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Original Article

Comparative Effectiveness of Rivaroxaban, Enoxaparin and Aspirin in Patients with Acute Ischemic Stroke

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Abstract

Objective: To compare effectiveness of Rivaroxaban, Enoxaparin and Aspirin therapy in acute ischemic stroke.

Methods: This randomized controlled trial in King Edward Medical University, Lahore included 210 patients, aged 18-75 years with acute ischemic stroke within last 24 hours. CT scan brain ruled out any evidence of intracranial bleeding. Functional status was assessed by modified Rankin Score (mRS) at presentation. Patients were randomized to receive 15mg Rivaroxaban, 40mg Enoxaparin twice daily or 300mg aspirin daily for 10 days. Patients were followed up at 14 days for new stroke events and mRS. Absence of major bleed was the safety parameter. Data was analyzed in SPSS 26.0 by ANOVA and chi-square keeping p-value ≤0.05 as significant.

Results: Among the 53.81% male and 46.19% females (total 210 patients), mean age was 60.44±4.48 years. Mean mRS at day 1 was 3.90±0.422, 3.86±0.460 & 3.81±0.460 in Rivaroxaban, Enoxaparin and Aspirin groups respectively (p-value 0.527). Day 14, mRS was 3.81±0.460, 3.80±0.437 & 3.83±0.450 in the three groups respectively (p-value 0.932). New stroke events in 20 cases and favorable outcomes in 190 were evenly distributed among the 3 groups (p-value 0.488). There was major bleeding event.

Conclusion: Anticoagulants (Rivaroxaban or Enoxaparin) are equivalent to Aspirin without increased risk of significant bleeding in the management of patients with acute ischemic stroke.

Keywords: Acute ischemic stroke, Aspirin, Enoxaparain.

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Introduction

Stroke is major cause of acquired disability in adult population and the second foremost cause of death worldwide.[1] Over 16 million people suffer from acute stroke every year resulting in 6.7 million deaths.[2] Khan et al reported that stroke resulted in 87% of total losses in terms of disability-adjusted life years.[3] Ischemic stroke is more common than hemorrhagic stroke and accounts for 87% of all strokes.[4] 65% of stroke sufferers become permanently disabled resulting in greater loss of manpower both at personal level and nationwide.[5]

Various efforts have been made to limit the morbidity associated with stroke. Antiplatelet drugs especially aspirin have a proven role in treatment of acute ischemic stroke and is most commonly used drug. However recurrence of stroke in 11.8% patients on aspirin therapy in the initial few days has highlighted the need for additional therapy.[6]

Tissue Plasminogen activator is the only accepted treatment for ischemic strokes.[7] Besides to a limited time window, thrombolysis is invasive and has increased risk of fatal bleeding particularly intracranial hemorrhage. In view of these limitations, efforts are being made to establish new protocols for limiting stroke associated mortality and morbidity.[8]

Anticoagulant drugs have an established role in treatment of ischemic events in other vascular beds especially myocardial infarction and ischemia.[9] On similar principles various researchers have studied the role of anticoagulants including heparins, heparinoids and oral drugs in limiting early neurological deterioration.[10]

Xingyang Yi et al found that management with low

molecular weight heparin resulted in significant reduction rates of early neurological deterioration and early recurrent ischemic stroke.[11] The incidence of intra cranial hemorrhage did not significantly differ from treatment with aspirin alone.[11]

Similar results were seen in FISStris trial which include 603 patients. Post hoc analysis of this trial showed reduction in early neurological deterioration in patients of acute stroke having large artery occlusive disease after low molecular weight heparin treatment. The American Heart Association and American Stroke Association has still not approved the routine use of anticoagulant treatment for acute ischemic stroke patients.[12]

Rivaroxaban is a new oral anticoagulant, approved for treatment others thromboembolic events including prophylaxis of DVT, VTE, and stroke in surgical patients and in patients with atrial fibrillation. This drug is also used in management of DVT and pulmonary embolism.[13] It has a number of advantages including direct targeting of coagulation cascade, quick onset and offset of action, low rate of major hemorrhage, low risk of drug interaction and more predictable response.[14] TRACE trail is an ongoing multicenter study which aims to compare the efficacy of Rivaroxaban versus aspirin in non-disabling patients of ischemic stroke.[15]

The rationale of our study was to establish the role of Rivaroxaban and Enoxaparin in limiting disability acute ischemic stroke patients. Limited literature is available on use of Rivaroxaban in ischemic stroke patients and previously these two anticoagulant drugs have not been compared. The objective of this study is to compare the effectiveness of Rivaroxaban, Enoxaparin and Aspirin therapy in patients with acute ischemic stroke with the hypothesis that rivaroxaban is superior to both Enoxaparin and Aspirin therapy in this group of patients.

Methods

This randomized controlled trial was completed in 6 months at the Department of Medicine, King Edward Medical University/Mayo Hospital, Lahore. Using the formula n = [Z21-α/2 {P1 (1-P1) + P2(1-P2)}]/d2, sample size of 210 patients (70 in every group) was estimated by using 95% confidence level, 10% absolute precision with expected percentage Enoxaparin as 6.7% and aspirin as 13.9%. Simple random probability sampling was done.

Male and female individuals, aged 18-75 years of age, presenting with acute ischemic stroke occurring within last 24 hours were included in the study. Acute ischemic stroke was defined as patients presenting with clinical features of stroke within last 24 hours and no evidence of bleed on CT scan brain. The clinical features of stroke included sudden numbness or weakness of face, arm or leg especially on one side of the body, sudden decrease in level of consciousness, new onset visual field deficits, aphasia, dysarthria, facial droop, ataxia and/or vertigo.

The exclusion criteria was quite extensive incorporating recurrent stroke, intracranial bleeding, other intracranial pathology identifiable on CT brain (vascular abnormalities, tumor, abscess or other major non ischemic cerebral disorders), medical conditions requiring long term anticoagulants (atrial fibrillation, mechanical heart valves, DVT, pulmonary embolism or known hypercoagulable conditions), contraindication to trial drugs, history of intra-cerebral bleed, patients taking heparin or oral anticoagulant treatment within 10 days prior to study enrolment, history of gastrointestinal bleeding or major surgical procedure in 3 months, intended or expected cardiac catheterization such as angioplasty or vascular surgical procedure in the coming 3 months, severe illness with life expectation less than 3 months, pregnancy and breast feeding, severe kidney insufficiency (eGFR < 30 ml/min), severe liver failure (Child-Pugh class B or C).

Written informed consent was taken after explaining the purpose of the study. CT scan brain without contrast was done to rule out any evidence of intracranial bleeding. CT scan was reported by radiologist to ensure uniformity of the data. Confounders were controlled by taking detailed history and examination and by carefully following the exclusion criteria. The functional status of the patients assessed by modified Rankin Score (mRS) at the time of presentation. mRS is based on the ability to carry out routine activities and the limitation imposed by symptoms of stroke with score ranging from 0-6.

Patients were randomized by computer generated program to group A, B and C each including 70 patients. Patients were given treatment according to the group allocation for 10 days. Group A received 10 mg of Rivaroxaban daily and 75mg of aspirin daily for 10 days which started within 24 hours of commencement of acute ischemic stroke in addition to standard treatment. Group B received 40mg of Enoxaparin twice daily and 75mg of aspirin daily for 10 days which started within 24 hours of commencement of acute ischemic stroke in addition to standard treatment. Group C received 300mg of aspirin daily for 10 days which started within 24 hours of commencement of acute ischemic stroke in addition to standard treatment.

Patients remained under follow up for the duration of treatment and again at 14 days to record for any new stroke events. The functional status was reassessed by administering mRS at 14 days and the treatment outcome was recorded. Effectiveness of the drug was defined as no new stroke events (ischemic or hemorrhagic including fatal stroke and favorable outcome at 14 days.

Stable functional status (same mRS at day 1 & day 14) as well as improved functional status (decreased mRS at day 14 at least by a score of 1) were both categorized as favorable outcome while any worsening of functional status (increase in mRS by a score of 1 or more at day 14) was labeled as adverse outcome. Safety was defined as absence of moderate to severe bleeding including fatal bleeding, intracerebral bleeding and other bleeding events leading to hemodynamic instability and/or requiring blood transfusion within the 14 days of follow up.

Data was entered SPSS-26.0 for analysis. Age was presented as mean ± standard deviation. Gender, mRS and outcomes were presented as frequency and percentage. Comparison of three study groups Rivaroxaban, Enoxaparin and Aspirin by applying ANOVA for quantitative variable and chi square chart for qualitative variables. p-value ≤ 0.05 was taken as significant.

Results

A total of 210 patients participated in this study. The mean age of the Rivaroxaban group patients was 60.79± 4.76 years and the Enoxaparin group patients was 60.40± 4.61 years and its mean value in aspirin group patients was 60.13±4.072 years. The groups were comparable with a p-value 0.6232. In this study the 113(53.81%) patients were male and 97(46.19%) patients were females. Male patients were 37 and 38 from Rivaroxaban and Enoxaparin groups respectively and 37 were from aspirin group. The female patients were 97 in which 32 were from Rivaroxaban and Enoxaparin groups respectively and 33 were from aspirin group.

Presentation of acute ischemic stroke was varied and symptoms; the commonest being sudden alteration in conscious level, aphasia, dysarthria and focal weakness. The sudden decrease in the level of unconsciousness was observed in 134 cases in which 45 were from Rivaroxaban and Enoxaparin groups each and 44 were from aspirin group. The sudden decrease in the level of unconsciousness was not observed in 76 cases in which 25 were from Rivaroxaban and Enoxaparin groups respectively and 26 were from aspirin group. Statistically insignificant difference (p-value=0.980) was observed between the groups. Visual field deficit was noted in 77 patients in which 26 were from Rivaroxaban and aspirin groups respectively and 25 were from Enoxaparin group. The differences were statistically insignificant difference (p-value=0.980). Facial weakness was observed in 129 patients, ataxia in 16 cases, vertigo in 18 cases. The comparison is shown in Table 1.

The mean value of mRS at day 1 in Rivaroxaban group patients was 3.90±0.422, in Enoxaparin group was 3.86±0.460 and in aspirin group was 3.81±0.460. Insignificant difference was found between the groups with mRS at day 1 of the patients i.e. p-value=0.527. The mean value of mRS at day 14 in Rivaroxaban group patients was 3.81±0.460, in Enoxaparin group was 3.80± 0.437 and in aspirin group was 3.83±0.450. Statistically insignificant difference was found between the groups with mRS at day 14 of the patients i.e. p-value=0.932. Table: 2

In this study new stroke events were found in 20 cases in which 7.14% (5/70) were from Rivaroxaban group, 8.57% (6/70) were from Enoxaparin group and 12.85% (9/70) were from aspirin group. Statistically insignificant difference was found between the groups with new stroke events of the patients i.e. p-value=0.488. The study results showed that favorable outcome at day 14 was noted in 190 cases in which 92.85% (65 cases) were from Rivaroxaban group, 91.42% (64 cases) were from Enoxaparin group & 87.14% (61 cases) were from aspirin group. Unfavorable outcome at day 14 was noted in 20 cases in which 5 were from Rivaroxaban group, 6 were from Enoxaparin group and 9 were from aspirin group. Statistically insignificant difference was found between the groups with favorable outcome at day 14 of the patients i.e. p-value=0.488. The outcomes of the study are summarized in Table 3

All the drugs were found to be safe and no adverse drug effect including major bleeding events was observed in any case.

Table 1: *Comparison of Presenting Complaints of the 3 Groups*

	Rivoraxoban	Enoxaparin	Aspirin	P value
Sudden decrease in the level of consciousness	45	45	44	0.98
Visula field deficits	26	25	26	0.98
Aphsaia	48	50	48	0.91
Dysarthria	27	27	27	1.00
Facial Weakness	41	45	47	1.00
Ataxia	4	7	5	1.00
Vertigo	6	7	5	1.00

Table 2: *Comparison of mRS at day 1 & day 14*

	Rivoraxoban	Enoxaparin	Aspirin	P value
mRS at day 1	3.90±0.42	3.86±0.46	3.81±0.46	0.52
mRS at day 14	3.81±0.46	3.80±0.43	3.83±0.45	0.92

Table 3: *Comparison of Outcomes*

	Rivoraxoban	Enoxaparin	Aspirin	P value
New Stroke events	5	6	9	0.488
Favourable Outcome	65	64	61	
Adverse Outcome	5	6	9	

Discussion

This randomized control trial was carried out at department of Medicine, Mayo Hospital, Lahore to compare the effectiveness of Rivaroxaban, Enoxaparin and Aspirin therapy in patients with acute ischemic stroke.

Stroke is a medical emergency having a high death rate than most type of cancer. It is the second foremost cause of death in developed countries and the most frequent cause of severe, long-term disability in adult population. The aim of the initial assessment is to validate that the patient's impairments are due to ischemic stroke and rule out other systemic or neurological disorder such as intracerebral bleeding.[16]

According to our study results the Rivaroxaban is more effective than Enoxaparin and Aspirin therapy in patients suffering from acute ischemic stroke. Statistically insignificant difference was found in comparison of mRS at baseline and at day 14 with study groups. Some of the studies are discussed below showing their results.

In a randomized control trial, oral Rivaroxaban 10 mg once daily was given to1584 patients and subcutaneous Enoxaparin 30 mg BD given to 1564 patients. The primary efficacy outcome was the composite of DVT, non-fatal pulmonary embolism, or all-cause death ≤17 days following knee arthroplasty. The primary efficacy outcome observed in 6.9% and 10.1% of Rivaroxaban and Enoxaparin treated patients respectively, for an absolute risk reduction of 3.19% (P = 0.0118). Severe bleeding was observed in 0.7% and 0.3% of Rivaroxaban and Enoxaparin treated patients respectively (P = 0.1096).[17]

One study showed that the new oral anticoagulants appear to be safe and effective but a small number of clinical studies has been conducted to assess their effect in non-disabling ischemic stroke events. Use of Rivaroxaban following TIA or minor stroke, may prevent more cerebro-vascular events with an acceptable risk profile compare with aspirin, thus helping to improve the outcome of the illness.[14]

A study by Zannad et al presented that among patients with a current acute coronary syndrome, Rivaroxaban decreases the risk of the composite end point of death from cardiovascular etiology, heart attack, or stroke, while increasing the risk of non-fatal major bleeding and intracerebral hemorrhage.[18]

Xingyang Yi et al found that treatment with low molecular weight heparin resulted in significant reduction rates of early neurological deterioration and early recurrent ischemic stroke. The incidence of intra cranial hemorrhage did not significantly differ from treatment with aspirin alone.[11]

Matos et al, concluded that Rivaroxaban was non-inferior to warfarin for the prevention of stroke events or systemic embolization in patients with AF. The risk of major bleeding was not significant between-group difference and intracerebral and fatal bleeding incidence was less frequent in the Rivaroxaban group.[19]

AR Harrington et al showed that the Rivaroxaban is the most cost-effective drug in patients with non-valvular atrial fibrillation for stroke prevention among the three novel oral anticoagulants, i.e. apixaban, dabigatran and Rivaroxaban.[20]

There are certain limitations of the present study. It was a single centre trial. The sample size though adequate to achieve desired power and significance was quite small as compared to other trials. Only short term follow up was done as per study design. It is recommended that larger multi-centre trials with longer follow up periods may be done to evaluate the effects of anticoagulant drugs in management of acute stroke.

Conclusion

It has been proved in our study that anticoagulatant therapy i.e., Rivaroxaban and Enoxaparin are equivalent Aspirin therapy without increased risk of significant bleeding in the management of patients with acute ischemic stroke.

Conflict of Interest *None*

Funding Source *None*

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