The Effect of D- Dimer in Predicting Prognosis Among Ischemic Stroke Patients in Aseer Region, Saudi Arabia, A Clinico-Epidemiologic study

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1. Abstract

Background: Stroke is a major Cerebro-vascular disease resulting in high mortality and persistent disability in adults across the world, WHO reported in 2012 that stroke was the second leading cause of death in KSA.

Objectives: To assess neurological changes among Cerebro-vascular Accident (CVA) patients at the same time as D-dimer being measured and to test the predictive capacity of D-dimer to detect clinical improvement and correlate it with National Institute of health Stroke Scale (NIHSS).

Subjects and methods: A Prospective longitudinal then comparative case control study based on NIHSS was carried out. All CVA patients admitted to AFHSR in a Period of three months from January 1st till April 1st 2016 was included in the study, every patient was evaluated according to NIHSS at the 10th day of admission, D-dimer was measured and every patient was followed for three months then evaluated to either improved or not.

Results: D-dimer showed to be significant (p=0.02) after three months follow up which means that D-dimer level can predict whether the cases of ischemic CVA can improve or not.

Conclusion: D-dimer can play a role in predicting prognosis among ischemic CVA patients.

2. Keywords: Stroke; Cerebro-Vascular Accident; D-dimer

3. Introduction

Stroke is a major cerebrovascular disease resulting in high mortality and persistent disability in adults

across the world. Besides coronary heart disease and cancer, stroke is the commonest cause of death in most industrialized countries. The Kingdom of Saudi Arabia (KSA) is the largest country in the Middle East occupying approximately four-fifths of the Arabian Peninsula supporting a population of more than 28 million. Stroke is becoming a rapidly increasing problem and an important cause of illness and deaths in Saudi Arabia.

Few researches have been done on incidence and prevalence of stroke in Saudi Arabia but over the past decade there was one study which reported that the crude incidence rate for first-ever incidence of stroke in Saudi Arabia was 29.8/100,000/year. They also reported that ischemic strokes (69%) predominated and Sub-Arachnoid Hemorrhage (SAH) was extremely rare (1.4%) [1].

D-dimer is a fibrin degradation product generated during fibrinolysis, and levels are elevated in the setting of active clot formation and turnover [2].

In clinical practice, D-dimer levels are incorporated into diagnostic algorithms used to identify patients with deep vein thrombosis and pulmonary embolism. In addition, measurement of D-dimer in the setting of cryptogenic stroke is helpful to assess the likelihood of cancer-related hypercoagulability, though optimal cutoff values for individual assays are undefined. Similar to its role in deep vein thrombosis, D-dimer may be useful for evaluation of prognosis in patients with suspected ischemic cerebral stroke [3].

In 2016 tow researches has been published, one discusses the relation between D-Dimer and the International Normalized Ratio of Prothrombin time in ischemic Stroke Patients treated with Sufficient Warfarin which conclude that the D-dimer level correlated positively and significantly with the volume $(r = .49, P < .05)$, severity $(r = .54, P < .05)$, and outcome of ischemic stroke $(r = .61, P < .01)$ and did not correlate with the PT-INR $(r = -0.27, P = 0.23)$ [4].

The 2nd was in Taiwan published in the same year

concluded that in univariate analysis, patients with unfavorable outcome (n = 79) had significantly higher levels of D-dimer than those with favorable outcome (median D-dimer = 1.4 vs. 0.7 µg/ml, p <0.001). After adjustment for clinical variables, a higher level of D-dimer remained significantly associated with an unfavorable outcome (OR 1.90, 95% CI 1.27-2.86, p = 0.002) and the occurrence of symptomatic ICH (OR 2.97, 95% CI 1.15-7.70, p = 0.025).

This means that D-dimer level within 24 h after stroke onset can be an early outcome indicator in Acute Ischemic Stroke patients receiving recommended therapy [5].

Other study conclude that the biomarker was correlated significantly with the severity and disability of stroke at onset and 30 days [6].

While this study conclude that patients had the best outcome with the lowest level of D-dimer. High-level plasma D-dimer of acute period strongly indicates an unfavorable clinical outcome [7].

In 2011 total of 382 patients were included in the analyses. Levels of D-dimer and other markers of hemostatic activation were not significantly higher in patients with stroke progression than in other patients [8].

4. Study Rational and Objectives

There are a small number of studies about D-dimer with contradictory result so more studied are needed to reach final Conclusion. There are no known research done in the kingdom of Saudi Arabia to evaluate prognosis of ischemic CVA [cerebro vascular accident] using D-dimer level. Assessing D-dimer capability of predicting prognosis in ischemic CVA will help in assessing new management strategy.

5. Subjects and Methodology

Prospective longitudinal then comparative case control study including all CVA patients conscious and were willing to participate who's admitted to [AFHSR] armed force hospital southern region in a

Period of three months from January 1st till April 1st 2016. Excluded Patients were those with hemorrhagic stroke, DVT, PE and Thrombophilia.

All patients were interviewed and all clinical and laboratory data was collected. First interview was done 10 days from admission after passing acute stage and after first recommended assessment with National Institute of health Stroke Scale [NIHSS] scale for clinical improvement. D-dimer was measured at 10th day to be correlated with clinical Improvement after three months.

All cases are followed up for three months for Neurological Improvement as end point measured as recommended by NIHSS score. The cases were divided according to neurological improvement to improved and not improved and the comparison was done between both groups. The outcome after three months was in a form of binary dichotomous in form of improved and not improved.

Data Collecting Tool using sociodemographic data and medical sheet data and NIHSS scale, the NIHSS

score can was assessed by a neurologist as well as non-neurologists after appropriate training [9,10].

6. Statistical Analysis

The results were edited, coded and entered on SPSS for IBM version 22. The data described as mean and Standard deviation and percentage. Mann-Whitneytest, t-test, Chi-square and Odds ratios (OR), 95% confidence intervals (95%CI) was calculated. ROC curve to determine cut off value for the 10th day measure with highest sensitivity and specificity to predict improvement of cases. P value less than 0.05 was considered significant.

Administrative and Ethical approval were obtained before starting the research. Informed consent was obtained from every participant in the study. This study was done according to the principles of World Medical Association (WMA) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects [11]. Confidentiality and privacy was guaranteed for all participant.

7. Results

Table 1: Demographic characteristics of the studied group (n=54).

Variable	Description	No. [%]
Gender	Male	33 [61.1%]
	Female	21 [38.9%]
Marital	Single	1 [1.9%]
Status	Married	50 [92.5%]
	Widow	3 [5.6%]
Educational	Illiterate	34 [63%]
Level	Primary	12 [22.2%]
	Secondary	2 [3.7%]
	High school	6 [11.1%]
Job	Governmental	7 [13%]
	Employee	
	Retired	26 [48.1%]
	House wife	20 [37%]
	None	1 [1.9%]
Residence	High altitude	24 [44.4%]
	Low altitude	30 [55.6%]
Income	Sufficient and save	54 [100%]

Age	Mean ± SD[min:max]	68.85 ±11.23 [18:90]
	Median	70

Table 2: Risk factors among studied group.

Variable	No.	%
Stress	3	5.6
Hypertension	32	59.3
Dyslipidemia	25	46.3
Smoking	10	18.5
D.M.	33	61.1
Over weight	0	0
Sedentary life	24	44.4
Ageing	43	79.6
Family history	11	20.4
Cardiac disease	1	1.9

Table 3: Prognosis among cases after 3 months follows up Period according to quantitative parameter.

	Improved (48)	Not improved (6)	Statistical test	P
Age	68.85± 11.83	68.83± 4.4	t=0.004	0.99
Mean ± SD				
D-dimer	1[0.35:33]	0.47[0.47:3.83]	Z= 2.29	0.02*
Median[min:max]				
NIHSS Median[min:max]	2[1:27]	6[6:34]	Z=1.51	0.144

Table 4: Receiver operating characteristic curve and Area Under the Curve.

Test Result Variable(s):D DIMERLEVEL	
Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval
	Lower Bound
0.022	0.547
a. Under the nonparametric assumption	
b. Null hypothesis: true area = 0.5	

Test Result Variable(s): D-DIMERLEVEL.

Positive if Greater Than or Equal To	Sensitivity	Specificity
0.5	0.917	0.833

Table 5: Prognosis among cases after 3 months follows up Period according to associated risk factors.

Variable	Description	Not	Improved	P	OR [95 % CI]
Stress	Yes	1[16.7%]	2[4.2%]	0.2	4.66[0.35-60.2]
	No	5[83.3%]	46[95.8%]		
Hypertension	Yes	0[0%]	32[66.7%]	0.002**	1.37[1.06-1.77]
	No	6[100%]	16[33.3%]		
Dyslipidemia	Yes	5[83.3%]	20[41.7%]	0.054	7[0.75-64.6]
	No	1[16.7%]	28[58.3%] [68.8%]		
Smoking	Yes	5[83.3%]	5[10.4%]	<0.001***	43[4.1-445]
	No	1[16.7%]	43[89.6%]		
D.M.	Yes	5[83.3%]	28[58.3%] [68.8%]	0.23	3.5[0.38-32.9]
	No	1[16.7%]	20[41.7%]		
Over weight	Yes	0[0%]	0[0%]	1	-
	No	6[100%]	48[100%]		
Sedentary life	Yes	5[83.3%]	19[39.6%]	0.042*	7.6[0.82-70.5]
	No	1[16.7%]	29[60.4%]		
Ageing	Yes	6[100%]	11[22.9%]	0.18	0.86[0.7-0.97]
	No	0[0%]	25[52.1%]		
Family history	Yes	5[83.3%]	6[12.5%]	<0.001***	35[3.47-353]
	No	1[16.7%]	42[87.5%]		
Cardiac disease	Yes	0[0%]	1[2.1%]	0.72	1.12[1.02-1.24]

8. Discussion

In table1 there were a total of (54) cases age ranged from (18) years old and (90) years old with a mean of 68.85, standard deviation of 11.23 and a median of 70. More than half of the cases were males and the rest were females. Only one case was single, three were widow and the rest were married.

Also, about third of cases didn't receive any education and most of those people were very old in age so they didn't catch up in the illiterate fighting program that was established by the government at the beginning of the first development program which was launched 40 years ago in the year 1970 [12].

Almost half of the cases were retired as they reached

the retirement age, almost all of the females were house wives, and one case had no job as she still a student and the rest work in the government. Almost half of the cases lived in high altitude and the other half live in low altitude and that is normal due to the geographical location of ASEER region where it is 2200 meter above sea level [13]. And it is connected to the west coast by a very short distance road that goes done the mountains of ASEER to sea level.

In the demographic characteristics of the study group all of the cases had a sufficient income which is normal considering they live in a wealthy country.

In table 2 most of the risk factors were related to sedentary life, dyslipidemia and chronic diseases HTN and DM while aging was the most dominant risk factor among the study group which proves that age is the single most important risk factor for stroke but Other risk factors like stress, smoking, overweight, family history and cardiac diseases were less obvious although they play an important role in CVA development in agreement with Sacco RL research who reported that age is the most important CVA risk factor [14].

In table 3 after analyzing the quantitative data for prognosis after three months, all showed to be non-significant except the level of D-dimer which showed to be significant (p=0.02) after three months follow up which means that D-dimer level can predict weather the cases of ischemic CVA can improve or not.

12. References

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This result prove what was mention in the literature review which said that out of the 19 article reviewed 16 indicates that D-dimer can predict the prognosis among ischemic CVA patients with a sensitivity of (92%) and a specificity of (83%) as shown in table 4, the area under the curve was 0.788(95% confidence interval [CI], 0.547–1) as shown in which is almost near to the result demonstrated by the Chinese prospective observational study done in 2014 where sensitivity of 83.7% and a specificity of 81.5%, the area under the curve was 0.862(95% confidence interval [CI], (0.811–0.912) [15].

In table 5 showing the prognosis after three months follow up related to risk factors HTN (p=0.002), smoking (p<0.001), sedentary life (p=0.042) and family history (p<0.001) showed to play a significant role in preventing good prognosis among the cases [14].

9. Conclusion

This study prove that D-dimer can play a very important role in predicting prognosis among ischemic CVA patients which will help later on in planning an testing different models of therapy according to the predicted prognosis which will have a great impact on the recovery of CVA patients.

10. Conflict of interests:
The authors have declared that they have no competing interests.

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