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QTc Interval Prolongation and Hemorrhagic Stroke: Any Difference Between Acute Spontaneous Intracerebral Hemorrhage and Acute Non-traumatic Subarachnoid Hemorrhage?

Osama Shukir Muhammed Amin[1], Sarwer Jamal Al-Bajalan[2], Alaa Mubarak[2]

[1]Department of Medicine, School of Medicine, International Medical University, Malaysia

[2]Department of Neurology, Shar Hospital, Iraq

Corresponding author: Osama Shukir Muhammed Amin MD, FRCP(Edin), FRCP(Glasg), FRCP(Ire), FRCP(Lond), FACP, FAHA. Associate Professor of Neurology and Consultant Neurologist, Department of Medicine, School of Medicine, International Medical University, Kuala Lumpur, Malaysia. E-mail: osamashukir@imu.edu.my

ABSTRACT

Background: A variety of ECG changes occur as an aftermath of stroke. Prolongation of the QTc interval is a well-documented change. We analyzed QTc interval prolongation among patients with acute hemorrhagic strokes. **Methods:** This observational study was conducted at the Emergency Department of Sulaymaniyah General Teaching Hospital and Shar Hospital from September 1st, 2014 to August 31st, 2015. Fifty patients who developed acute spontaneous hypertensive intracerebral hemorrhage (ICH) and 50 patients who developed acute non-traumatic subarachnoid hemorrhage (SAH) were included in the study. All patients underwent resting 12-lead ECG within half an hour of admission. The QTc interval was calculated and analyzed in those 100 patients. **Results:** Females (62%) outnumbered males (38%) with a female to male ratio of 1.6:1. Forty percent of the patients were between 60-69 years of age. Hypertension was seen in 82% of patients while left ventricular hypertrophy was documented in 40% of patients. The QTc was prolonged in 38 patients (17 patients in the ICH group and 21 patients in the SAH group). In both groups, males demonstrated QTc prolongation more than females. However, there were no statistically significant gender difference between both groups and within the same group. There was a statistically significant association between SAH and QTc prolongation (p-value<0.001); the ICH group did not demonstrate any significant relationship with QTc prolongation. **Conclusion:** Prolongation in the QTc interval was "statistically" associated with acute SAH only. No gender difference was noted; whether this observation is clinically significant or not, it needs further analytic studies.

Keywords: subarachnoid hemorrhage; intracerebral hemorrhage; stroke; QTc interval prolongation; ECG.

1. INTRODUCTION

Cardiovascular complications are extremely common following stroke and represent a major form of morbidity. These complications may be caused by focal cerebral injury or may be a manifestation of preexisting cardiac disease, which is common. According to international guidelines all patients with acute stroke need an ECG performed at the moment of admission to document any heart abnormalities (1). The association between heart-rate corrected QT (QTc) interval and cardiovascular morbidity and mortality is well established (2-5). A multitude of ECG changes have been observed in patients who presented with acute strokes, both ischemic and hemorrhagic. In particular, repolarization changes, such as prolongation in the QTc interval, have been noticed in as much as 90% of unselected stroke victims; these may well result in a management and diagnostic dilemma, both to physicians and neurologists. Another concern is that these cardiac electrophysiological changes might be responsible for sudden death in stroke sufferers (6).

2. PATIENTS AND METHODS

This cross sectional observational study was carried out at This observational study was conducted at the Emergency Department of Sulaymaniyah General Teaching Hospital and Shar Hospital from September 1st, 2014 to August 31st, 2015. Patients

Variable	ICH		SAH	
	Total Number	Prolonged QTc*	Total Number	Prolonged QTc*
Male	18	9	20	12
Female	32	8	30	9
Total	50	17	50	21

Table 1. Patients' total number, gender, and their QTc interval prolongation with respect to their stroke pattern; intracerebral hemorrhage (n=50), subarachnoid hemorrhage (n=50). *Defined as a corrected QT interval of >440 ms in males and 460 ms in females.

Gender	Number	SMD	P-value	95% Confidence Interval	
				Lower	Upper
Male	9	31.178		451.336	482.470
Female	8	18.7	0.38	465.462	501.753
Total	17	29.635			

Table 2. Comparison between males and females within the intracerebral hemorrhage group who had prolonged QTc interval.* -SMD, standardized mean difference. *Defined as a corrected QT interval of >440 ms in males and 460 ms in females.

aged ≥ 50 years who developed their first-ever spontaneous hypertensive intracerebral hemorrhage or acute non-traumatic subarachnoid hemorrhage of less than 48 hours from the onset were included in the study. A total of 100 consecutive patients were taken; 50 intracerebral hemorrhages and 50 subarachnoid hemorrhages.

Patients were excluded from our study if they had a history of ischemic stroke/transient ischemic stroke; subdural and epidural hematomas; electrolyte disturbances (e.g., hypocalcemia); and cardiac dysrhythmia/heart block. Likewise, a history of ingestion of any medication which could affect the QTc interval (e.g., antiarrhythmic or antidepressants).

All patients (n=100) underwent routine blood tests, including complete blood counts, erythrocyte sedimentation rate, liver function, urea and electrolyte, lipid profile, thyroid function, and prothrombin and activated thromboplastin times. An urgent non-contrast CT brain scanning was done at the time of emergency department admission in all patients. A transthoracic echocardiographic assessment was carried out within 2-3 days of hospital admission. All patients were examined by neurologists and neurology trainees.

A single 12-lead resting ECG examination was done within 30 minutes of emergency department admission. The QT interval was measured manually by a single person, from the onset of the QRS complex to the point at which the T wave ends. It was measured for 3 to 5 consecutive beats and averaged (6, 7). Lead II was chosen for this purpose as most normal reference ranges are based upon measurements from this limb lead (6, 8). The corrected value (QTc) was then calculated using the Bazett formula (9). Automated ECG machines were not used to calculate the QT and QTc intervals, as the accuracy of these automated tools has been shown to be limited (6, 10). A QTc interval of >44 ms in men and >46 ms in women was considered prolonged and abnormal (6, 7). The collected data were organized, tabulated, and statistically analyzed using Statistical Package for Social Sciences (SPSS) version 23.0 by an independent statistician. A comparison of variables was performed by Student's t-test and Levene's test for equality of variance. We calculated the P-value and 95% confidence interval (95% CI). Significance levels were set at P-value of less than 0.05 in all cases.

Gender	Number	SMD	P-value	95% Confidence Interval	
				Lower	Upper
Male	12	30.28		459.745	491.857
Female	9	28.31	0.18	478.782	528.782
Total	21	32.057			

Table 3. Comparison between males and females within the subarachnoid hemorrhage group who had prolonged QTc interval.* -SMD, standardized mean difference., *Defined as a corrected QT interval of >440 ms in males and 460 ms in females.

Variable	Number	SMD	P-value	95% Confidence Interval	
				Lower	Upper
Intracerebral hemorrhage	9	31.177		451.22	493.457
Subarachnoid hemorrhage	12	18.76	0.69	464.748	491.865
Total	21	26.79		461.652	487.578

Table 4. Comparison between males of the intracerebral hemorrhage group versus those of the subarachnoid hemorrhage group who had prolonged QTc interval.* -SMD, standardized mean difference. *Defined as a corrected QT interval of >440 ms in males and 460 ms in females.

Variable	Number	SMD	P-value	95% Confidence Interval	
				Lower	Upper
Intracerebral hemorrhage	8	18.96		472.645	501.727
Subarachnoid hemorrhage	9	28.32	0.41	483.810	532.822
Total	17	25.132		482.718	506.179

Table 5. Comparison between females of the ICH group versus those of the hemorrhagic group who had prolonged QTc interval.* -SMD, standardized mean difference. *Defined as a corrected QT interval of >440 ms in males and 460 ms in females.

3. RESULTS

A total of 100 patients with stroke were included in present study; 50 patients had acute hypertensive spontaneous intracerebral hemorrhages while the other 50 patients developed acute non-traumatic subarachnoid hemorrhage. The mean age of stroke patients was 64±9 years; 40% of them were in the group of 60-69 years. Females outnumbered males, with a female to male ratio as 1.6:1. Most (82%) of the stroke patients were hypertensives, 47% of them were hyperlipidemic, and 42% of them were diabetic (Tables 1-4). There was a significant association between the age of the patients and subarachnoid hemorrhage ($p<0.001$). No significant difference was observed among stroke patients with hemorrhage types with respect to gender ($p=0.6$).

Echocardiography findings were unremarkable among 56% of stroke patients; concentric left ventricular hypertrophy (and diastolic dysfunction) was found in 40 patients with intracerebral hemorrhage while 12 subarachnoid hemorrhage patients demonstrated left ventricular hypertrophy.

The mean RR interval of stroke patients was 603.8±246.9 msec; 87% of stroke patients had long RR interval. The mean QTc interval of stroke patients was 355.3±86.6 msec; 38% of them demonstrated prolonged QTc interval. A significant association was observed between intracerebral hemorrhage and hypertension ($p<0.001$) and a similar significance was noted between intracerebral hemorrhage and left ventricular hypertrophy ($p<0.001$).

Both hemorrhagic groups revealed no statistically significant difference with respect to the RR interval ($p=0.1$). The QTc interval was prolonged in 17 intracerebral hemorrhage patients while 21 patients with subarachnoid hemorrhage showed prolongation of that interval. There was a significant association between subarachnoid hemorrhage and prolongation of the QTc interval ($p<0.001$). However, no statistically significance gender difference was found within the same group and between the 2 groups (Tables 1-5).

4. DISCUSSION

Neurologists and cardiologists are frequently involved in coordinating the care of patients with a variety of conditions, the most common being stroke. A multitude of ECG changes have been observed in patients who presented with acute strokes, both ischemic and hemorrhagic. In particular, repolarization changes, such as prolongation in the QTc interval, have been noticed in as much as 90% of unselected stroke victims.

The mean age of our patients was 64±9 years. This finding is similar to the results of Al-Asadi and Habib study among Iraqi patients in 2014 (11) which reported a mean age of stroke patients as 63.8±12.3 years. This age reported by our study is in agreement with that reported in many Asian and developing countries (12, 13) but it was about one decade lower than that reported in Western countries (14). This difference from Western countries might be attributed to health lifestyles adopted by these communities in last decades, in addition to highly organized health services. There was a significant association between older age of the patients and subarachnoid hemorrhage ($p<0.001$). This is similar to results of Degos et al study in the USA (2012) (15). In our study, females outnumbered males. This study disagrees with many studies in finding a male preponderance (a male: female ratio of 1.27:1) (16). It was reported that stroke incidence rates are 1.25 times greater in men, but because women tend to live longer than men, more women than men die of stroke each year (17).

The main risk factor for stroke among our patients was hypertension. This is consistent with results of Sidhartha et al study in India (2015) (18) which concluded that hypertension was a major risk factor for medical complications of hemorrhagic stroke. There was a significant association between Intracerebral hemorrhage and systemic hypertension ($p<0.001$). A study from Italy (19) found that hypertension is more associated with intracerebral hemorrhage rather than ischemic stroke.

Echocardiographic findings were unremarkable in more than half of our patients; 40% of the patients had left ventricular hypertrophy. This is similar to results of Goldstein et al study in USA (2011) (20) which reported that strokes resulting from cardiac diseases and cardiac abnormalities-associated with neuromuscular disorders are examples of the many points of contact between neurology and cardiology.

In the present study, the mean RR interval of stroke patients was 603.8±246.9 msec; 87% of them had prolonged RR interval but no statistically significant difference was observed between intracerebral and subarachnoid hemorrhage patients regarding this RR interval prolongation. The mean QT interval was 371.6±61.9 msec; 15% of the patient demonstrated long QT interval. Long QT intervals were significantly found among SAH patients. This is consistent with results of van den Bergh et al study in Netherlands (2003) (21) which reported that ECG abnormalities frequently occur after aneurysmal subarachnoid hemorrhage (SAH). ECG abnormalities usually disappear within a day with no any change in the neurological or cardiac condition (22). They are considered markers of the severity of the SAH but not predictors for potentially serious cardiac complications or clinical outcome (23).

The mean QTc interval of stroke patients in our study was 355.3±86.6 msec; 38% of of the patients had long QTc interval. This is close to results of Malik et al study in Pakistan (2013) (24). Sakr et al found that 34% of the subarachnoid hemorrhage patients had a prolonged QTc (25). On the other hand, Bergh *et al* found that 61% of their patients had a prolonged QTc within 72 hours of hospital admission because ruptured cerebral aneurysm (26). Maramattom studied 110 patients with supra-tentorial intracerebral hemorrhage and concluded that changes in the ECG were observed in 64% of patients; 8% of them had prolonged QTc interval (27). Akbar et al analyzed 84 patients who had developed acute hemorrhagic stroke; he found that 63.4% and 68.29% of the patients had prolongation of the QTc interval in lead III and VI respectively (28).

The QTc was prolonged in 21 patients with subarachnoid hemorrhage while 17 patients in the spontaneous intracerebral hemorrhage group demonstrated QTc internal prolongation; there was a statistically significant association between subarachnoid hemorrhage and QTc interval prolongation in our study ($p<0.001$). This observation is consistent with the results of Colkesen et al study in UK (2007) (29). However, the "statistically" non-significant relationship between QTc interval prolongation and intracerebral hemorrhage needs to be refuted by further analytic studies. We found no gender differences within the each stroke type and between both stroke types with regard to QTc prolongation. This might have resulted from the relatively small target number and female preponderance.

Disturbances in the autonomic nervous system and a surge in the sympathetic nervous system output are thought to be responsible for these ECG abnormalities and changes. The frontal lobe, insular cortex, amygdala, and the stellate ganglia play a central role in controlling the autonomic nervous system and therefore, influencing the cardiac conduction system and heart rate (7, 28). When the QTc interval prolongs, the myocardium becomes unstable and ventricular ectopic beats develop frequently. The latter can readily degenerate into polymorphic ventricular tachycardia or even ventricular fibrillation (30, 31).

Khechinashvili and Asplund (30) concluded that the presence of QTc interval prolongation in acute stroke (ischemic and hemorrhagic) usually represents pre-existing coronary artery disease rather than a direct consequence of the stroke itself on the heart. On the other hand, Soliman and colleagues (32) found that QTc interval prolongation is associated with a significantly increased risk of incident stroke independent of traditional stroke risk factors. In addition, Maebuchi and coworkers (33) had linked QTc interval prolongation to the future development of cardiovascular disease in the general population.

Limitations of the study:

1. The number of cases was relatively small.

2. This is a single institutional study which does not reflect the practice of stroke in the whole of Iraq.

3. The target population was composed of patients of Kurdish ethnicity only, who might well have different genetic/cardiovascular risk factors from Arab patients (the latter group constitutes the majority of the Iraqi population and was not involved in the study).

4. There was no "healthy" group as well as no locally or nationally published articles which target the same topic, so that we might compare the results with.

5. The size and location of the stroke and their relationship with the QTc interval prolongation were not assessed.

6. Only a single ECG examination was done, at the time of the emergency room admission. No 24-hour cardiac Holter monitoring was done.

Therefore, the findings might well have been different if the aforementioned factors were addressed.

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