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ELECTROCARDIOGRAPHIC PREDICTORS OF MORTALITY IN ACUTE STROKE

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ABSTRACT
Objectives; The study is aimed at establishing the prognostic importance of various ECG changes as predictors of in-hospital mortality from acute stroke. **Study Design;** Cross-Sectional. **Patients and methods;** Two hundred patients of acute stroke who presented within 48-hours of the onset of neurological symptoms, were enrolled in the study, irrespective of the comorbid conditions like hypertension, diabetes mellitus, valvular heart disease, coronary artery disease and cardiomyopathy. A non-contrast computerized tomographic scan (CT Scan) of the brain and a 12-lead ECG were recorded at the time of admission to define the stroke type and to determine the ECG variables. A follow-up of the patients was recorded during their stay in the Medical Department for calculating in hospital mortality. The ECG variables categorized as, disturbances of heart rate and rhythm, ischemic changes and heart rate corrected QT interval (QTc interval), were correlated with the death during the hospital stay, by analyzing the data using SPSS-20 version for statistical analysis. **Results;** Majority of the patients had ischemic stroke, while mortality was higher with hemorrhagic stroke. ECG changes due to variations in heart rate and rhythm were frequent but less helpful than ischemic changes and QTc alterations, in predicting in hospital deaths due to stroke. **Conclusion;** In hospital mortality in sufferers of stroke is mostly of cardiac origin. Electrocardiographic changes resulting from QTc prolongation, ischemic changes, and rhythm disturbances are most helpful in this regard.
Keywords; ECG, CT-Scan, QTc interval

Introduction

It has been known for centuries that primary cardiac disorders can lead to stroke[1]. But the idea that CNS-disorders such as stroke may produce ECG changes and arrhythmias is fairly recent. For the first time in 1944, Byer and colleagues described the ECG changes in sufferers of subarachnoid hemorrhage[2]. ECG changes are present in anywhere from 60-90% of patients with intrapraenchymal or subarachnoid bleed and in about 5-20% of patients with acute ischemic stroke[3]. The underlying basis is disordered repolarization process[4]. There is a relation between these changes and sudden death in sufferers of stroke[5]. The possible mechanism is through disturbances in autonomic regulation[6], which results in massive stimulation along the outflow tract of the sympathetic limb of the autonomic nervous system. The frontal lobe, insular cortex and amygdale play an important role in regulating the heart rate via these autonomic nerves[7, 8]. Experimental studies even reveal that the left stellate ganglion influences the posterior wall of the ventricles and the right stellate ganglion has influence over the anterior ventricular walls. The ECG abnormalities most frequently noted are ischemic changes (35%), prolongation of QT-interval (45%), and disturbances in rate and rhythm (25%) e.g. atrial fibrillation, premature atrial and ventricular complexes, supraventricular and ventricular tachycardias (SVT and VT), torsade de pointis or polymorphic ventricular tachycardia[9].
Stroke induced ECG changes are evanescent, resolving over a period of days to months[10]. However the frequency and severity of changes is highest within 48-hours of the onset of stroke which explains the importance of continuous ECG monitoring for these patients[11]. The objective of this article is to establish the significance of these changes in predicting the risk of in hospital death due to stroke.

Patients and methods

This cross sectional study was conducted at the Emergency Department and the Department of Medicine of District Headquarters Hospital, Sahiwal, Paksitan. It included 200 patients with acute stroke, admitted within 48 hours of the onset of neurological symptoms. A non-contrast CT-scan of brain was used to define the stroke type. A 12 lead ECG was recorded at the time of admission. The first ECG was analyzed by a cardiologist blinded to the clinical data, as to the occurrence of the electrocardiographic abnormalities defined according to

the following established criteria.

i. Sinus tachycardia (sinus rhythm > 100 min)
ii. Atrial fibrillation
iii. Premature ventricular complexes > 6/minutes(3)
iv. Bundle branch block (either left or right)
v. Left ventricular hypertrophy. $SV_1/V_2 + RV_5/V_6 > 3.5$ mv (voltage criteria only)[12]; in men, RaVL + $SV_3 > 3.5$ mv; in men < 40 yrs of age, $TV_1 > 0$mv; in men > 40years of age, $TV_1 >= 0.2$ mv; in women, RaVL + $SV_3 > 2.5$ mv, ($TV_1 > 0$ mv in women < 40 years of age; and in women > 40 years of age $TV_1 > 0.2$ mv[13,14].
vi. Ischemic changes: ST-segment depression; horizontal or downsloping ST-segment with ST-j depression (>=0.05 mv) with or without T-wave inversion.
vii. QT-interval. Electrocardiographic complexes inn Leads-III and V_6 were used for this, due to their higher importance in this aspect as compared to other leads[15]. Rate corrected QT-interval (QTc) in these lead was calculated by using the Bazett's formula.

$$QTc = \frac{QT}{\sqrt{R-R}}$$

Different cut off values for QTc were used for assessment of statistical significance[15]. ECG findings done on the day of admission were considered for analysis of in hospital mortality. Pre-stroke ECG changes were not taken into account. However the following groups of patients were excluded from the study.

i. Patients with TIA (Transient ischemic attack)
ii. Stroke with CT scan of brain, negative for cerebral infarction or hemorrhage.
iii. Sufferes of ischemic stroke who had received thrmbolytic therapy.
iv. Patients with hemorrhagic stroke who had undergone operative intervention.
v. Stroke patient, presenting after 48-hours of onset of symptoms[11].
vi. Those having atrial fibrillation, bigeminy, atrial flutter, paced rhythm and bundle branch block, were excluded for the measurement of QT-interval and ST/T chances, due to technical difficulty[15].
vii. Where suspected, drug intoxications and electrolyte disturbances which could influence the QT-interval and ST/T changes (class-1 antiarrhythmic drugs, phenothiazines, tricyclic antidepressants, hypocalcaemia, hypokalemia, congential long QT-syndromes) were excluded by appropriate history, clinical examination, and biochemical / drug screening[16].
viii. Strokes related to trauma, meningitis / encephalitis were also excluded.

The relevant statistics was computed using SPSS-20 software and Chi-square test was applied to various qualitative variables of ECG, predictive of in hospital mortality due to stroke.

Results

A total of 200 patients were studied. Majority suffered (58%, n=116) cerebral infarction while 42% (n=84) had hemorrhagic stroke. Patients with ischemic stroke were relatively older (mean age 62 + 12 years) to those with hemorrhagic stroke (55 + 14 years). In hospital mortality was much higher in the sufferers of intracerebral hemorrhage (61.24%) as compared to cerebral infarction (16.24%) giving on overall mortality figure of 41%. Median stay in the hospital was 6.0 days. Due to technical difficulty with electrocardigrahic assessment, ischemic changes could not be assessed in 26-patients with cerebral infarction and 2 patients with hemorrhagic cerebral lesions. Similarly QT interval could not be calculated in 28 patients with ischemic stroke and 2 patients

with intracerebral hemorrhage.

The relationship of cardiac rate and rhythm abnormalities with in-hospital mortality (table-I) clearly shows that the rhythm changes as compared to sinus tachycardia were less sensitive but highly specific parameters for predicting early death due to acute stroke. Sinus tachycardia although much frequent, sensitive and statistically important (50% P<0.05 41.46%) ECG change, carried a relatively less specificity.

As compared to rate and rhythm changes left ventricular hypertrophy and ischemic changes (table-II) were statistically more significant parameters (P<0.001 & <0.05) for correlating them with mortality. T-wave inversion was more sensitive and specific than ST-depression (81.25% vs 71.15% & P<0.001 vs P<0.05) as an ischemic cardiac marker of in hospital death. Among all the electrocardiographic changes helpful of predicting early death, QT prolongation stands the highest significance. QTc > 430 msec (table-III), invariably reflected the high risk of early death. This was true for both leads III & V_6. (P<0.001 each), for all the cut-off values > 430 msec.

Table I
Rate and Rhythm Abnormalities

ECG variable	**No. of patients**	Frequency	Sensitivity	Specificity	**p-value**
Sinus tachycardia (Sinus rhythm >= 100/min)	200	50%	41.46%	45.76%	P<0.05
Atrial Fibrillation	200	11%	12.19%	89.83%	P<0.95
Bundle Branch Block	200	6%	9.75%	96.6%	P<0.95
PVCs> 6/min	200	5%	9.75%	98.3%	P<0.05

Table II
Left Ventricular Hypertrophy and Ischemic Changes

ECG variable	**No. of patients**	Frequency	Sensitivity	Specificity	**p-value**
Left ventricular hypertrophy (LVH)	200	40%	60.97%	74.57%	P<0.001
ST-segment depression	172	36.04%	47%	71.15%	P<0.05
T-inversion	172	36.04%	57.9%	81.25%	P<0.001

Table III

QT_c in Leads III & V_6

QT_c	**Total**	Frequency	Sensitivity	Specificity	**P-value**
QTc III >= 430	170	57.69%	69.69%	50%	P<0.05
QTc III >= 450	170	42.35%	63.63%	71.15%	P<0.001
QTc III >= 480	170	18.82%	42.42%	96.15%	P<0.001
QTc V_6 >= 430	170	65.88%	81.81%	44.23%	P=0.01
QTc V_6 >= 450	170	54.11%	81.81%	63.46%	P<0.001
QTc V_6 >= 480	170	34.11%	54.54%	78.84%	P<0.001

DISCUSSION

Cardiac autonomic imbalance generated by acute cerebral lesion plays an important role, not only in producing electrocardiographic abnormalities, but also in predisposing the patients towards early mortality[17]. Massive autonomic discharge along the sympathetic outflow tracts of the nervous system produces tachyarrythmias, which form the basis of more lethal abnormalities of heart rate and rhythm like torsade de points, ventricular fibrillation, asystole, and hence death[18]. Sinus tachycardia is a manifestation of such catacholaminic surge. Our study shows it a specific as well as sensitive parameter for predicting early mortality. Sinus tachycardia of higher magnitude may reflect a proportionately higher degree of autonomic discharge. Christensen emphasized its importance (p=0.001)[19] by using a sinus tachycardia of > 120/min as a variable for predicting early mortality. But he included only the patients with insular lesions, who are more likely to suffer a higher severity of cardiac autonomic dysregulation. Our study includes insular as well as non-insular lesions. Due to unavailability of previous ECG record of many patients, it was not possible to calculate exactly the frequency of stroke induced atrial fibrillation. However the study correlates with the results given by Bozluoclay[20]. The statistical values in our study highlight the importance of atrial fibrillation for expecting early death and also reemphasizes the importance of conclusion given by Wong and colleagues that atrial fibrillation is a parameters of early mortality due to stroke[21]. High risk of mortality with atrial fibrillation in stroke patients can be explained by concepts given by Chesebro, who has labeled atrial fibrillation as a marker of multiple abnormalities of cardiovascular system in general[22]. Our study doesn't describe the terminal arrhythmias responsible for mortality. The early death under such circumstances could be due to a higher tendency towards more dangerous cardiac arrythmias. Atrial fibrillation like many other ECG changes in less sensitive a parameter for predicting early mortality, the high specificity of it (89.83%) for predicting this catastrophic outcome, necessitates more sophisticated and sensitive methods of its detection, to be taken into consideration. Observations of Jabaudon & colleagues has shown that 5% sufferer of acute stroke can have atrial fibrillation detected by Holter monitoring, despite negative surface ECG. Similarly 5.7% have atrial fibrillation detected by event-loop-recorder (ELR) with a normal standard ECG and Holter[23]. Such a study clearly concludes that surface ECG underdiagnoses cardiac arrhythmias. From diagnostic and therapeutic point of view therefore, cardiac monitoring following acute stroke, with equipments like Holter and event-loop-recorder, should be mandatory. Goldstein in 1979 gave a figure of 26% for left ventricular hypertrophy (40% in ours). As Bozluoclay showed, preexisting cardiac illness, rather than acute stroke, forms the basis for left ventricular hypertrophy and Bundle Branch Blocks. The underlying mechanism could be volume/pressure overload[20]. Prolonged QRS complex due either to left ventricular hypertrophy, premature ventricular complexes or Bundle Branch Block, decreases the stability of the myocardium[18]. This instability is more marked when heart is exposed to high catacholaminic state e.g. post stroke setting[24]. This makes a suitable setting for predisposition & generation of ventricular arrythmias. Such

situation is clearly reflected in this study, by statistical values (P<0.001, P<0.05, <0.95) of these variables for predicting early mortality. Ectopic beats are precursors of ventricular tachyarrythmias. At a higher rate, premature ventricular complexes readily degenerate into conditions like torsede de pointis and ventricular fibrillation[11]. Our study utilizes only a single surface electrocardiogram for detecting such arrythmias which might have underestimated the importance of this ECG variable, but even then, the results are significant as indicated by high specificity value (98.3%, P<0.005) of it for expecting in-hospital mortality. Christensen & colleagues, assessed the same ECG variable and highlighted its importance for estimating the risk of early mortality[19] (p=0.032). However their study group include a subset of stroke population i.e. sufferers of right insular lesion only. Patients with right insular lesion are at a higher risk of autonomic imbalance than those with non-insular lesions[19]. Our patient population includes sufferers of insular as well as non-insular lesions. This might have underscored the results of our study.

The frequency of ischaemic change given in our study is 36.04% which is close to the result calculated by Goldstein (35%)[25] and Bozloucly (37.9%)[20]. Their statistical significance (P<0.05, P<0.001) is supported by results of several international studies including those of Christensen[16] & Dogan[26]. Since coronary heart disease and ischaemic stroke, share the same risk factors which may co-exist in the same patient, early mortality may be related to underlying coronary artery disease[27]. Our study doesn't adjust the frequency of ischaemic change for coronary artery disease which might have overestimated their statistical significance in sufferers of acute stroke. Regardless of origin, ischemic changes can be a predictor of early mortality and these changes are more or less similar in the two types of stroke[26,28]. Among all the ECG changes QTc prolongation-a manifestation of repolarization abnormality is the most important predictor of early death due to stroke. A prolonged QTc is well known to serve as an ancestor electrical change for ventricular tachyarrhythmias. Although threshold of prolonged QTc is not stated in our study, it is evident from the statistical results (Table III) that higher the cut-off value of QTc goes, the more specific & less sensitive the change becomes for predicting death in early post-stroke period. These results are also supported by the study of Wong & Walter[15]. The specificity values for QTc are comparable in both the studies[15]. Moreover QTc values in leads III & V_6 are equally reliable for this purpose. Several studies including those of Oppenheimer have given the impression that mortality following acute stroke is of cardiac origin[27]. Our study also reflects a similar conclusion. But this is probably not the whole story. Studies do exist which indicate that electrocardiographic changes do not form the entire basis of mortality in acute stroke. The complex interaction between the acute CNS-insult, autonomic tone and the sudden death in sufferers of stroke is also shown by the development of neurogenic pulmonary edema in these patients. This involves a complex interplay between sympathetic nervous system and various humoral mediators governing the pulmonary microcirculation[29]. This gives another reason of in hospital death in these patients, which should be considered regardless of ECG changes. Our study doesn't take into consideration such factors for stroke induced mortality and therefore might have overemphasized the importance of ECG changes. To determine the effect of new onset ECG changes in-patients with acute stroke, on the immediate and long-term mortality, well designed randomized control studies are essential. Such studies may also provide the opportunity for appropriate drug treatment[20].

CONCLUSION

Electrocardiographic changes are frequent finding in sufferers of acute stroke. The cardiac consequences of stroke are likely to contribute to stroke related mortality. The re-polarization abnormalities are most significant for expecting in-hospital deaths due to acute stroke. The ischaemic changes, left ventricular hypertrophy, sinus tachycardia, atrial fibrillation and premature ventricular complexes rank later. Patients with acute stroke should receive continuous cardiac monitoring, during the hospital stay.

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