



The Outcome of Acute Ischemic Stroke in Sudanese patients on Dual Anti-platelet Therapy Clopidogrel and Aspirin vs. Aspirin using modified Ranking scale at the National Centre for Neurological Science

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Article info

Received 26 February 2019

Revised 25 March 2019

Published 09 April 2019

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Abstract

Background: Stroke or cerebrovascular accident (CVA) is defined as the sudden occurrence of a focal, non-conclusive neurological deficit; with variable consequences, ranging from subtle to very severe disabilities, depending on the area of the brain involved and the nature of the attack. Anti-platelet therapy such as aspirin and clopidogrel is used for both management and prevention of stroke, it reduced the incidence of stroke in patients at high risk for atherosclerosis and in those with known symptomatic cerebrovascular disease.

Objective: To assess the difference in the outcome of dual anti platelet therapy clopidogrel and aspirin vs. aspirin, in acute ischemic stroke using Modified Ranking scale.

Methods: A prospective Cohort study was conducted at the National center of neurological Science within the period of Jan- December 2018. Data collected through structural closed ended questionnaire. Data entered, cleaned, analyzed using SPSS version 25.0. The change in the outcome using Modified Ranking Scale after treatment was done.

Results: This study covered 92 study participants, 75% were above 60 years of age, with ratio male: female. 1.2: 1. 45.6% were housewives while 95.1% were from rural residential areas. 93.5% complained of weakness, dysphasia 60.9%, loss of consciousness 19.6% and swallowing difficulties among 15.2%. Investigations showed 54.3% had middle cerebral artery occlusion, 18.5% had lacunar infarcts, 10.9% had vertebral-and basilar artery occlusion while only 1.1% had cavernous sinus thrombosis. 9.8% had abnormal complete blood count results, 12% had abnormal renal functions, 16.3% had abnormal random blood glucose, and 28.3% had abnormal urine analysis results. In this study, cross tabulation was done to assess the possible association between the type of treatment given in presentation with the change in Modified Rankin Scale using t paired statistical test. The analysis found that there was a significant reduction in Modified Rankin Scale from 4.2 to 3.2 (p value < 0.001) among all study participants. The difference in Modified Rankin Scale was higher among patients who used aspirin with clopidogrel from 4.1 to 2.3 compared to patients who used aspirin only from 4.2 to 3.5 with p value less than 0.05.

Conclusion: The study concluded there is a significant improvement in the outcome of stroke during follow up using modified Ranking Scale in patients who used dual anti platelet vs. aspirin only. The combination therapy is superior to aspirin alone regarding the management, prevention and the outcome. Furthermore, it does not increase the risks of haemorrhage.

Citation: Ibrahim EAA, Ahmed MAM. *The Outcome of Acute Ischemic Stroke in Sudanese patients on Dual Anti-platelet Therapy Clopidogrel and Aspirin vs. Aspirin using modified Ranking scale at the National Centre for Neurological Science. J Neurol Neurosurg Psychiatry Res 2019; 1: 105. doi: [10.31531/edwiser.jnnpr.1000105](https://doi.org/10.31531/edwiser.jnnpr.1000105)*

Keywords: Dual Anti-platelet; Stroke, Sudan; Clopidogrel; Aspirin; Acute Ischemic Stroke

Introduction

Stroke or cerebrovascular accident (CVA) is defined as the sudden occurrence of a focal, non-conclusive neurologic deficit; with variable sequences, ranging from subtle to very severe disabilities, depending on the area of the brain involved and the nature of the attack. Stroke is caused by the interruption of the blood supply to the brain, usually because a blood vessel bursts or is blocked by a clot. This cuts off the supply of oxygen and nutrients, causing damage to the brain tissue [1,2].

Stroke is the fifth cause of death if considered separately from other cardiovascular diseases. In the United States, an estimated 795,000 strokes occur annually, and the prevalence of stroke increases with age. The lifetime risk of all strokes is higher in women; however, this is attributed to longer life-expectancy.

Statistics showed that there are more than one hundred thousand strokes each year that is around one stroke every five minutes, according to the latest WHO data published in May 2014 stroke deaths in Sudan reached 16,053 or 6.6% of total deaths [3,4].

The main risk factor for stroke is high blood pressure [5]. Other risk factors include tobacco smoking, obesity, high blood cholesterol, diabetes mellitus, a previous TIA, and atrial fibrillation. An ischemic stroke is typically caused by blockage of a blood vessel, though there are also less common cause. A hemorrhagic stroke is caused by either bleeding directly into the brain or into the space between the brain's membranes [3]. Bleeding may occur due to a ruptured brain aneurysm. Diagnosis is typically based on a physical exam and supported by medical imaging such as a CT scan or MRI scan. A CT scan can rule out bleeding, but may not necessarily rule out ischemia, which early on typically does not show up on a CT scan. Other tests such as an electrocardiogram (ECG) and blood tests are done to determine risk factors and rule out other possible causes. Low blood sugar may cause similar symptoms [4].

Prevention includes decreasing risk factors, as well as possibly aspirin, statins, surgery to open up the arteries to the brain in those with problematic narrowing, and warfarin in those with atrial fibrillation. A stroke or TIA often requires emergency care. An ischemic stroke, if detected within three to four and half hours, may be treatable with a medication that can break down the clot.

aspirin should be used. Some hemorrhagic strokes benefit from surgery. Treatment to try to recover lost function is called stroke rehabilitation and ideally takes place in a stroke unit; however, these are not available in much of the world [4].

Early rehabilitation for stroke patients is beneficial and should be performed. Very early rehabilitation, within 24 h, should not be performed. The AVERT trial randomized patients to receive very early rehabilitation within 24 h of stroke compared to usual stroke-unit care and early mobilization demonstrated less favourable outcomes using the modified Rankin's score [4].

The role of anticoagulation in the treatment of cerebral ischemia has changed, for many years, it was used routinely in acute ischemic stroke, however more recent studies are helping to refine it is role in the treatment and prevention of stroke [6].

Aspirin is used for prophylaxis of TIA and or stroke except in patients with an allergy to aspirin or salicylate, clopidogrel is used to reduce future atherosclerotic events in patients with recent stroke. Combination of clopidogrel and aspirin is used to reduce future atherosclerotic events in patients with recent stroke or patients who had a stroke while on clopidogrel [5].

Anti-platelet therapy is used for both the management of acute ischemic stroke and for the prevention of stroke, Anti platelet therapy reduced the incidence of stroke in patients at high risk for atherosclerosis and in those with known symptomatic cerebrovascular disease [7].

Clopidogrel in high risk patients with acute non disabling cerebrovascular events (CHANCE) showed that the combined treatment of clopidogrel and aspirin decreases the 90-day risk of stroke without increasing haemorrhage compared with aspirin alone but provided insufficient data to establish whether the benefit persisted over longer period of time beyond the trial termination [8].

This study was intended to assess the combination therapy of clopidogrel with aspirin outcome in protection against subsequent stroke than aspirin alone.

Objective

To assess the difference in the outcome of Sudanese patients on dual anti platelet therapy clopidogrel and aspirin vs. aspirin alone using modified Ranking scale in acute ischemic stroke.

Materials and Methods

This is a prospective Cohort study conducted at the National Center of Neurological Sciences, Khartoum within the period of Jan-Dec 2018. 92 Sudanese patients diagnosed as ischemic stroke and followed up over one year were included.

Data was collected using comprehensive, structured, questionnaire. Including demographics, clinical, risk factors, treatment, side effect and the outcome of the studied participants. Data was analyzed using SPSS version 25.0.

Represented after analysis in form of univariable tables, cross tabulation (bi variable tables), figures and narrative illustration value of 0.05 or less is considered statistically significant.

Written ethical clearance and approval for conducting this study was obtained from the Administrative authority of the National Centre of Neurological Science. And consent was taken from the study participants.

Result

This study covered 92 patients, 75% were above 60 years with 1.2:1, male:female ratio. 45.6% were housewives. The commonest symptoms were weakness (93.5%), dysphasia (60.9%), loss of consciousness (19.6%) and swallowing difficulties among (15.2%).

Nearly two thirds of the studied participants were hypertensive, (26.1%) were diabetic, (19.6%) had valvular lesion, (14.1%) had previous ischemic stroke or TIA, (12%) Hyperlipidemia, (6.5%) were smokers and (6.5%) had atrial fibrillation (**Tables 1-3**).

Cardiovascular examination showed (19.6%) of the study participants were not in sinus rhythm, (58.7%) had high blood pressure and only 19.6% had valvular lesions. 22.8% presented with impairment of level of consciousness, 89.1% had cranial nerves affection, 44.6% had grade 0 in power, 52.2% were hypertonic, 54.3% with hyper-reflexia, 50% had up going planter reflex and only 7.6% had affected sensory system (**Tables 4 and 5**).

Regarding the investigation results, the study found that 9.8% had abnormal complete blood count results, 12% had abnormal renal functions, 16.3% had abnormal random blood glucose, 50% had abnormal level of C-reactive protein, and 28.3 had abnormal urine analyses results. Brain imaging showed, 54.3% had middle cerebral artery occlusion, 18.5% had lacunar infarcts, and 10.9% had occlusion in vertebral basilar artery while only 1.1% had cavernous sinus thrombosis (**Table 6**).

Table 1: Demographical characteristics of participants (n=92).

Demographical characteristics	Frequency	Percentage	
Age in years	20 - 30	2	2.2
	31 - 40	3	3.3
	41 - 50	9	9.8
	51 - 60	9	9.8
	> 60	69	75
Gender	Male	51	55.4
	Female	41	44.6
Occupation	House wife	42	45.6
	Worker	16	17.4
	Retired	12	13
	Farmer	10	10.9
	Employee	3	3.3
	Student	2	2.2
	Driver	1	1.1
	Mechanics	1	1.1
	Carpenter	1	1.1
	Merchant	1	1.1
	Animal	1	1.1
	Lecturer	1	1.1
	Not working	1	1.1
Residence	Rural	47	51.1
	Urban	45	48.9

The study found that 29.3% of the study participants had pneumonia, 25% had urinary tract infection, 5.4% had haemorrhagic stroke, 3.35% had deep vein thrombosis, and only 1.1% had bed sore. 70.7% of the studied patients used aspirin alone, while (29.3%) used aspirin and clopidogrel.

Modified Rankin Scale was used in this study two times; once before the medication taken and the other

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3months after the medication. The difference in Modified Rankin Scale were used as an indicator for the effect of the treatment used on the functional outcome.

Table 2: Distribution of the study participants according to their clinical presentation (n=92).

Clinical presentation	Frequency	%
Weakness	86	93.5
Swallowing difficulty	14	15.2
Loss of consciousness	18	19.6
Dysphasia	56	60.9
Urine incontinence	5	5.4
Others	2	2.2

Table 3: Distribution of the study participants according to the presence of previous risk factors (n=92).

Previous risk factors	Frequency	%
Diabetes	24	26.1
Hypertension	57	62
Previous ischemic stroke or TIA	13	14.1
Atrial fibrillation	6	6.5
Valvular lesion	18	19.6
Smoking	6	6.5
Hyperlipidemia	11	12
DCM	2	2.2

**Note: Some study participants had more than one previous risk factor*

In this study, cross tabulation was done to assess the possible association between the type of treatment given at presentation with the change in Modified Rankin Scale using t paired statistical test. The analysis found that there was a significant reduction in Modified Rankin Scale from 4.2 to 3.2 (p value <0.001) among all study participants. The difference in Modified Rankin Scale was higher among patients who used aspirin with clopidogrel from 4.1 to 2.3 compared with patients who used aspirin only from 4.2 to 3.5 with p value less than 0.05 (Tables 7-10).

Table 4: Distribution of the study participants according to the examination findings-cardiovascular system (n=92).

Cardiovascular system findings		Frequency	%
Pulse rate	Sinus rhythm	74	80.4
	Not in sinus rhythm	18	19.6
Blood Pressure	Normal	32	34.8
	Average	6	6.5
	High	54	58.7
Valvular lesion	Yes	8	8.7
	No	84	91.3

Table 5: Distribution of the study participants according to the examination findings-Neurological findings (n=92).

Neurological findings		Frequency	%
Impairment of level of consciousness	Yes	21	22.8
	No	71	77.2
Cranial nerve affection	Affected	82	89.1
	Not affected	10	10.9
Power grade	G0	41	44.6
	G1	18	19.6
	G2	18	19.6
	G3	11	12
	G4	3	3.3
	G5	1	1.1
	Hypertonia	48	52.2
Tone	Normal tone	1	1.1
Reflex	Hypotonia	43	46.7
	Hyper-reflexia	50	54.3
	Normal reflexia	4	4.3
	Hypo-reflexia	38	41.3

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	down going	3	3.3
Planter reflex	Mute	43	46.7
	Up-going	46	50
Sensory system	Affected	7	7.6
	Not affected	85	92.4

Moderate severe disability	31	33.7	23	25
Severe disability	44	47.8	3	3.3
Dead	0	0	12	13
Total	92	100	92	100

Table 6: Distribution of the study participants according investigations results (n=92).

Investigations results		Frequency	%
CBC	Normal	83	90.2
	Abnormal	9	9.8
RFT	Normal	81	88
	Abnormal	11	12
RBG	Normal	77	83.7
	Abnormal	15	16.3
CRP	Normal	46	50
	Abnormal	46	50
Urine analysis	Normal	66	71.7
	Abnormal	26	28.3
Imaging findings	Middle CA	50	54.3
	Lacunar infarct	17	18.5
	Vertebral basilar artery	10	10.9
	Posterior CA	10	10.9
	CVT	1	1.1
	None	4	4.3

Table 8: Distribution of the study participants according Modified Rankin Scale for patients who treated with aspirin and clopidogrel.

Scale	Modified Rankin Scale			
	Pre-medication		After follow-up	
	Frequency	%	Frequency	%
No symptoms	0	0	3	4.6
No significant disability	3	4.6	3	4.6
Slight disability	1	1.5	10	15.4
Moderate disability	8	12.3	15	23.1
Moderate severe disability	21	32.3	21	32.3
Severe disability	32	49.2	3	4.6
Dead	0	0	10	15.4
Total	65	100	65	100

Table 7: Distribution of the study participants according Modified Rankin Scale (n=92).

Scale	Modified Rankin Scale			
	Pre-medication		After follow-up	
	Frequency	%	Frequency	%
No symptoms	0	0	7	7.6
No significant disability	5	5.4	6	6.5
Slight disability	1	1.1	18	19.6
Moderate disability	11	12	23	25

Table 9: Distribution of participants at medication used at presentation.

Medication used at presentation	Mean Modified Rankin Scale		P-value
	Pre-medication	After follow-up month	
Aspirin alone	4.2	3.5	<0.001
Aspirin with clopidogrel	4.1	2.3	<0.001
Overall average	4.2	3.2	<0.001

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Table 10: Difference in modified Rankin scale according to the Medication used at presentation (n=92).

Scale	Modified Rankin Scale			
	Pre-medication		After follow-up month	
	Frequency	%	Frequency	%
No symptoms	0	0	4	14.8
No significant disability	2	7.4	3	11.1
Slight disability	0	0	8	29.6
Moderate disability	3	11.1	8	29.6
Moderate severe disability	10	37	2	7.4
Severe disability	12	44.4	0	0
Dead	0	0	2	7.4
Total	27	100	27	100

Discussion

This study aimed to assess difference in the outcome of dual anti platelet therapy clopidogrel and aspirin and aspirin alone, in acute ischemic stroke after one month and covered 92 study participants; three quarters of them (75%) were above 60 years in age, with 1.2:1 male: female ratio. Similarly, Wang et al. found that in the general population, men have been found to experience more ischemic strokes whereas women tend to have more infarctions involving the anterior circulation [9]. Moreover, other study by Pan et al. reported that the incidence of ischemic stroke is lower in women than men [10].

Concerning the clinical presentation, our study found that most of the study participants complained of weakness (93.5%), dysphasia (60.9%), loss of consciousness (19.6%) and swallowing difficulties among (15.2%). Similar results were obtained with other Chinese study by Zhou et al. reported that the most common presenting symptoms for ischemic stroke are difficulty with speech and weakness on one half of the body. Many stroke mimics exist; two of the most common are a postictal seizure and hypoglycaemia [11].

Regarding the previous risk factors, the study realized that nearly two thirds of the study participants were

hypertensive, (26.1%) were diabetic, (19.6%) had valvular lesion, (14.1%) had previous ischemic stroke or TIA, (12%) Hyperlipidemia, (6.5%) were smokers and (6.5%) had atrial fibrillation. These finding were in agreement with Wang et al. study, who realized that hypertension is a particularly important risk factor for atherosclerotic disease that can lead to ischemic stroke as well. Aalsom stated that Hyperlipidemia, on the other hand, is a particularly important risk factor for strokes due to atherosclerosis of extra cranial and intracranial blood vessels, just as it is a risk factor for coronary atherosclerosis. Atrial fibrillation is a risk factor for cardio embolic stroke [12].

As imaging has revolutionized acute ischemic stroke diagnosis and management, our study found that more than half of them (54.3%) had findings in middle cerebral artery, (18.5%) in lacunar infarcts, (10.9%) inn vertebral basilar artery while only (1.1%) had cavernous sinus thrombosis. Other study by Palacio et al. found that in some cases, CVA occurred in brain areas which supplied by more than one main cerebral artery. Among the ischemic strokes, the stenosis in main cerebral arteries was seen in 709 (70.1%) patients, consisting of 488 MCA strokes, 208 PCA strokes, and 53 ACA strokes [13].

Our study found that (29.3%) of the study participants had pneumonia, (25%) with urinary tract infection, (5.4%) had hemorrhagic stroke, (3.35) had deep vein thrombosis, and only (1.1%) had bed sources. These finding were in agreement with other study by Johnston et al. who stated that fever >38 degrees C (13.2%), severe arterial hypertension (7.5%) and pneumonia (7.4%) were the most frequent medical complications [14].

Regarding the treatment used at presentation, the study found that (70.7%) used aspirin alone, while (29.3%) used aspirin and clopidogrel. The study of clopidogrel in high risk patients with acute non disabling cerebrovascular events (CHANCE) showed that the combined treatment of clopidogrel and aspirin decreases the 90-day risk of stroke without increasing haemorrhage compared with aspirin alone but provided insufficient data to establish whether the benefit persisted over longer period of time beyond the trial termination [8].

In our study, the analysis found that there was a significant reduction in Modified Rankin Scale from 4.2 to 3.2 (p value < 0.001) among all the study participants. The difference in Modified Rankin Scale was higher

among patients who used aspirin with clopidogrel (from 4.1 to 2.3) compared with patients who used aspirin only (from 4.2 to 3.5) with p value less than 0.05. Similar results found by Wang et al. who concluded that the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the first 90 days and do not increase the risk of haemorrhage [9]. Moreover, Johnston et al. stated that the study concluded that in patients with minor ischemic stroke or high-risk TIA, those who received a combination of clopidogrel and aspirin had a lower risk of major ischemic events but higher risk of major haemorrhage at 90 days than those who received aspirin alone [14]. Similarly, Pan et al. concluded that clopidogrel-aspirin treatment may have a benefit of reducing stroke risk outweighing the potential risk of increased bleeding especially within the first 2 week compared with aspirin alone in patients with minor stroke or TIA [10].

Also, Wang et al. claimed that in patients with minor stroke or TIA, the combination of clopidogrel and aspirin appears to be superior to aspirin alone in improving the 90-day functional outcome, and this is consistent with a reduction in the rate of disabling stroke in the dual anti platelet arm [15]. Palacio et al. stated in their study that there is substantial relative risk reduction in stroke by clopidogrel plus aspirin vs. aspirin alone that is consistent across different trial cohorts. Major haemorrhage is increased by dual anti platelet therapy [13].

Moreover, Wang et al. similarly, claimed that for the patients with minor ischemic stroke and TIA, when treated within 24 h of the combination of clopidogrel-aspirin therapy, combination therapy (clopidogrel-aspirin) is superior to aspirin alone for preventing the risk of stroke and does not increase the risks of haemorrhage [12]. An explanation mentioned by SPS3 Investigators group that among patients with recent lacunar strokes, the addition of clopidogrel to aspirin did not significantly reduce the risk of recurrent stroke and did significantly increase the risk of bleeding and death [16].

The study had some limitations. The relatively limited number of study participant 92 study participants from one study area only may affect negatively the probability of found more significant relevant findings among patient with ischemic CVA in Sudanese hospitals.

Conclusion

Our study concluded that combination therapy clopidogrel with aspirin is superior to aspirin alone for preventing the risk of stroke and does not increase the risks of haemorrhage. There is significant improvement in the outcome of stroke during follow up using modified Ranking Scale in patients who used dual antiplatelet vs. aspirin only.

Conflict of Interest

None declared.

Funding

None declared.

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This manuscript was peer-reviewed

Mode of Review: Single-blinded

Academic Editor: Dr. Ruqaiyah Khan

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