Section: Neurology

Original Research Article

DIAGNOSTIC ACCURACY OF N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE (NT-PROBNP) FOR DETECTING PAROXYSMAL ATRIAL FIBRILLATION (PAF) IN CRYPTOGENIC STROKE

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ABSTRACT

Background: 40 % of all ischemic events remain classified as cryptogenic. pAF is often suspected in cases of cryptogenic stroke. Most relevant complication of AF is stroke and this risk is similar in pAF and permanent AF. Patients with AF and ischemic stroke need anticoagulation and it cuts down the risk for recurrent stroke by nearly 2/3rd. Thus the identification of pAF by NT-proBNP is highly relevant in patients with ischemic stroke and sinus rhythm.
Aims & Objectives: To determine diagnostic accuracy of NT-proBNP for pAF.
Material and Methods: Patients with acute cerebral ischemia were included. NT-proBNP were measured within 72 hrs after stroke. Patients free from AF at presentation received 3 days cardiac rhythm monitoring or holter monitoring. Mean values of NT-proBNP were compared between patients with AF and sinus rhythm (SR) at presentation; and patients with pAF and no-AF using t-test. Receiver operating curves were used to test the ability of NT-proBNP values to identify patients with paroxysmal AF.
Results: 200 patients were included (67 with AF and 133 with SR). Among 133 patients with SR at presentation 13 patients were found to have pAF. Mean NT-proBNP values in patients with AF, pAF, no-AF were 2202.3, 1108.3 and 399.84 pg/dl respectively (p value < 0.001). Receiver operator characteristic (ROC) curve constructed for stroke of defined etiology had area under curve (AUC) of 0.92. Another ROC curve constructed for patients with pAF had AUC of 0.89. The optimal cutoff level of NT-proBNP in our study was 334.5 pg/ml with sensitivity of 100 % and specificity of 65.1 % for predicting pAF.
Conclusion: In our study 6.5 % patients developed pAF during cardiac rhythm monitoring and NT-proBNP had good accuracy in predicting the presence of pAF in patients with cryptogenic stroke and these patients can be considered for prolonged cardiac rhythm monitoring.
Key Words: Cryptogenic stroke, Paroxysmal AF, BNP

INTRODUCTION

Stroke is a leading cause of death,[1] and each year 5 million people die of stroke.[2] Because ischemic stroke is an etiologically heterogeneous disease, identification of the specific cause in every patient has important clinical implications, because prognosis, acute management, and long-term strategies to prevent recurrences may vary considerably for the different types of ischemic stroke. Sacco et a1,[3] noted that mortality was higher among patients with large-artery atherosclerotic lesions than among patients with
lacunes. Recurrent strokes are more likely among patients with cardioembolic stroke than among patients with stroke of other causes.[4,5] Determining the cause of stroke does influence choices for management. Carotid endarterectomy is of proven usefulness in preventing recurrent stroke in patients with large-artery stenosis, as are aspirin in patients

with small-artery occlusive disease or lesser degrees of large-artery stenosis.[6]

Anticoagulants,[7] or even cardiac surgery may be prescribed to prevent recurrent cardio-embolic stroke. Embolic or thrombotic occlusions of large arteries have been identified as the main cause of ischemic stroke.

Atrial fibrillation (AF) is important cause of embolic stroke and paroxysmal AF

often suspected in cases of cryptogenic stroke, and identifying AF is important because it necessitates a change in therapy from antiplatelet agents to a more effective prophylaxis with oral anticoagulation in almost all patients.[8] Stroke related to AF tends to be severe, with high recurence and mortality rates.[9] Identification of AF in patients with stroke is consequently of paramount importance and has therapeutic implications. AF is usually classified as permanent, persistent, or paroxysmal. Paroxysmal AF (pAF) is reported to have the same risk as persistent or permanent AF to cause ischemic strokes.[10]

However, identifying pAF can be difficult. Although it is frequently related to structural heart disease, about 45 % of patients with pAF have no echocardiographically detectable heart disease.[11] The currently available electrophysiological methods [electrocardiogram (ECG), routine telemetry during inpatient admission, holter monitoring, 30-day event monitoring devices] for detecting PAF all have a low sensitivity.[12] If diagnostic tests fail to identify pAF, stroke etiology may be incorrectly classified as cryptogenic (undetermined etiology).[13] Therefore alternative ways to detect

pAF in cryptogenic stroke are being evaluated. Recent studies suggest that N-terminal pro-brain natriuretic peptide (NT-proBNP),a peptide produced by the heart, may be useful to identify cardioembolic stroke associated with AF.[14] In previous studies, NT-proBNP had good accuracy in predicting ischemic stroke of cardioembolic cause associated with AF. BNP is a 32 amino acid protein,[15] and is mainly secreted from the heart and mostly from the ventricle in both healthy individuals and patients with heart failure. The precursor of the BNP, Pro-BNP is cleared by a protease into its biological active form BNP and N-terminal Pro-BNP, the biological inactive aminoportion. Recently many studies have reported that the plasma NT-Pro

BNP levels in cardioembolic stroke due to AF is significantly higher than that in other stroke subtypes. AF in the absence of left ventricular disease is associated with increased concentrations of BNP, and restoration of sinus rhythm can decrease plasma BNP concentrations.[16] A study by Inoue ET AL,[17] has in fact suggested mostly atrial BNP secretion in atrial fibrillation.

In many previous studies, NT-proBNP had good accuracy in predicting ischemic stroke of cardioembolic cause associated with AF. In one of these studies two cutoff points of 265.5 pg/ml and 912.0 pg/ml, had high negative and positive predictive value for the diagnosing AF (97.2% and 90.9%, respectively) were obtained.[14]

Aims and Objectives

1. To determine diagnostic accuracy of NT-proBNP to identify paroxysmal AF in patients with cryptogenic stroke.

MATERIALS AND METHODS

Among 200 patients included in our study, 67 had AF whereas 133 patients were in sinus rhythm (SR) at presentation. [Table 1] All patients in sinus rhythm were monitored for a minimum period of 72 hours in hospital for paroxysmal AF. Thirteen patients (6.5%) developed pAF after admission during hospitalization in our study (Table 2). pAF was reported in 5.5% of patients by Y. Okada et al,[31] in their study whereas R. Wachter et al,[51] reported pAF in 12.7% of patients. This is probably because of the difference in the duration of cardiac monitoring. R. Wachter et al,[51] did a 7- day holter monitoring in their patients whereas Y. Okada et al,[31] did 72 hours holter monitoring only. Mean age of patients was 71.15±11.83 yrs and 62.17±9.45 yrs in patients with AF and SR at presentation. In our study mean age was 73.08±3.97 years and 60.99±9.11 years in patients with pAF and No AF. In the study by A.C. Fonseca et al,[46] mean age for patients with new AF (pAF) and no AF was 74±7 and 68±15 years respectively. Mean age in the new AF group was comparable with our study but mean age of patients in no AF group was higher in their study. This is probably because of younger age of onset of atherosclerotic disease in our population. Higher mean age of patients with AF is because of increase in the incidence of AF with age.[26] Among patients with AF at presentation 37 (55.2%) were females and 30 (44.8%) were males. Whereas for patients with sinus rhythm at presentation 55 (41.4%) were females and 78 (58.6%) were males. Similar female preponderance were reported in AF group (56.4% of patients) by A.C Fonseca et al.[46] Y. Okada et al,[31] also reported a female preponderance in patients with AF (51.4%).

RESULTS AND DISCUSSION

Among 200 patients included in our study, 67 had AF whereas 133 patients were in sinus rhythm (SR) at presentation (Table 1). All patients in sinus rhythm were monitored for a minimum period of 72 hours in hospital for paroxysmal AF. Thirteen patients (6.5%) developed pAF after admission during hospitalization in our study.[Table 2] pAF was reported in 5.5% of patients by Y. Okada et al,[31] in their study whereas R. Wachter et al,[51] reported pAF in 12.7% of patients. This is probably because of the difference in the duration of cardiac monitoring. R. Wachter et al,[51] did a 7- day holter monitoring in their patients whereas Y. Okada et al,[31] did 72 hours holter monitoring only. Mean age of patients was 71.15±11.83 yrs and 62.17±9.45 yrs in patients with

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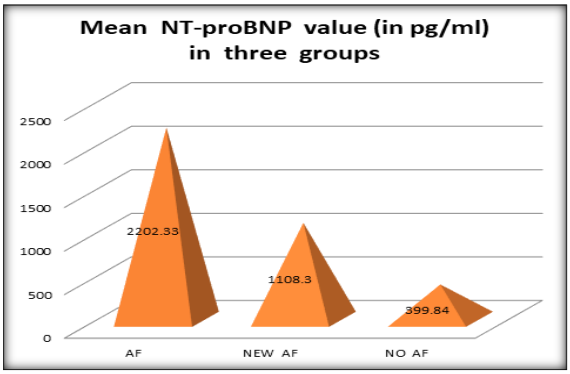

Figure 1: Showing mean NT-proBNP levels in AF, New-AF and No-AF group

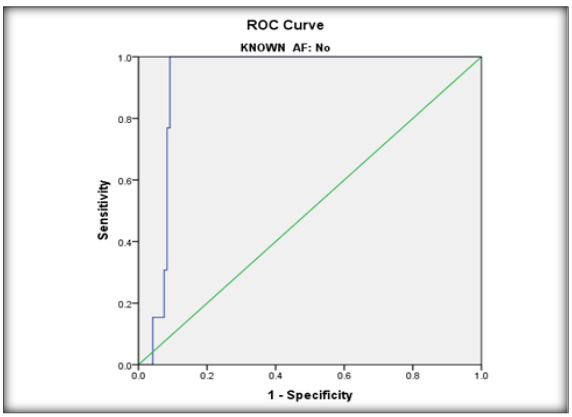

Figure 2: Receiver operating characteristics (ROC) curve of NT-Pro BNP for the diagnosis of atrial fibrillation (AF) in patients with known etiology. Area under the curve is 0.92. The cut off value of 334.5 pg/ml had a sensitivity and specificity of 100% and 79.2% respectively

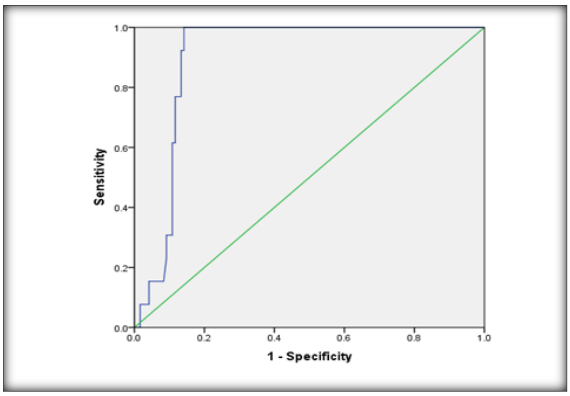

Figure 3: Receiver operating characteristics (ROC) curve of NT-Pro BNP for the diagnosis of paroxysmal atrial fibrillation (AF) . Area under the curve is 0.89. The cut off value of 334.5 pg/ml had sensitivity of 100%, specificity of 65.1%, positive predictive value of 63.6% and a negative predictive value of 100%

Table 1: Showing atrial fibrillation and sinus rhythm with Age and Gender distribution in our study

	ATRIAL FIBRILLATION (AF)	SINUS RHYTHM (SR)	P-Value
NO. OF PATIENTS	67	133	
AGE (years) Mean ±SD	71.15 ±11.829	62.17 ±9.445	0.0001*
FEMALE	37 (55.2%)	55 (41.4%)	
MALE	30 (44.8%)	78 (58.6%)	**0.072**

Table 2: Showing atrial fibrillation and sinus rhythm with Age and Gender distribution in our study

Variable	*PAROXYSMAL ATRIAL FIBRILLATION (AF) (n=13)*	*SINUS RHYTHM (SR) (n=120)*	*P-Value*
AGE (years) Mean±SD	73.08± 3.97	60.99±9.11	<0.001*
FEMALE	5 (38.5%)	50 (41.7%)	
MALE	8 (61.5%)	70 (58.3%)	**0.076**

CONCLUSION

According to our study that NT-proBNP levels can reliably identify patients at high risk of having paroxysmal AF. These high risk patients can be considered for prolonged cardiac rhythm monitoring.

REFERENCES

1. Health Organization. World Health Report 2002. Geneva, Switzerland : World Health Organization; 2002.
2. Hankey G, Warlow C. Treatment And Secondary Prevention Of Stroke: Evidence, Costs, And Effects On Individuals And Populations. Lancet. 1999; 354:1457-1463.
3. Sacco Se, Whisnant Jp, Broderick Jp, Philips Sj, O'fallon Wm: Epidemiological Characteristics Of Lacunar Infarcts In A Population. Stroke 1991; 22:1236-1241
4. Koller Rl: Recurrent Embolic Cerebral Infarction And Anticoagu- Lation. Neurology 1982; 32:283-285
5. Sage Ji, Van Uitert Rl: Risk Of Recurrent Stroke In Atrial Fibrillation And Nonvalvular Heart Disease. Stroke 1983; 14:668-676
6. Nascet Collaborators: Beneficial Effect Of Carotid Endarterec- Tomy In Symptomatic Patients With High Grade Carotid Stenosis. N Engl Jmed 1991; 325:445-453
7. Marsh Ee Iii, Adams Hp Jr, Biller J, Wasek P, Banwart K, Mitchell V, Woolson R: Use Of Antithrombotic Drugs In The Treatment Of Acute Ischemic Stroke: A Survey Of Neurologists In Practice In The United States. Neurology 1989; 39:1631-1634
8. Lin Hj, Wolf Pa Et Al. Stroke Severity In Atrial Fibrillation: The Framingham Study. Stroke 1996; 27:1760-1764.
9. Marini C, De Santis F, Sacco S Et Al. Contribution Of Atrial Fibrillation To Incidence And Outcome Of Ischemic Stroke:Results From A Population-Based Study. Stroke 2005; 36:1115-9.
10. Saxonhouse Sj, Curtis Ab. Risks And Benefits Of Rate Control Versus Maintenance Of Sinus Rhythm. Am J Cardiol 2003; 91: 27-32.
11. Morias J, Osterspey A, Tamargo Jl Et Al. Acc/Aha/Esc 2006 Guidelines For The Management Of Patients With Af. Circulation 2006; 114 :E257-E354.
12. Thomas G, Lerman Bb. Prediction Of Stroke Risk In Atrial Fibrillation, Prevention Of Stroke In Atrial Fibrillation, And The Impact Of Long-Term Monitoring For Detecting Atrial Fibrillation. Curr Atheroscler Rep 2011; 13:290-7.
13. Elijovich L, Josephson A, Fung Gl Et Al. Intermittent Atrial Fibrillation May Account For A Large Proportion Of Otherwise Cryptogenic Stroke : A Study Of 30-Day Cardiac Event Monitors. J Stroke Cerebrovasc Dis 2009; 18 : 185-9.
14. Fonseca Ac, Matias Js, Pinho E Melo T, Falcao F, Canhao P, Ferro Jm. N-Terminal Probrain Natriuretic Peptide As A Biomarker Of Cardioembolic Stroke. Int J Stroke 2011 6:398-403.
15. Sudoh J, Kangawa K, Minamino N Et Al A New Natriuretic Peptide Porcine Brain. Nature 1988; 332: 78-81.
16. Wozakowska-Kapton B Et Al. Effect Of Rhythm Restoration On Plasma Brain Natriuretic Peptide In Patients With Atrial Fibrillation. Am J Cardiol 2004; 93:1555-1558.
17. Inoue S, Murakami Y, Sano K Et Al. Atrium As A Source Of Brain Natriuretic Polypeptide In Patients With Atrial Fibrillation. J Card Fail 2000; 6:92-96.