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Addition of Low Molecular Weight Heparin to Antiplatelet in Patients with Stroke Ineligible for Thrombolysis: Can it Improve Outcome?

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Abstract

Objective: Stroke is one of the most frequent causes of death and disability, urgent thrombolytic therapy can save thousands of lives and disabilities but unfortunately not all patients are eligible for thrombolysis. Dual antiplatelet are superior to anticoagulants in management of stroke and the use of full dose anticoagulants alone or in combination with aspirin is still debatable and carry the risk of hemorrhagic complications.

Aim of study: We aimed to compare the use double antiplatelet (oral Aspirin plus Clopidogrel) versus oral aspirin plus subcutaneous low dose enoxaparin in treatment of progressing stroke ineligible for thrombolysis.

Methods: The study was carried out on fifty-six patients presented with progressing stroke from February 2017 to the end of January 2019. Patients eligible for thrombolytic therapy (recombinant tissue plasminogen activator (r-TPA), TIA, Hemorrhagic stroke and stroke with stationary course were excluded from the study. The included patients were randomly divided into two groups, group (A) were treated with double antiplatelet aspirin 81 mg plus Clopidogrel 75 mg preceded by the loading dose of both and group (B) were treated with aspirin plus subcutaneous enoxaparin 40 mg (Clexane) once daily for 3 days. After 3 days, both groups continued on double antiplatelet aspirin 81 mg plus Clopidogrel 75 mg.

Results: We found that, at time of discharge 59.3% of group A showed progression in neurological symptoms and remaining 40.7% showed improvement in neurological symptoms while in group B only 13.8% of patients showed progression and remaining 86.2% showed improvement at this time. After one month, 55.56% of group A and 89.66% of group B of patients showed improvement and after 3 months, 66.67% of group A and 89.66% of group B showed improvement with significant difference of the outcome between both groups

Conclusion: We concluded that aspirin plus enoxaparin 40 mg could be superior to aspirin plus Clopidogrel in the early treatment of stroke.

Keywords: Stroke; Aspirin; Clopidogrel; Enoxaparin

Introduction

Stroke is one of the most frequent causes of death and disability in developed countries, having an estimated overall adult prevalence of 2.5%. Arterial ischemic stroke (AIS) is one of the three leading causes of death in developed countries; with one death caused by stroke for each 15-18 total deaths [1]. Treatment on specialized stroke units is essential in secondary prevention leading to an 18-46% reduction of relative mortality and 29% reduction of assistance-depending disability [2]. Rapid administration of intravenous recombinant tissue-type plasminogen activator (r-tPA) to appropriate patients remains the mainstay of early treatment of acute ischemic stroke [3]. The benefit of the treatment diminishes significantly and is lost after 4.5 hours for IV treatment and after 6-8 hours for endovascular treatment. There are several limitations for use of r-TPA in certain patient populations including narrow time window and many patients are not candidates for IV thrombolysis due to various contraindications [3]. Acute aspirin is recommended for patients with acute ischemic stroke who are ineligible for thrombolysis [4]. Unfortunately, aspirin monotherapy has its limitations. It has been suggested that aspirin alone produces only a 10-15% relative risk reduction in stroke recurrence compared with placebo. Combination anti-platelet therapy seeks to block platelet aggregation through multiple mechanisms [5].

In 30% to 40% of stroke patients, clinical symptoms progress over minutes to days after onset [6]. Neurological worsening or progression was defined as an increase in National Institutes of Health Stroke Scale (NIHSS) score by 2 points from the baseline [7,8]. Risk factors associated with progression include systolic blood pressure, diabetes, initial stroke severity, and lesion size [9,10]. In particular, the progression of motor deficits is associated with a relatively poor functional outcome [11]. The mechanisms that underlie symptomatic progression are likely complex and multifactorial. Growth in lesion size, a relatively consistent phenomenon during the first three days, is thought to contribute, at least in part, to the progression of symptoms [12,13]. Other proposed mechanisms for symptomatic progression include advancing stenosis of a major artery, [14] thrombus propagation, local tissue necrosis, a mass effect due to edema [15,16], hemorrhage [17] and a molecular imbalance of neurotransmitters [18]. Progressing stroke or "stroke in evolution" are terms describing a temporal pattern in which there has been progression (increased severity of the neurologic signs) within recent minutes. If the disorder is progressing stroke (stroke in

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evolution), immediate treatment to stop progression is indicated, since there is no evidence that cerebral infarction is reversible once it has occurred [19].

Aim of study

This study was prospective comparative study amid at comparison between use of double antiplatelet (aspirin plus Clopidogrel) versus aspirin plus subcutaneous Enoxaparin 40 mg in treatment of progressing stroke ineligible for thrombolysis.

Patients and Methods

Sixty patients presented with progressing stroke (increased severity of the neurologic signs more than 2 points of NIHS score from base line)7-8 attended in the neurology and cardiovascular department of Aljadaani Hospital that belong to Ibn Sina Faculty of Medicine, Jeddah, Saudi Arabia, during the period from February 2017 to the end of January 2019. Fifty-six patient were completed the total follow up in this study (four patients didn`t complete follow up). All patients were admitted at Aljadaani Hospital for one week. This study has been approved by ethical committee of Aljadaani Hospital. Patients eligible for thrombolytic therapy r-TPA and those who had stationary course, Hemorrhagic stroke, TIA, cardio-embolic reasoning (rheumatic heart disease, atrial fibrillation, patent foramen oval or cardiomyopathy) or significant carotid artery stenosis, drug abusers were excluded from the study. Also, patients who deteriorate due to other causes than neurological cause such as chest infection were excluded from the study.

The included patients were randomly divided into two groups, group (A) were treated with double antiplatelet aspirin 81 mg plus Clopidogrel 75 mg (four tablet loading dose from each followed by one tablet daily) and group (B) were treated with single antiplatelet aspirin 81 mg (four tablet loading dose followed by one tablet daily) plus subcutaneous enoxaparin 40 mg (Clexane) once daily for 3 days. After 3 days, both groups continued double antiplatelet aspirin 81 mg plus Clopidogrel 75 mg. All patients were subjected to detailed medical history including age, gender, smoking, diabetes mellitus, hypertension, and any other medical disease. Detailed neurological history including onset, duration, course, and risk factors of stroke. Neurological examination including mental state, cranial nerves, motor, sensory systems and cerebellum. Evaluation of all patients were done by using NIHS score at time of admission, daily during admission, at time of discharge (one week from onset), one month and three months after onset. The degree of improvement was assessed according to NIHS score. Patient who had increase in NIHS score more than 2 points was consider deteriorated while patient who had decrease, slight increase less than 2 point or same NIHS score were considered improved (stop progression). CT or MRI brain at time of admission and 2 days after admission, carotid duplex, ECG and echocardiography were done for all patients. Laboratories were done including random blood sugar, HbA1c, serum cholesterol and triglyceride. All analyses were performed using the (SPSS 16.0) software package. Continuous variables were presented as mean ± standard deviation. Contingency table was analyzed to test differences between proportions using Chi-squared test. We defined statistical significance as $P< 0.05$.

Results

The study was carried out on fifty-six patients (41 male and 15 female) with mean age 60.63 ± 10.82 divided into two groups. Group A were 27 patients (20 male and 7 female) with mean age 59.14 ± 10.43 years while group B were 29 patients (21 male and 8 female) with mean age 63.24 ± 10.43 years. The prevalence of smoking, diabetes mellitus, hypertension and hypercholesterolemia were 41.1%, 53.6%, 85.7% and 60.7% respectively without statistically significant difference between both groups (Table 1).

At time of discharge (after one week), we found that, 59.3% of group A showed progression in neurological symptoms (increase in NIHS score >2 point more than base line) and remaining 40.7% showed improvement in neurological symptoms while in group B only 13.8% of patients showed progression and remaining 86.2% showed improvement at this time. After one month, 55.56% of group A and 89.66% of group B showed improvement and after 3 months, 66.67% of group A and 89.66% of group B showed improvement with significant difference between both groups (Table 2).

Evaluation of patients at time of admission, at time of discharge, after one month and after 3 months by NIHS score showed insignificant difference between both groups at time of admission while at time of discharge, after one month and after 3 months, there were significant differences between both groups (Table 3).

CT brain or MRI brain finding showed the majority of patients had subcortical infarction (75%), complete middle cerebral artery occlusion and brain stem infarction were higher in group A than group B without significant difference (Table 4).

Discussion

Acute ischemic stroke is a medical emergency that requires timely and appropriate therapy. Patients with suspected acute ischemic stroke should be urgently assessed for thrombolysis [4]. If the disorder is progressing stroke (stroke in evolution), immediate treatment to stop progression is indicated [19]. Aspirin is recommended for patients with acute ischemic stroke who are ineligible for thrombolysis [4]. Combination treatment of Clopidogrel and aspirin taken soon after a

Variables	Group A (n=27)		Group B (n=29)		Total (n=56)		p-value
	No	Percent	No	Percent	No	Percent	
Sex							
Male	20	74.1%	21	72.4%	41	73.2%	0.392
Female	7	25.9%	8	27.6%	15	26.8%	
Smoking	12	44.44%	11	37.9%	23	41.1.%	0.642
DM	13	48.1%	17	58.6%	30	53.6%	0.286
HTN	22	81.5%	26	89.7%	48	85.7%	0.273
Hypercholesteraemia	16	59.3%	18	62.1%	34	60.7%	0.245
Age (M ± SD)	59.14 ± 10.43		63.24 ± 10.43		60.63 ± 10.82		0.146
Cholesterol (M ±SD)	224.3 ± 43.5		249.1 ± 38.2		236.64 ± 42.5		0.034

Table 1: Demographic data of the studied patients.

Variables	Group A (n=27)		Group B (n=29)		Total (n=56)		p-value
	No	Percent	No	Percent	No	Percent	
At time of discharge							
Improvement	11	40.7%	25	86.2%	36	64.29%	0.001
Progression	16	59.3%	4	13.8%	20	35.71%	
After one month							
Improvement	15	55.56%	26	89.66%	41	73.21%	0.007
Progression	12	44.44%	3	10.44%	15	26.79%	
After 3 months							
Improvement	18	66.67%	26	89.66%	44	78.57%	0.041
Progression	9	33.33%	3	10.44%	12	11.43%	

Table 2: Outcome of patients after treatment.

Variables	Group A (n=27)	Group B (n=29)	p-value
At admission (M ± SD)	6.94 ± 2.14	8.00 ± 2.11	0.309
At discharge (M ± SD)	14.44 ± 6.96	9.6 ± 6.02	0.028
After one month (M ± SD)	12.06 ± 6.82	7.6 ± 6.22	0.039
At 3 months (M ± SD)	9.23 ± 6.54	6.1 ± 6.32	0.045

Table 3: Correlation between NIHS score at time of admission, time of discharge, after one month and after 3 months in both groups.

Group A (n=30)	Group A (n=27)		Group B (n=30)		Total (n=60)		p- value
	No	Percent	No	Percent	No	Percent	
Complete MCA occlusion	5	18.52%	2	6.9%	7	12.5%	0.34
Subcortical infarction	18	66.67%	24	82.76%	34	75.00%	
Brain stem infarction	4	14.81%	3	10.34%	7	12.5%	

Table 4: CT brain or MRI brain finding in both groups.

minor ischemic stroke or TIA was showed to reduce the early risk of new stroke without increasing the risk of bleeding [20,21]. Studies that assessed the effectiveness of anticoagulants compared with antiplatelet agents in acute ischemic stroke concluded that anticoagulants offer no net advantages over antiplatelet agents [22]. The use of antiplatelet therapy in treatment of ischemic stroke was superior to anticoagulation however, the use of anticoagulation in combination with antiplatelet is still debatable regarding the type of anticoagulant, its dose, duration, and onset of use also the incidence of hemorrhagic complication when it used in the acute phase. Several studies have demonstrated that history of diabetes and hypertension are associated with early neurological worsening [9-15,16,23,24]. while other studies did not find significant association between neurological deterioration and history of hypertension or diabetes mellitus [25,26].

The results of this study showed that patients treated with aspirin plus enoxaparin (Group B) had better neurological outcome than those treated with aspirin plus Clopidogrel (Group A) with significant difference without development of any hemorrhagic complications. Aspirin is rapidly absorbed in the upper gastrointestinal (GI) tract and results in a measurable inhibition of platelet function within 60 minutes [27,28]. This antiplatelet effect is associated with prolongation of the bleeding time and inhibition of TXA 2-dependent platelet aggregation [29], that occur even before acetylsalicylic acid is detectable in the peripheral blood, owing to the exposure of platelets to aspirin in the portal circulation [30]. Enteric coating of aspirin significantly delays its absorption [31]. The plasma half-life of aspirin is only 20 minutes; however, because platelets cannot generate new COX, the effects of aspirin last for the duration of the life of the platelet (10 days). But if 20% of platelets have normal COX activity, hemostasis may be normal [32,33]. Single doses below 100 mg result in a dose dependent effect on TXA 2 production; the effect of repeated daily doses is cumulative, although 24 hours may be required to achieve maximal COX inhibition [33-35]. A 75 mg/d Clopidogrel maintenance dose required at least 5 days and a 600 mg loading dose of Clopidogrel required up to 8 hours to achieve 50% steady state of inhibition of ADP-induced platelet aggregation [36-38]. Enoxaparin is low molecular weight heparin that inactivate factor Xa but don't prolong apt [39,40]. Peak anti-Factor-Xa activity of Enoxaparin occurs about 3-4 h following a subcutaneous dose [41,42]. The plasma half-life is 4-7 h, LMWH is almost renaly excreted, and it undergoes first-order elimination [43,44]. Guidelines issued in 2007 by the American Heart Association/American Stroke Association stated that urgent anticoagulation is not recommended for the treatment of patients with acute ischemic stroke. Similarly, guidelines from the American College of Chest Physicians (ACCP) 8th edition issued in 2008 recommend against full-dose anticoagulation for patients with acute ischemic stroke [45].

Conclusion

In this work, we studied the use of combination of aspirin in the recommended dose with the low dose enoxaparin not the full dose as was recommended in another studies and we found that the use of this combination was significantly superior to the usual regimen of use of dual antiplatelet therapy in a special group of patients (stroke in evolution) who are not eligible for thrombolytic therapy even if the reason of stroke is not clearly embolic. We thought that the rapid use of enoxaparin in addition to aspirin will give a rapid onset of action with additional mechanism other than antiplatelet at the same time avoiding the complication of the full therapeutic dose of enoxaparin. This could explain the absence of hemorrhagic complications in our patients. Because of this good result that we observed in our study with the use of this regimen, we recommend performing a multicenter study in a high number of patients to evaluate this regimen in the management of patients with acute stroke who are not eligible for thrombolytic therapy.

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