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RESEARCH ARTICLE

Detection of cardio embolic stroke attributable to subclinical atrial fibrillation in patients of cryptogenic stroke presenting to a tertiary referral centre in Indian context

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Manuscript Info	Abstract

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Introduction

In a prospective study of 1,805 hospitalized patients in the Stroke Data Bank of the National Institute of Neurological and Communicative Disorders and Stroke Five hundred and eight cases (40%) were labeled as infarcts of undetermined cause (IUC) [1]. Thirty-one cases (22.5%) could be reclassified as due to stenosis or thrombosis of a large artery, and 16 (11.6%) as lacunar infarction. This still left a substantial proportion of cases in which the cause of stroke was obscure and an embolic source of unidentified nature was open for investigation. Many studies have highlighted the importance of subclinical cardiac arrhythmia as a cause of *cryptogenic stroke*. Recently there have been efforts to pick up these arrhythmias through various devices. There are unanswered questions as to which device should be used and how important is the duration of monitoring in cases of stroke. In the recent ASSERT Trial there was more than a doubling of embolic risk with the presence of atrial arrhythmias [2] . Patients older than 65 or younger with risk factors have an annual risk of stroke of 4% or greater [3]

 Atrial fibrillation and flutter (AF) account for 10% of all strokes and 50% of cardioembolic strokes [4].Stroke associated with AF carries a poor prognosis as more than 50% of the survivors remain with a severe deficit, and recurrence may be as high as 12% per year [5]. Because anticoagulant treatment dramatically reduces the recurrence rate, detection of AF after stroke is essential [6]. Once identified, introduction of oral anticoagulant therapy provides an additional 40% risk reduction in recurrent stroke compared with anti platelet therapy [7]. Recent evidence suggests that therapeutic oral anticoagulation may also be associated with reduced stroke severity, if ischemic stroke does occur in patients with AF. Thus, establishing the presence of underlying AF is of clear clinical importance .

Unfortunately, AF remains under diagnosed as it is often asymptomatic: up to 30% of patients with AF are unaware of their diagnosis and 25% of those with AF-associated stroke have no prior diagnosis of AF. Moreover, the fibrillation pattern is intermittent in 30% of patients with stroke and may not appear on a single recording [8].In a recent study, "Subclinical atrial tachyarrhythmias, without clinical atrial fibrillation, were associated with a significantly increased risk of ischemic stroke or systemic embolism"[9].In patients of acute stroke, a single ECG will miss cases of PAF which can be detected by longer duration monitoring such as Holter monitoring, cardiac event recorders and serial ECGs. The largest study addressing the cost effectiveness of screening for AF in high risk population as in stroke, the SAFE study clearly indicates that such opportunistic screening is cost effective.

 Harris et al in a recent review of all the studies done so far with the aim to detect subclinical AF by various means concluded that opportunistic screening is more cost-effective than systematic screening and if a 12-lead ECG fails to

show AF, then a number of different technologies are available that allow for longer term ECG monitoring[10].. The relative cost effectiveness of these technologies needs to be evaluated before a firm recommendation can be made in favor of any specific approach However, there is controversy in the literature regarding the use of noninvasive cardiac rhythm monitoring with previous reviews reporting a low detection rate with routine monitoring . Although it is accepted that the stroke risk in PAF, persistent and permanent AF is similar, uncertainty exists over the importance of short-duration atrial arrhythmias [11]. Device-detected atrial events of short duration may be as relevant as having a clinical history of PAF [12]. Low event rate may be a consequence of a short follow-up period or reflect under-reporting of embolic events. In the relatively longer ASSERT study (mean 3-year follow-up) the overall rate of the TE complications was 0.72% per year. Because of poor sensitivity of single ECG for paroxysmal AF, 24-hour ECG recording (Holter) is often used, allowing the detection of previously unrecognized AF[13] .Data regarding attempts to screen for atrial fibrillation/subclinical cardiac arrhythmias are especially scanty in Indian scenario. There are hardly any published studies from India regarding device detected AF in stroke patients hence this study was designed .

MATERIALS & METHODS

This is a cross sectional [descriptive] study done in patients presenting to Department of Neurology at Sri Aurobindo Medical College & PG Institute ,Indore during the period June 2012 to July 2013. A standard questionnaire based on the inclusion & exclusion criteria was used to identify patients more than 18 years of age presenting with ischemic stroke.The study was approved by the institutional ethics committee. A detailed history & physical examination was done to identify stroke risk factors. Investigations were done in patients thus selected for causes of stroke which included complete blood count with erythrocyte sedimentation rate, direct ophthalmoscopy , 12 lead electrocardiogram, 2D Echocardiography (Transesophageal Echocardiogram where feasible), Blood urea nitrogen,blood sugar, serum creatinine,serum lipids,coagulation profile ,homocysteine levels & urine routine microscopy.Patients with abnormality in these tests or a history of palpitations or unexplained syncopal attacks were excluded. Patients with   hemorrhagic   or   venous   strokes ,valvular   heart   disease,long   standing hypertension,dyslipedimia or significant arterial stenosis and patients with cardiac pacemaker were thus excluded.All patients underwent MRI Angiography brain on a 1.5 Tesla scanner to rule out intracranial/extracranial stenosis reported by a qualified radiologist blinded to the study. Included patients had a single 12 lead electrocardiogram, which & labeled positive if AF was detected. Following this, a continuous inpatient 24 hour Holter monitoring was done in the patients included. All cases reported as AF were labeled positive for final analysis. ECG, 2D & transesophageal echocardiography& 24 Hour Holter were interpreted by a qualified cardiologist blinded to the study.

The data was entered in Microsoft excel format and analyzed using the Vassar stats software. Chi square test was applied. A p value of < 0.05 was considered as significant for the analysis of results.

RESULTS

Sixty consecutive patients of ischemic stroke were enrolled during the study period. Age of patients ranged from 48 to 82 years. Twenty eight percent(28%) patients were less than 50years, 55% were 50-75 years & 17% were more than 75 years of age (Figure 1).There were 77% males and 23 % females (Figure2). There were 43 patients with MCA territory stroke , 2 patients with ACA territory stroke and 15 patients with posterior territory stroke

Of the total cohort, positive cases (i.e. with AF), were eight (13% of cohort). Three (37.5%) of these were male & five (62.5%) were female. Mean age of patients with atrial fibrillation was 62.5 years. Baseline 12 lead ECG was able to detect subclinical atrial fibrillation in three (37.5%)   of these eight patients. ECG positive group was made up of 67% males & 33% females but the data is too small to draw conclusions Rest of the patients were subjected to a 24 hour Holter monitoring .The time to application of Holter device was day 2-4 from the time of admission. Among patients on 24 hour Holter monitoring five patients were found to have subclinical atrial fibrillation i.e. (62.5% of AF positive cohort) and (8% of total cohort).The other three (37.5%) were detected by ECG (5% of total cohort).Thus, in absolute terms 13% of patients were found to have subclinical atrial fibrillation (including both ECG + Holter) (Table 1). In other words, in fifty two patients (87% of total cohort), subclinical atrial fibrillation could not be detected by ECG and even after a 24 hour Holter monitoring.

Holter positive group was 20% males and 80% females. Age of patients was 12 % were less than 50, 63% in 50-75 & 25 % were more than 75 years in the atrial fibrillation group and 20% , 60% & 20% in the holter group (Table 2); respectively .As compared to the total cohort ,the percentage of patients more than 50 years of age is higher in

patients with atrial fibrillation. Patients with atrial fibrillation were older (mean age 62.5 years) than patients in whom the ECG and Holter were normal (mean age 57.7 years) ,but this difference was not statistically significant. Limitations of this study are the small sample size especially of the positive cohort. Another limitation was that the cumulative duration for which the patients remained in AF during the 24 hour monitoring was not assessed because the results of our primary aim did not reach statistical significance

DISCUSSION

The results of this study show that the prevalence of atrial fibrillation among patients of ischemic stroke increases with age,[only 1 out of 8 i.e. 12.5% patients of atrial fibrillation was less than 50 years of age in our study] with 87.5 % of people aged 50 or more .This trend was seen consistently in both males and females and across various subtypes of stroke. Although subclinical atrial fibrillation was detected in 8 of our 60 [13%] patients; this was not statistically significant. Eighty percent [52 out of 60] patients did not have subclinical atrial fibrillation on study protocol. Twenty five percent of those with AF-associated stroke have no prior diagnosis of AF [14]. In our study we were able to detect 13% of such subclinical cases. Our number was smaller because of smaller monitoring time used [24 hour] as compared to previous studies which have used longer [up to 7 days] monitoring and also continuous cardiac telemetry. A single ECG will miss cases of AF, as consistently shown in literature and corroborated in our study ;only (37.5%) of total AF positive cases were picked up by ECG. The yield can be increased by longer duration monitoring such as Holter monitoring, cardiac event recorders and serial ECGs. On using 24 hour Holter device ,we were able to diagnose AF positive cases in another 62.5% subjects, which is statistically significant when compared to a single ECG which showed 8.3% detection rate in absolute terms when all cases of ischemic stroke are included. This can be interpreted as a significant trend towards AF detection rate with longer and continuous monitoring, though not enough in absolute terms to use as a routine screening tool. In a recent review of studies looking at AF following stroke the authors stated that " it is difficult to draw any firm conclusions, other than that the longer the monitoring is carried out, the more cases of AF are detected" [10]. Compared to other studies using similar monitoring protocols as ours ;Douen et Al in a retrospective study of 126 patients on Holter ECG, detected AF in 9.5% [15].Yu et Al in a retrospective study of 96 patients using 24-hour Holter monitor detected AF in 9.4% [16] .Alhadramy et al in another retrospective study of 413 patients with Holter ECG, average 22.6 hours reported 9.2% positive cases[17] . Barthelemy et al in 55 patients found 5.0%, but they used two ECGs prior to applying Holter, which would have excluded more patients than with one ECG screening as in our protocol [18]. Jabaudon et al in their 139 patients applied Holter at 8th day of admission [2-4 days in our study] which could have led to a lower detection rate [5.0%]. Koudstaal et al similarly used Holter at 15.2 days and reported 5% AF cases.In a recent study, Stahrenberg et al used 24hour Holter, 48-hour Holter and 7 day Holter in 224 patients and reported a pickup rate of 4.8%, 6.4% &12.5 % respectively.Thus clearly showing that longer the monitoring, more the sensitivity [19].Many, especially older studies, have even reported rates as low as 1.2 % but they applied the Holters very late [3 weeks],and probably were also limited by devices that were less advanced than today. On the other hand ,Elijovich et al ,in a small retrospective study of 21 patients used 30-day cardiac event monitor and found a 20% yield but this was not reproduced in a couple of other studies and not much data is available with continuous cardiac event recorder. Recently completed EMBRACE trial found that one in six patients over age 55 years with a cryptogenic stroke or TIA had previously undiagnosed paroxysmal atrial fibrillation .The authors concluded that "we can no longer rely on one or two Holter monitors. Prolonged monitoring is feasible and significantly more effective, has an incremental yield over 30 days, and resulted in a significant increase in the number of patients who were anticoagulated"[20]. Ongoing CRYSTAL AF study is further trying to address this issue of long term cardiac telemetry [21]

CONCLUSION

Opportunistic screening for atrial fibrillation is useful to make treatment decisions in cases of cryptogenic strokes. 12-lead ECG remains the standard investigation, but has poor sensitivity.24 hour holter monitoring in the immediate post stroke period can significantly improve atrial fibrillation detection rate compared to a single ECG .However, 24 hour Holter alone is not sufficient to recommend it for routine screening in stroke workup. Other technologies which use a longer monitoring time, including cardiac telemetry may be more sensitive but the effectiveness of these needs to be evaluated in future studies before a firm recommendation can be made in favor of any specific approach.

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