) have lower risk of stroke and systemic embolism. Comparative data regarding ischemic and hemorrhagic stroke among patients using anticoagulation therapy is limited. Only few studies are published and majority of them are from international authors of developed countries. This study aims to fill the scientific gap present local level and to provide data regarding prevalence of ischemic and/or hemorrhagic stroke in patients using anticoagulation therapy due to any cause.

Methodology

This was a prospective hospital-based observational study conducted in the Department of Medicine, Department of Neurosurgery, and Department of Cardiology, Liaquat University of Medical & Health Sciences (LUMHS), Hyderabad/Jamshoro for a period of 14 months from September 2022 to November 2023. Ethical approval was taken before commencement of this study and informed written consent was also sought from patient or their attendants before enrolment into this study. The inclusion criteria for this study were patients taking anticoagulation therapy such as warfarin or NOACs due to any underlying cause, age ranges between 25 years to 80 years, both male and female, and hospitalized for acute ischemic or hemorrhagic stroke. Patients had previous history of ischemic or hemorrhagic stroke, patients with congenital bleeding diathesis, pregnant women, patients receiving concomitant antiplatelet therapy, patient's intolerant to anticoagulation therapy, and those who do not consent to participate. All the enrolled patients presented in aforementioned departments were examined and detailed history were taken at the time of admission. Patients were given standard care to all the patients according to the recent American guidelines. Diagnosis of ischemic or hemorrhagic stroke were made through history, physical examination, and confirmed through CT scan. Detail regarding dose, type, and duration of anticoagulation therapy were also collected. Baseline and clinical variables such as age, gender, area of residence, marital status, addiction habits (active cigarette smoking and alcohol consumption) body mass index (BMI), comorbid conditions (diabetes mellitus, hypertension, dyslipidemia), and type of ischemic or hemorrhagic stroke were collected. Statistical package for the social sciences version (SPSS v. 26) was used for data entry and data analysis. Frequencies and percentages were calculated for categorical variables such as gender, BMI, area of residence, addiction habits, comorbid conditions, type and dose of anticoagulation therapy, and type of ischemic or hemorrhagic stroke. While mean and SD were calculated for continuous variables such as age and duration of anticoagulation therapy. Chi-square test/fisher's exact test was used for determination of association between categorical variables and independent t-test was performed to determine the association between continuous variables. A p value of <0.05 was considered as statistically significant.

Results

A total of 296 patients were enrolled for final analysis who were taking anticoagulation therapy. The overall mean age, BMI, and duration of anticoagulation therapy was 62.14±8.44 years, 25.38±3.19 kg/m^2, and 8.34±12.51 months. `Majority of the patients (n = 213, 71.95%) belongs to age between ≥51-80 years. Males were more prevalent than females, 64.52% (n = 191) and 35.47% (n = 105), respectively. Among all study participants, current cigarette smokers were 35.81% (n = 106). In this study, the most common comorbid condition was presence of hypertension (37.5%, n = 111) followed by diabetes mellitus (26.31%, n = 78), and dyslipidemia (26.01%, n = 77). Table I. Among all 296 study participants, 57.43% (n = 170) were taking NOACs while 42.56% (n = 126) were taking warfarin. Graph 1 shows association between anticoagulation therapies with frequency of strokes. The overall prevalence of stroke was 14.18% (n = 42) and among them hemorrhagic stroke was more common (57.14%, n = 27) than ischemic stroke (35.71%, n = 15). Patients taking NOACs were more likely to have hemorrhagic stroke as compared to ischemic stroke, 74.07% (n = 20/27) and 40.0% (n = 7), respectively, p value <0.001.



Graph 1: Prevalence of Ischemic Vs Hemorrhagic Stroke among Patients Taking Anticoagulant Therapy

Table I: Baseline and Clinical Characteristics of Study Participants taking Anticoagulants

Variables	**Overall**	
	Frequency	**Percentage**
Age – years		
Mean±SD	62.14±8.44	
≥25 – 50	83	28.04
≥51 – 80	213	71.95
Gender		
Male	191	64.52
Female	105	35.47
BMI - kg/m2	25.38±3.19	
Duration of anticoagulation therapy - months	8.34±12.51	
Area of residence		
Urban	208	70.27
Rural	88	29.72
Marital Status		
Single	27	9.12
Married	251	84.79
Widowed	12	4.05
Separated	6	2.02
Current cigarette smoker	106	35.81
Comorbid conditions		
Hypertension	111	37.5
Diabetes mellitus	78	26.31
Dyslipidemia	77	26.01
Type of anticoagulation		
Warfarin	126	42.56
NOACs	170	57.43

BMI = Body mass index, NOACs = Novel oral anticoagulants

Table 2 shows factors associated with ischemic and hemorrhagic strokes. Higher mean age 65.11±7.12 years and patients with diabetes mellitus (70.37%, n = 19) were significantly associated with hemorrhagic stroke while increased duration of

anticoagulation therapy 11.09±4.62 months was associated with increased risk of ischemic stroke, p value <0.05.

Table II: Association between Baseline and Clinical Characteristics with Outcomes (N =296)

Variables	Ischemic stroke	Hemorrhagic stroke	P value
	(N = 15)	(N = 27)	
Age - years			
Mean±SD	61.08±9.76	65.11±7.12	0.004*
≥25 - 50	4 (26.66)	2 (7.40)	0.001*
≥51 - 80	11 (73.33)	25 (92.59)	
Gender			
Male	10 (66.66)	16 (59.25)	0.08
Female	5 (33.33)	9 (33.33)	
BMI - kg/m2	25.06±4.03	25.46±3.76	0.43
Duration of anticoagulation therapy - months	11.09±4.62	9.55±9.34	0.001*
Area of residence			
Urban	11 (73.33)	20 (74.07)	0.16
Rural	4 (26.66)	7 (25.92)	
Marital Status			
Single	1 (6.66)	2 (7.40)	0.98
Married	12 (80.0)	24 (88.88)	
Widowed	2 (13.33)	0 (0)	
Separated	0 (0)	1 (3.70)	
Current cigarette smoker	4 (26.66)	9 (33.33)	0.09
Comorbid conditions			
Hypertension	10 (66.66)	16 (59.25)	0.02*
Diabetes mellitus	6 (40.0)	19 (70.37)	
Dyslipidemia	5 (33.33)	12 (44.44)	
*p value <0.05 is statistically significant			
BMI = Body mass index, NOACs = Novel oral anticoagulants			

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Discussion

Cerebrovascular accidents are the leading causes of disability and deaths worldwide particularly in older patients with multiple comorbids such as hypertension, diabetes mellitus, dyslipidemia[10,11]. Besides these risk factors, patients who are taking anticoagulation therapy are also at high risk for development of CVA[12,13]. In a recently published randomized controlled trial included 42 studies and more than 300000 patients from 1995 to 2020 have shown that risk of intracranial bleed and hemorrhagic stroke significantly increased in patients taking antithrombotic and antiplatelet therapy as compared to ischemic stroke (RR 1.36, 95% CI 1.00-1.86[14]. The same findings were observed in our study in which we have observed that patients had significantly higher rates of hemorrhagic stroke using NOACs as compared to warfarin 74.07% (n = 20/27). On the other hand, our study also shows that ischemic stroke was common in patients taking warfarin. On the contrary, study conducted by Shpak M and colleagues [15] in 2018 have observed higher prevalence of ischemic strokes among patients receiving NOACs. Varied prevalence of strokes observed in different population. The reason behind this difference could be selection antithrombotic therapy, underlying risk factors, duration of therapy, as increased age, patients with multiple comorbid conditions and labile PT and INR are associated with increased prevalence pf stroke.

In our study we have also observed that Higher mean age 65.11±7.12 years and patients with diabetes mellitus (70.37%, n = 19) were significantly associated with hemorrhagic stroke while increased duration of anticoagulation therapy 11.09±4.62 months was associated with increased risk of ischemic stroke, p value <0.05. The same findings are observed in previously published studies[16,18]. Risk of intracranial bleeding also increases with type of anti-thrombotic drugs such as patients who were taking rivaroxaban poses highest risk of bleeding as compared to patients taking aspirin, dabigatran, or

apixaban (RR 2.12; 95% CI 1.31-3.44)[19]. That is why choice of anti-thrombotic agent is necessary for patient's safety and desired results. On the other hand, drug compliance also plays and important role in drug safety, prevent from poor outcome, and also complication free therapy[20,21]. For that, patients with non-adherence to drug should be excluded to determine the real–world experience of stroke among patients taking anti-thrombotic therapy. There are certain limitations in this study. Firstly, it would be beneficial to conduct a comparison between various types of NOACs to determine their respective prevalence rates of ischemic versus hemorrhagic strokes. Secondly, increasing the sample size by including multiple hospitals from various regions across Pakistan could enhance the generalizability of the findings. Lastly, exploring the association between the indication for anti-thrombotic therapy and the prevalence rates of ischemic versus hemorrhagic strokes could provide valuable insights into treatment strategies and patient outcomes.

Conclusion

The risk of stroke is quite high in patients receiving anti-thrombotic therapies. Hemorrhagic stroke is higher in patients receiving NOACs. Risk factors mentioned in our study leading to highest risk of stroke should be considered at the time of commencement of anti-thrombotic therapy and also, multi-center studies should be conducted in Pakistan to validate the findings this study.

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