COMPARISON OF ANTI-PLATELETS VERSUS ANTI-COAGULANTS IN PATIENTS WITH CRYPTOGENIC STROKE IN PREVENTION OF RECURRENT STROKE AND TIA

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ABSTRACT

Objective: To compare the efficacy of anti-platelets and anti-coagulants in patients with cryptogenic stroke in prevention of recurrent stroke and TIA.

Study Design: Cross-sectional comparative study.

Place and Duration of Study: Department of Medicine, Combined Military Hospital Quetta, from Jan 2017 to Dec 2017.

Material and Materials: Total of 30 patients with cryptogenic stroke fulfilling the inclusion/exclusion criteria were included in study, 22 were males and 08 females. They were divided into two groups with 15 patients in each. Group A was treated with anti-platelets and group B with anti-coagulants.1.5 tesla MRI was used to assess the results of the two therapies.

Results: About 46.67% (n=7) in group A and 6.67% (n=1) in group B had repeated ischemic stroke (*p*-vlaue=0.01). 40% (n=6) in group A and 13.33% (n=2) in group B had TIA like episodes at one year (*p*-vlaue=0.02).

Conclusion: Anti-coagulants were more effective in secondary stroke prevention in cryptogenic stroke as compared to anti-platelets at one year, provided no contraindications were present to either.

Keywords: Anti-coagulants, Anti-platelets, Cryptogenic stroke.

INTRODUCTION

Ischemic strokes traditionally classified as cryptogenic stroke (CS) or Embolic strokes of undetermined source (ESUS) remain frequent despite advances in the diagnostic techniques to determine stroke etiology[1]. CS is a non-lacunar ischemic stroke in which subsequent investigations do not show any specifically treatable cause, atrial fibrillation, stenosis in a proximal extra-cranial or intracranial artery (>50%), or other major-risk cardioembolic source[2]. A recent prospective global registry reported that 16% of ischemic stroke patients met criteria for ESUS (19% if stroke patients who did not undergo the complete evaluation required for diagnosis were excluded)[3].

Most non-lacunar cryptogenic ischemic strokes are presumed to be embolic, originating from various cardiac and arterial sources or occasionally from venous thromboembolism (i.e. via paradoxical embolism)[4]. Patients with ESUS tend to be younger with lower rates of traditional vascular risk factors than other stroke subtypes, have minor strokes with a mean National Institutes of Health Stroke Scale of 5, but retain a significant risk for recurrent stroke (4.5% per year) and death (3.9% per year)[5].

In most cases cardiac embolism secondary to subclinical atrial fibrillation (AF) has been suggested as the cause of underlying cryptogenic stroke[6]. Anticoagulants have been supported for their efficacy in prevention of embolic stroke in AF patients[7]. Compared with warfarin and its congeners, Direct Oral Anticoagulants carry a lower risk of intracranial hemorrhage, the most devastating complication of anticoagulation[8]. Rivaroxaban 15 mg daily dose appears to be efficacious for stroke prevention in Japanese patients with atrial fibrillation[9].

The present study was planned to compare the effectiveness of the antiplatelet and anti-coagulant therapies in patients presented with

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new onset cryptogenic stroke. The results of this study will not only point out the superior mode of therapy for cryptogenic stroke but also help the clinician to make an informed choice when selecting among anti-platelets and anti-coagulants, thus decreasing the risk of morbidity and mortality.

PATIENTS AND METHODS

This comparative study was conducted at Combined Military Hospital Quetta which is a tertiary care hospital, over a period of 01 year, from January 2017 till December 2017. Permission from hospital ethical review committee was taken. A total of thirty patients out of which 22 were males and 8 were females, recruited through non probability purposive sampling. All patients were between 20-50 years old who had presented with new onset ischemic stroke. They were diagnosed as cryptogenic stroke after performing standard evaluation that is done routinely for every ischemic stroke and then special evaluation done for CS. The evaluation included following work up; Antinuclear Antibody, Rheumatoid Factor, Anti-Nuclear Cytoplasmic Antibody, anti-Extractable Nuclear Antibody, C-Reactive Protein, Magnetic Resonance Imaging brain with Magnetic Resonance Angiogram, Venereal Disease Research Laboratory, Treponema Pallidum Hemeagglutinin Assay, 2-D echocardiography, and carotid Doppler of neck vessels.

Patients between 20-50 years of age with new onset ischemic stroke were inclusion of the study.

Patients with diabetes mellitus, hypertension, Ischemic heart disease, Structural heart disease, Atrial Fibrillation, Chronic Kidney Disease, Chronic Liver Disease, signs of vasculitis clinically, previous stroke of any type, or if the patient has been taking any anti-platelets or anti-coagulants for other reason was exclusion from the study.

Patients were divided into two groups each with 15 subjects. Equal number of males (11) and females (4), were ensured in each group so that gender should not be a bias. Group A was treated with antiplatelets while B was treated with anti-coagulants. The patients in anti-platelet group received aspirin during acute stroke and clopidogrel was used as follow up. The patients in anti-coagulant group were given subcutaneous Enoxaprin then rivaroxaban in standard doses. Patients were evaluated on monthly basis and 1.5 tesla MRI was used to assess the symptoms of recurrent stroke and TIA.

RESULTS

A total of 30 patients fulfilling the inclusion/ exclusion criteria were included in study. Mean age was 40.73 ± 6.45 in group A and 44.40 ± 5.329 in group B, *p*-value=0.525. In both groups, 11 (73.3%) were male and 4 (26.7%) were female patients, *p*-value=1.00 (table-I).

The frequency of recurrent stroke was 7 (46.67%) in group A and 1 (6.67%) in group B, *p*-value 0.01. Whereas frequency of TIA was 6 (40.0%) in group A and 2 (13.33%) in group B, *p*-value = 0.02 (table-II).

We selected 30 patients who had a persistent brain before the subject event. Every patient was followed on monthly interval basis or in case of TIA /Recurrent stroke on emergent basis. It was observed that as compared to antiplatelets group patient with anticoagulant group had fewer recurrent stroke (1 versus 7 with *p*-value 0.01) and TIA (2 versus 6 with *p*-value 0.02).

DISCUSSION

Antithrombotic therapy for prevention of ischemic stroke has been complicated by multiple potential causes, imprecise pathogenic entities, and a narrow therapeutic window for intracranial bleeding[10]. Cryptogenic stroke is particularly resistant to therapeutics due to conflicting definitions, potential to identify multiple causes in a single patient, and failure of clinical trials to demonstrate a definite benefit for different strategies other than aspirin[4]. One approach is to increase the complexity and number of the initial investigations[11]. This approach is expensive and not accessible to individuals in our health system. Oral anticoagulants role for secondary prevention

of cardioembolic strokes is well established, and cryptogenic strokes have been recognized to share many features with cardioembolic strokes. However, currently there are no well established guidelines for optimal long-term treatment for secondary prevention in cryptogenic strokes. According to the American Stroke Association/ American Heart Association and the American College of Chest Physicians, antiplatelet agents are preferred for non-cardioembolic ischemic strokes. A global survey of hospitals in 48 countries found that antiplatelet therapy was routinely administered for secondary prevention of cryptogenic stroke in majority cases (94%)[12], yet there is growing evidence that cryptogenic stroke patients may benefit from anticoagulation.

Despite the absence of large, randomized controlled trials, emerging data linking cardiac abnormalities to cryptogenic strokes have shifted management increasingly in favor of anticoagulation. Recent studies show that using prolonged cardiac monitoring devices provides better detection of paroxysmal AF in patients with cryptogenic stroke[13]. The Cryptogenic Stroke and Underlying AF (CRYSTAL-AF) trial demonstrated that the use of an implantable cardiac monitor increased the rate of AF detection significantly compared to standard monitoring at 6 months (8.9% vs. 1.4%, $p<0.001$). Similarly, the 30-Day Cardiac Event Monitor Belt for Recording AF After a Cerebral Ischemic Event (EMBRACE) trial showed that use of a 30-day loop recorder increases the yield of AF detection in patients diagnosed with cryptogenic stroke (16.1% vs. 3.2%, $p<0.001$)[14]. While no causal link between paroxysmal AF and cryptogenic stroke has been claimed by these studies, however prolonged monitoring was associated with significantly higher rate of subsequent oral anticoagulation use. There was 2.5-fold increased risk of ischemic stroke ($p=0.008$) in patients without a prior history of AF with detection of subclinical atrial tachyarrhythmia (AT) lasting for at least 6 minutes in Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT)[15]. Taken together, these studies imply that detection of occult AF in cryptogenic stroke may warrant treatment with anticoagulation.

Table-I: Age & Gender wise distribution of patients in each group.

Age (Years)	**Group A**	**Group B**	***p*-value**
Mean ± SD	40.73 ± 6.453	44.40 ± 5.329	0.525
Gender			
Male	11 (73.3%)	11 (73.3%)	1.00
Female	4 (26.7%)	4 (26.7%)	

Table-II: Recurrent Stroke & TIA cross tabulation in each group.

	Group A		**Group B**		***p*-value**
	Yes	**No**	**Yes**	**No**	
Recurrent stroke	7 (46.67%)	8 (53.33%)	1 (6.67%)	14 (93.33%)	0.01
TIA	6 (40.0%)	9 (60.0%)	2 (13.33%)	13 (86.67%)	0.02

The purpose of present study is to help clinicians to identify the parameters of cryptogenic stroke and also a safe and state of the art therapeutic approach even if advanced testing facilities are not available including trans esophageal and pro coagulant work up which is not available in most of the set ups in our country. Our study is the bench mark for further studies in this regard.

To date, the only RCT data comparing the efficacy of anticoagulation versus antiplatelet therapy in cryptogenic stroke is derived from the WARSS trial, which suggested fewer recurrent strokes with warfarin than aspirin in cryptogenic stroke patients[16]. Despite the absence of large, randomized controlled trials, emerging data linking cardiac abnormalities to cryptogenic

strokes have shifted management increasingly in favor of anticoagulation.

This is also supported by work of Merkler *et al* that anticoagulation provides a reduction in the risk of recurrent ischemic events[17].

Finally, the role of non-vitamin K oral anticoagulants in cryptogenic stroke has yet to be established. The superior efficacy and improved safety profile as compared to warfarin have prompted interest in the prevention of strokes presumably due to embolism, beyond those attributed to nonvalvular AF. Two recently launched randomized controlled trials, Rivaroxaban versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source (NAVIGATE ESUS) and Dabigatran Etexilate for Secondary Stroke Prevention in Patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS), will assess the efficacy of rivaroxaban and dabigatran, respectively, compared to aspirin in secondary prevention of cryptogenic stroke specifically in ESUS patients.

Our study very clearly highlighted the importance of identifying cryptogenic stroke and then further treatment decision. It is always very important to provide a definite answer to general physicians in this regard. Our study will prove to be a land mark for future studies in this direction.

CONCLUSION

Anti-coagulants are superior in prevention of secondary stroke in case of acute onset cryptogenic stroke as compared to anti-platelets at one year, provided no contraindications are present to either.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Li L, Yiin GS, Geraghty OC, Schulz UG, Kuker W, Mehta Z, et al. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: A population-based study. Lancet Neurol 2015; 14(9): 903-13.
2. Hart RG, Sharma M, Mundl H, Shoamanesh A, Kasner SE, Berkowitz SD, et al. Rivaroxaban for secondary stroke prevention in patients with embolic strokes of undetermined source: Design of the NAVIGATE ESUS randomized trial. EurStroke J 2016; 1(3): 146-54.
3. Perera KS, Vanassche T, Bosch J, Giruparajah M, Swaminathan B, Mattina KR,et al. Embolic strokes of undetermined source: Prevalence and patient features inthe ESUS Global Registry. Int J Stroke 2016; 11: 526-33.
4. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: The case for a new clinical construct. Lancet Neurol 2014; 13(4): 429-38.
5. Hart RG, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic stroke of undetermined source: A systematic review and clinical update. Stroke 2017; 48(4): 867–72.
6. Scheitz JF, Nolte CH, Laufs U, Endres M. Application and interpretation of high sensitivity cardiac troponin assays in patients with acute ischemic stroke. Stroke 2015; 46(4): 1132-40.
7. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Heart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. N Engl J Med 2011; 364(9): 806-17.
8. Ruff CT, Giugliano RP, Brauwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomized trials. Lancet 2014; 383(9921): 955–62.
9. Hori M, Matsumoto M, Tanashashi N, Momomura S, Uchiyama S, Goto S, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation. The J-ROCKET AF Study. Circ J 2012; 76(9): 2104-11.
10. Sharma M. Embolic Stroke of Uncertain Source: An entity slowly coming into focus. J Am Heart Assoc 2017; 6: e007286.
11. Bang OY, Ovbiagele B, Kim JS. Evaluation of cryptogenic stroke with advanceddiagnostic techniques. Stroke 2014; 45(4): 1186-94.
12. Giruparajah M, Bosch J, Vanassche T, Mattina K, Connolly SJ, Pater C, et al. Global survey of the diagnostic evaluation and management of cryptogenic ischemic stroke. Int J Stroke 2015; 10(7): 1031-6.
13. Choe WC, Passman RS, Brachmann J, Morillo CA, Sanna T, Bernstein RA, et al. A comparison of atrial fibrillation monitoring strategies after cryptogenic stroke (from the Cryptogenic Stroke and Underlying AF Trial). Am J Cardiol 2015; 116(6): 889-93.
14. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J et al. Atrialfibrillation in patients with cryptogenic stroke. N Engl J Med 2014; 370(26): 2467-77.
15. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med 2012; 366(2): 120-9.
16. Sacco RL, Prabhakaran S, Thompson JL, Murphy A, Sciacca RR, Levin B, et al. Comparison of warfarin versus aspirin for the prevention of recurrent stroke ordeath: Subgroup analyses from the Warfarin-Aspirin Recurrent Stroke Study. Cerebrovasc Dis 2006; 22(1): 4-12.
17. Merkler AE, Gialdini G, Murthy SB, Salehi Omran S, Moya A, Lerario MP, et al. Association between troponin levels and embolic stroke of undetermined source. J Am Heart Assoc 2017; 6(9): e005905.