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Betimi i Hipokratit

Në çastin kur po hy në radhët e anëtarëve të profesionit mjekësor premtoj solemnisht se jetën time do ta vë në shërbim të humanitetit. Ndaj mësuesve do ta ruaj mirënjohjen dhe respektin e duhur.

Profesionin tim do ta ushtroj me ndërgjegje e me dinjitet. Shëndeti i pacientit tim do të jetë brenga ime më e madhe. Do t'i respektoj e do t'i ruaj fshehtësitë e atij që do të më rrëfëhet. Do ta ruaj me të gjitha forcat e mia nderin e traditës fisnike të profesionit të mjekësisë.

Kolegët e mi do t'i konsideroj si vëllezër të mi.

Në ushtrimin e profesionit ndaj të sëmurit tek unë nuk do të ndikojë përkatësia e besimit, e nacionalitetit, e racës, e politikës, apo përkatësia klasore. Që nga fillimi do ta ruaj jetën e njeriut në mënyrë absolute. As në kushtet e kërcënimit nuk do të lejoj të keqpërdoren njohuritë e mia mjekësore që do të ishin në kundërshtim me ligjet e humanitetit. Këtë premtim po e jap në mënyrë solemne e të lirë, duke u mbështetur në nderin tim personal.

The Oath of Hippocrates

Upon having conferred on me the high calling of physician and entering medical practice, I do solemnly pledge myself to consecrate my life to the service of humanity. I will give my teachers the respect and gratitude which is their due. I will practice my profession with conscience and dignity. The health of my patient will be my first consideration. I will respect the secrets which are confided in me, even after the patient has died. I will maintain by all the means in my power, the honor and the noble traditions of the medical profession.

My colleagues will be my brothers.

I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient. I will maintain the utmost respect for human life from its beginning even under threat and I will not use my medical knowledge contrary to the laws of humanity. I make these promises solemnly, freely and upon my honor

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INVESTIGATING THE RELATIONSHIP BETWEEN ASPIRIN RESISTANCE AND CLINICAL SEVERITY IN ACUTE ISCHEMIC STROKE PATIENTS

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ABSTRACT

Objective: Ischemic stroke outcomes are influenced by initial severity. We aimed to explore the relationship between aspirin resistance (AR) and stroke severity. **Introduction:** Stroke severity significantly affects clinical outcomes. Established tools like NIHSS and MRS assess severity, yet the link between aspirin resistance and these measures remains uncertain.

Material and Methods: We enrolled 100 acute ischemic stroke patients, assessing severity with NIHSS and MRS and aspirin resistance using the Innovance PFA 200 system. Statistical analyses employed SPSS 20.0.

Results: Of 100 patients (mean age 61 years, 55% male), 32% showed aspirin resistance. While NIHSS and MRS correlated with certain clinical parameters, no significant correlation was found between aspirin resistance and stroke severity.

Discussion: Despite expectations, no significant link emerged between aspirin resistance and stroke severity measured by NIHSS/MRS. Other factors may outweigh aspirin responsiveness in influencing stroke severity. The positive correlation between age and aspirin resistance merits further exploration for treatment implications in older stroke patients. **Conclusion:** Aspirin resistance was prevalent among acute stroke patients but didn't impact stroke severity as measured by NIHSS and MRS. This underscores the need for personalized stroke management approaches.

Keywords: Aspirin resistance, Stroke, NIHSS Scale, MRS scale,

Introduction

Ischemic stroke ranks as a major global cause of morbidity and mortality, and the initial severity of the stroke significantly impacts clinical outcomes. Although aspirin is a cornerstone in the prevention and management of

stroke, the impact of aspirin resistance on the severity of strokes is still unclear. This study aims to investigate this gap in understanding, as the severity of the initial presentation of ischemic stroke significantly impacts patients' outcomes. The National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (MRS)

are essential instruments for assessing stroke severity, offering a standardized method for clinical evaluation. Despite their significance, the connection between aspirin resistance and these clinical metrics remains ambiguous. By closely examining data from one hundred consecutive acute ischemic stroke patients, this study aims to show the complex interplay between aspirin resistance and stroke severity. By using strong methodologies, including the assessment of aspirin resistance via the Innovance PFA 200 system and statistical analyses using SPSS 20.0, this research aims to show the various determinants of stroke outcomes. Additionally, we're underlining the importance of customizing treatment to fit each patient's unique requirements, especially when it comes to choosing the right type and dose of antiplatelet medication.

MATERIAL AND METHODS

One hundred consecutive patients presenting with acute ischemic stroke were enrolled in the study. Inclusion criteria included at least 30 days of prior aspirin therapy, (acetylsalicylic acid, 100 mg daily) before stroke onset, evidence of ischemic infarct on computed tomography (CT) or magnetic resonance imaging (MRI), and age over 18 years. Exclusion criteria comprised evidence of haemorrhage on imaging or platelet function disorders, and concurrent use of additional antiplatelet, anticoagulant, or nonsteroidal anti-inflammatory medications. Clinical stroke severity was assessed upon admission using NIHSS and MRS scales, while aspirin resistance was determined via the Innovance PFA 200 system. One hundred consecutive patients presenting with acute ischemic stroke were enrolled in the study, visiting the neurology department. Upon admission, clinical stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (MRS) by trained personnel blinded to the diagnosis of aspirin resistance. Additionally, all patients underwent clinical examination, blood sampling, and CT or MRI within the first 48 hours. Subsequently, aspirin resistance was determined using the Innovance PFA 200 system.

The Innovance PFA 200 system enabled a rapid assessment of ASA-induced platelet dysfunction. Blood samples were collected immediately before regular daily ASA intake, and platelet clot formation was measured in 800 microliters of citrated whole venous blood using disposable cartridges. Collagen/epinephrine cassettes,

employed in the evaluation, are capable of detecting qualitative platelet defects, including ASA-induced platelet dysfunction. Closure time, the time required for platelet plug formation, was utilized as a parameter to assess platelet function. Normal closure time values in our laboratory ranged from 80 to 150 seconds, with ASA resistance defined as closure time <150 seconds despite regular ASA intake.

Statistical analyses, including Pearson correlation and ANOVA tests, were performed using SPSS 20.0 to explore the relationship between aspirin resistance and stroke severity, as well as the impact of various clinical and demographic factors on stroke severity categories. Results are presented as mean \pm SD and percentages. By using the Kruskal-Wallis test, the normal distribution of the variables was proven. T-test for quantitative, χ^2 test for qualitative variables, and Pearson correlation. $P < 0.005$ was considered statistically significant.

Description of Assessment Scales: The National Institutes of Health Stroke Scale (NIHSS) is an essential standardized tool for gauging the severity of stroke symptoms. It evaluates various neurological functions, including consciousness, language, and motor skills, and assigns scores from 0 to 42 to reflect the level of impairment. Primarily utilized during the acute phase of stroke, the NIHSS helps guide decisions regarding treatments such as eligibility for thrombolytic therapy. On the other hand, the Modified Rankin Scale (MRS) focuses on measuring functional disability and overall outcomes after a stroke, assessing the patient's independence in daily activities. This scale ranges from 0 to 6, where higher scores indicate more severe disability. MRS assessments are crucial for understanding long-term outcomes and for planning rehabilitation efforts. Both the NIHSS and MRS are critical in stroke management, serving different purposes at various stages of care and highlighting the need for a thorough understanding of their strengths and limitations in providing effective treatment.

RESULTS

Of the 100 patients analysed, 55 were male, with a mean age of 61 ± 9 years and a mean BMI of $27.71 \pm 4.21 \text{ kg/m}^2$. Aspirin resistance was observed in 32% of patients. The median NIHSS score and MRS were 3 and 1, respectively. NIHSS and MRS statistically significantly positively correlated with haemoglobin value ($r=0.198$ and $r=0.216$, $p < 0.05$ (0.048 and 0.031)), hematocrit ($r=0.251$ and $r=0.283$, $p < 0.05$ and $p < 0.01$ (0.012 and 0.004) and

triglycerides ($r=0.202$ $r=0.219$, $p<0.05$ (0.044 and 0.028)). Only NIHSS was statistically significantly positively correlated with patients' age ($r=0.193$, $p=0.044$). There was no statistically significant correlation between the severity of the clinical presentation, assessed by NIHSS and MRS, and ASA resistance. The age of the patients was statistically significantly positively correlated with ASA resistance ($r=0.210$, $p<0.05$). We categorized stroke severity as assessed by the NIHSS score into 5 categories: no symptoms (score 0), minor (score 1-4), moderate (score 5-15), moderate to severe (score 16-20) and severe (score of 21-42) stroke. NIHSS and MRS scores demonstrated statistically significant positive correlations with hemoglobin, hematocrit, and triglyceride levels ($p<0.05$). NIHSS also correlates significantly with patient age ($p<0.05$). However, no significant correlation was found between aspirin resistance and stroke severity assessed by NIHSS/MRS. Age showed a positive correlation with aspirin resistance ($p<0.05$). Using ANOVA haemoglobin, hematocrit, age, fasting glycemia, and presence of diabetes mellitus had a statistically significant effect on stroke severity category ($p<0.05$) (Table 1).

Table 1. Influence of analyzed parameters on stroke severity

ANOVA						
		Sum of Squares	df	Mean Square	F	Sig.
HGB	Between Groups	3007,181	4	751,795	3,187	,017
	Within Groups	22409,569	95	235,890		
	Total	25416,750	99			
HbA1c	Between Groups	13,110	4	3,278	1,027	,398
	Within Groups	303,212	95	3,192		
	Total	316,322	99			
Glucose	Between Groups	87,593	4	21,898	2,696	,035
	Within Groups	771,607	95	8,122		
	Total	859,200	99			
TRG	Between Groups	8,541	4	2,135	1,630	,173
	Within Groups	124,449	95	1,310		
	Total	132,990	99			
HOL	Between Groups	1,508	4	,377	,236	,917
	Within Groups	151,631	95	1,596		
	Total	153,139	99			

urea	Between Groups	3,949	4	,987	,247	,911
	Within Groups	379,600	95	3,996		
	Total	383,548	99			
creatinin	Between Groups	981,901	4	245,475	,387	,817
	Within Groups	60230,216	95	634,002		
	Total	61212,117	99			
ASA	Between Groups	22367,928	4	5591,982	1,200	,316
	Within Groups	442783,312	95	4660,877		
	Total	465151,240	99			
ACA resistant	Between Groups	,526	4	,131	,588	,672
	Within Groups	21,234	95	,224		
	Total	21,760	99			
gender	Between Groups	1,211	4	,303	1,222	,307
	Within Groups	23,539	95	,248		
	Total	24,750	99			
age	Between Groups	901,484	4	225,371	2,734	,033
	Within Groups	7832,476	95	82,447		
	Total	8733,960	99			
BMI	Between Groups	147,122	4	36,780	2,170	,078
	Within Groups	1610,112	95	16,949		
	Total	1757,234	99			
alcohol	Between Groups	,295	4	,074	,637	,638
	Within Groups	11,015	95	,116		
	Total	11,310	99			
smoking	Between Groups	1,050	4	,263	1,057	,382
	Within Groups	23,590	95	,248		
	Total	24,640	99			
PLT	Between Groups	4484,744	4	1121,186	,275	,893
	Within Groups	387073,046	95	4074,453		
	Total	391557,790	99			
HCT	Between Groups	203,443	4	50,861	3,604	,009
	Within Groups	1340,842	95	14,114		
	Total	1544,285	99			

HTA	Between Groups	,081	4	,020	,301	,877
	Within Groups	6,429	95	,068		
	Total	6,510	99			
DM	Between Groups	10,637	4	2,659	2,832	,029
	Within Groups	89,203	95	,939		
	Total	99,840	99			
KVB	Between Groups	,834	4	,209	,931	,449
	Within Groups	21,276	95	,224		
	Total	22,110	99			
HBI	Between Groups	,051	4	,013	,216	,929
	Within Groups	5,589	95	,059		
	Total	5,640	99			
CLO	Between Groups	1330,938	2	665,469	,068	,934
	Within Groups	234560,914	24	9773,371		
	Total	235891,852	26			

DISCUSSION

The study aimed to explore the potential relationship between aspirin resistance (AR) and the clinical severity of ischemic stroke, assessed by the National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (MRS). Contrary to initial expectations, our findings revealed no statistically significant correlation between aspirin resistance and stroke severity measured by both scales. This indicates that factors beyond aspirin responsiveness may play a more substantial role in determining stroke severity. Our study's methodology involved analyzing data from one hundred consecutive patients with acute ischemic stroke, enhancing the reliability of our findings. Notably, approximately one-third of the patients exhibited aspirin resistance, highlighting a sizable proportion at risk of suboptimal response to aspirin therapy. Despite this, the lack of association between aspirin resistance and clinical severity suggests the involvement of other contributing factors.

While NIHSS and MRS demonstrated significant positive correlations with certain clinical parameters such as hemoglobin, hematocrit, triglycerides, and age, no such correlation was observed between aspirin resistance and NIHSS/MRS scores. This implies that clinical stroke severity may not be directly influenced by aspirin

responsiveness alone, indicating the complexity of stroke outcomes. Despite the identification of various potential mechanisms the underlying reasons for aspirin resistance and therapeutic failure are not fully understood [1]. These mechanisms range from patient non-compliance and inadequate dosing to poor absorption and enhanced metabolism of aspirin. Additionally, the biosynthesis of TXA2 through pathways not blocked by aspirin, alternative platelet activation routes not affected by aspirin, smoking habits, and hypercholesterolemia contribute to this phenomenon.

In a study involving 310 patients [2] diagnosed with acute ischemic stroke, high residual platelet reactivity (HRPR), indicative of aspirin resistance, was detected in 27.7% of cases. Those with HRPR displayed elevated initial stroke severity, with a median NIH Stroke Scale score of 6 compared to 3 in non-HRPR patients. Additionally, HRPR patients exhibited larger infarct volumes on diffusion-weighted imaging (DWI). Through multivariable analysis, HRPR was identified as significantly correlated with a 2.1-point increase in NIH Stroke Scale score and a 2.3 cm(3) rise in DWI infarct volume, indicating its predictive role in severe strokes and larger infarct sizes among aspirin-using individuals. A study from Colombia[3] investigating the prevalence of AR in ischemic stroke patients and healthy controls has illuminated key aspects of antiplatelet therapy. The research suggests a substantial link between AR and a history of prior ischemic strokes, which may indicate a connection to recurring strokes[4] [5]. This finding is consistent with earlier studies that associate AR with an increased risk of severe vascular events. Additionally, the detection of AR in healthy controls raises questions about the effectiveness of aspirin as a primary preventive measure, suggesting that AR testing might be warranted before starting aspirin therapy. Although the study did not reveal a statistically significant difference in AR prevalence between patients and controls, it points to the potential for developing secondary AR through prolonged use of aspirin[3]. Furthermore, the complexity of AR stems from various factors, including patient adherence, dosing, absorption, metabolism of aspirin, and alternative platelet activation pathways. Notably, inadequate medication adherence emerges as a significant contributor to AR, potentially being one of the primary causes [6]. Additionally, elevated platelet turnover associated with underlying inflammatory conditions like atherosclerosis and its complications can accelerate platelet regeneration, including COX-1, thereby diminishing the efficacy of

once-daily dosing [7]. Recent advancements include the identification of platelet glycoprotein IIIa as a potential biomarker and underlying mechanism for aspirin resistance, as well as the discovery of an anion efflux pump responsible for expelling intracellular aspirin from platelets [8]. Moreover, the genetic underpinnings of AR are suggested by its occurrence in healthy individuals, and ongoing research is investigating polymorphisms of COX enzymes and platelet surface receptors[9] (Goodman T., 2007).

In a study of 50 patients [10] with recurrent stroke, comorbidities like hypertension, diabetes, and hyperlipidemia were prevalent. Most recurrent stroke patients were elderly (>60 years), hypertensive, and non-compliant with aspirin. Aspirin resistance correlated with antiplatelet on-compliance. Elevated inflammatory biomarkers (hsCRP, PLA2, TNF- α) were observed compared to controls, suggesting a link between inflammation, atherosclerosis, and ischemic stroke [11]. While previous studies examined inflammatory biomarkers in stroke, their role in predicting recurrence remains unclear. The positive correlation between age and aspirin resistance raises intriguing questions about the interplay between age-related factors, aspirin response, and stroke severity. As age is a known risk factor for stroke, understanding its relationship with aspirin resistance could have implications for planning treatment strategies and risk assessment in older stroke patients.

CONCLUSION

In conclusion, while aspirin resistance was prevalent among acute stroke patients, it did not significantly impact clinical severity as assessed by NIHSS and MRS. This underscores the necessity for further exploration of additional factors influencing stroke outcomes and the development of personalized treatment approaches in stroke management. Further research is needed to clarify the complex interplay between aspirin resistance, age, and stroke severity, offering valuable insights for optimizing stroke management strategies.

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