A look into prolonged Qtc Interval in Patients undergoing Long-Term Hemodialysis at Ibn Sina Hospital, Khartoum, Sudan - 2020

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Abstract

Cardiovascular diseases, including sudden cardiac death, are the leading cause of death in hemodialysis (HD) patients. A prolonged QT interval on the electrocardiogram (ECG) is a risk factor for sudden cardiac death in HD patients. Previous studies show a correlation between years of dialysis and Qtc prolongation. The aim of this cross-sectional study was to assess the prolonged Qtc interval as well as the associated electrolytes imbalances in long- term hemodialysis patients in Ibn Sina Hospital. It is an institution-based cross-sectional study, with total coverage sampling of the population. Our results illustrated that most of our participants were either 20-40 years old or 40 – 60 years old with a male predominance of approximately 68%. The association between Qtc prolongation and years of dialysis was nonsignificant (P value 0.611) in our study. When comparing between Qtc before and after the dialysis, a significant correlation (P value 0.002) was noted, which provoked the hypothesis that the dialysis affects the Qtc whilst the patient is undergoing the dialysis. Moreover, we found a significant correlation between magnesium (P value 0.009) and calcium (P value 0.044) levels with QT prolongation, potassium levels, on the other hand, showed a non-significant association (P value 0.283). **In conclusion**, the comparison between the Qtc before and after the patients underwent dialysis showed a significant correlation.

Keywords: Qt-interval; Hemodiyalysis; ECG; HD; Cardiac effects of dialysis

Introduction and Literature Review:

Cardiovascular diseases, including sudden cardiac death (SCD), are the leading cause of death in patients undergoing hemodialysis (HD) (1). Cardiac diseases account for approximately 40% of all-cause mortality in patients undergoing Maintenance hemodialysis (MHD). According to the United States Renal Data System, the single largest specific cause of death is arrhythmia (2). Dialysis, in and of itself, can be considered an arrhythmogenic stimulus. Moreover, uremic patients are characterized by a pro-arrhythmic substrate as a

result of them being at risk of ischemic heart disease, left ventricular hypertrophy and autonomic neuropathy, myocardial dysfunction, as well as changes in electrolyte concentration like calcium and potassium (3). In addition to other modalities, the electrocardiogram (ECG) remains an important method to identify cardiac abnormalities (4). ECG conduction abnormalities would be higher and cardiac conduction interval times longer among patients on dialysis when compared to those with CKD (4). The reasons for great incidences of arrhythmia and death are complex and multifactorial (5). Among the noninvasive techniques which can be useful for predicting the patients at risk for sudden death is the measurement of QT interval changes with a 12-lead surface electrocardiogram (6). QT dispersion (QTd), defined as maximum QT interval minus minimum QT interval for a given set of electrocardiogram lead, was proposed as an approximation for repolarization abnormalities and measured for regional heterogeneity of myocardial refractoriness (7,8). Prognostic value of QTd was evaluated in patients with end stage renal disease patients requiring hemodialysis and in patients with diabetes mellitus (9). A prolonged QT interval on the electrocardiogram (ECG) usually indicates delayed ventricular myocardial repolarization. Previous reports have shown that abnormal heart rate-corrected QT (Qtc) prolongation is an independent risk factor for SCD in patients with heart failure and in the general older population, and that prolonged Qtc interval predicts mortality in patients with Takotsubo cardiomayopathy or type 1 diabetes. A study demonstrated that prolonged Qtc was associated with SCD and total mortality in a case series of patients undergoing HD (1). A prolonged QT interval is defined by AHA/ACCF as a rate-corrected QT (Qtc) interval greater than the 99th percentile for females and males, which is 4480 ms and 4470 ms, respectively. Many standard EKGs continue to label a Qtc interval of 4440 ms as borderline Qtc interval prolongation (10). Progressive prolongation of the Qtc interval increases the risk for torsade de point, and the risk increases exponentially when the Qtc interval exceeds 500 ms (11). In 2011, the FDA released an announcement stating that the psychiatric drugs citalopram and escitalopram cause Qtc interval prolongation in a dose-dependent fashion, an effect which was determined to be of clinical significance for citalopram at the 60 mg dose (12). In recent years, methadone has come under scrutiny due to its potential to cause Qtc prolongation and increased risk for torsade de point. Of 43 cases of methadone-induced torsade de point reported to MedWatch, 8% were fatal and involved doses of methadone that exceeded 100 mg/day (13). Multiple studies have considered the Qtc-interval-prolonging potential of ondansetron. Of the six published studies, five found ondansetron to significantly increase the Qtc interval up to 24.9 ms; however, there is only one published report of torsade de point, which occurred in a child with occult congenital LQTS (14). Recently, azithromycin has been added to the growing list of drugs that can lead to Qtc interval prolongation and torsade de point. Compared to other macrolides, azithromycin may pose a lower risk of TdP (15). Hospitalized patients often receive Qtc-interval-prolonging drugs, placing them at greater risk (16). A risk score for Qtc interval prolongation was developed and validated in patients admitted to coronary care units (17). This risk score incorporates easily obtainable clinic risk factors including age, female sex, serum potassium, admitting Qtc interval, comorbid conditions such as acute myocardial infarction and heart failure, and specific concomitant drug therapy to calculate a risk score and categorize patients' risk of Qtc interval prolongation as low, moderate or high (17).

Chronic kidney disease (CKD) is Defined as impaired renal function for >3 months based on abnormal structure or function or suboptimal GFR with or without evidence of kidney damage. Symptoms usually only occur once stage 4 is reached (GFR <30) (18). A number of causes exist; including 1) Diabetes, 2) Glomerulonephritis, 3) Unknown 4) Hypertension or Renovascular diseases, and 5) Pyelonephritis and reflux nephropathy (18). CKD consists of 5 stages (18); these are:

1: GFR >90 ml/min. Here, GFR is of normal range (maybe slightly elevated). However, evidence of renal damage exists.

2: GFR = 60-89 ml/min. Here, GFR is slightly decreased. Evidence of renal damage exists

3A: GFR = 45-59 ml/min. GFR is moderately decreased. Evidence of renal damage may or may not exist

3B: GFR = 30-44 ml/min. GFR is moderately decreased. Evidence of renal damage may or may not exist

4: GFR = 15-29 ml/min. GFR is severely decreased. Evidence of renal damage may or may not exist

5: GFR = <15 ml/min. This is established renal failure.

Management of patients can be split into:

1. **Investigations:** Identifying and treating reversible causes: relieve obstruction, stop nephrotoxic drugs, deal with high Ca2+ and cardiovascular risk (stop smoking, achieve a healthy weight), tight glucose control in DM (18)
2. **Limiting progression/complications:** Even a small drop in BP may save significant renal function. Target BP is <130/80 (<125/75 if diabetic or ACR >70). Choice of drug is as per local guidance; in diabetic kidney disease, even with normal BP, treat with an ACE-I or ARB. Renal bone disease (risk of Osteodystrophy or adynamic bone disease): Check PTH and treat if raised (19). PO43 − rises in CKD, which increase PTH further, and also precipitates in the kidney and vasculature. Restrict diet, give binders (eg Calcichew) to decrease gut absorption. Vit D analogues (eg alfacalcidol) and Ca2+ supplements decrease bone disease and hyperparathyroidism (18). Cardiovascular modification: In CKD stages 1 and 2, risk from cardiovascular death is higher than the risk of reaching ESRF. Give statins to CKD patients with raised lipids as per guidelines for any patient. Give aspirin also (CKD is not a contraindication to the use of low-dose aspirin). Diet: Multidisciplinary team care is essential and all patients should be reviewed by a dietician for advice on a healthy, moderate protein diet, K+ restriction if hyperkalaemic, and avoidance of high phosphate foods (eg milk, cheese, eggs) (18).
3. **Symptom control:**

Anemia: Check haematinics and replace iron/B12/folate if necessary. If still anemic consider recombinant human erythropoietin. There are many formulations, all of which should increase Hb in an iron, B12 and folate replete patient. If Hb falls despite this, and no infection, haemolysis, or blood loss, etc. suspect red cell aplasia (anti-epo antibodies). Stop at once and get help from hematology. Keep Hb 100−120g/L; above this risks IV access thrombosis, increase BP, MI).

Acidosis: Consider sodium bicarbonate supplements for patients with low serum bicarbonate; this not only improves symptoms but may slow progression of CKD. Caution in patients with hypertension, as sodium load can increase BP.

Edema: High doses of loop diuretics may be needed (eg furosemide 250mg− 2g/24h} metolazone 5− 10mg/24h PO each morning), and restriction on fluid and sodium intake.

Restless legs/cramps: Check ferritin (low levels worsen symptoms), clonazepam (0.5−2mg daily) or gabapentin may help. Quinine sulfate (300mg) can help with cramps (18).

4. **Preparation for renal replacement therapy (RRT) – Hemodialysis (HD)**

Blood is passed over a semi-permeable membrane against dialysis fluid flowing in the opposite direction, thus blood is always meeting a less-concentrated solution and diffusion of small solutes occurs down the concentration gradient. Larger solutes do not clear as effectively (3). Ultrafiltration creates a negative transmembrane pressure and is used to clear excess fluid. Possible adverse effects of this intervention include: Disequilibration syndrome, hypotension, time consuming, access problems (arteriovenous fistula: thrombosis, stenosis, steal syndrome; tunneled
venous access line: infection, blockage, recirculation of blood) (18).

Initiation of dialysis: In clinical practice there is a wide variation in the timing of the starting dialysis therapy in patients with stage 5 CKD. There is a general tendency to start dialysis earlier with GFR close to 15 mL/min rather than below 10 mL/min, despite a recent study showing that early initiation of dialysis was not associated with an improvement in survival or clinical outcomes (19). This underscores the fact that decisions about the timing of starting dialysis therapy should be taken individually rather than by a numerical parameter.

Frequency and duration: Frequency and duration of dialysis are adjusted to achieve adequate removal of uremic metabolites and to avoid excessive fluid overload between dialysis sessions. An adult of average size usually receives 4–5 hours′ treatment three times a week. Twice-weekly dialysis is adequate only if the patient has considerable residual renal function. However, published data patients treated with hemodialysis six times a week benefited more with respect to the composite outcomes of death or change in left ventricular mass and quality of life but required more frequent interventions related to vascular access. Adequate/optimal dialysis should be adjusted to individual patients' needs. All patients are anticoagulated (usually with heparin) during treatment as contact with foreign surfaces activates the clotting cascade (19).

Previous Studies:
One study reported no significant differences among participants regarding the beginning PWV but the ending PWV was significant (20). Another study conducted to investigate whether the Qtc became prolonged with the years of dialysis reported that the Qtc interval is significantly longer in 4 and 7 years more than 1 year (1). A 2020 study focusing on newly-discovered patients reported Qtc prolongation in about 88% of patients which correlated positively with post dialysis Qtc (21). Another 2020 study postulated that the prolonged Qtc can by congenital or acquired and one of the acquired causes is CKD(22).
Another study reported that the following are associated with prolonged QT interval: 1) old age, 2)impaired kidney function, 3) hemodialysis, 4) low serum potassium, and 5) low left ventricular ejection fraction(23).

An Iranian study reported that the mean of pre and post dialysis R-R intervals were 859.22±96.85 ms and 870.43±91.45 ms, respectively ($p>0.05$). The mean of corrected QT cmax intervals increased significantly from 423.45±24.10 to 454.41±30.25 ms ($p<0.05$). The mean of QT dispersions and the corrected QT interval dispersions changed from 51.56±12.45 to 63.21±14.43 ms ($p<0.05$) from 59.40±13.58 to 68.33±14.55 ms ($p<0.05$), respectively. The changes in serum potassium and calcium levels were related with QT interval prolongation (3).

A Turkish study reported that HD patients (pre-HD and post-HD) had an abnormally prolonged QT interval compared to CKD patients (24).

Problem Statement and Justification:

With cardiovascular illness being the main cause of death amongst patients with renal failure and chronic hemodialysis, and with prolonged Qtc amongst patients undergoing HD is associated with higher mortality (3). Making studies into this topic of the upmost importance to see to it that it is addressed properly..

Objectives:
General Objective: To assess the prolonged Qtc interval in long term Hemodialysis patients in Ibn Sina Hospital 2020. Specific Objectives: 1. To correlate Qtc prolongation with the duration of hemodialysis. 2. To correlate Qtc prolongation with predialysis and after dialysis. 3. To correlate Qtc prolongation with electrolyte disturbance.

Research Methodology:
Study design: This was a hospital-based cross-sectional study conducted in Ibn Sina teaching hospital in Sudan. **Study population:** This study utilized total coverage sampling for hemodialysis patients the aforementioned hospital From August 2020 to December 2020. **Inclusion Criteria**: All patients undergoing regular hemodialysis in Ibn Sina dialysis center. **Exclusion Criteria:** Refusal to participate in the study, all patients suffering from long standing diabetes and hypertension before dialysis, all patients with history of

cardiovascular diseases, patients undergoing emergency hemodialysis, Patients who use or have recently used antidepressant medication. **Sample size & technique:** Total coverage for the study population in the specified period of study. Data was collected through a check-list which was filled by the researcher. ECG was conducted before and after the dialysis and readings of took serum Mg, K, Ca before dialysis.
Data Analysis: All data was analyzed using the statistical program of social science for computer (SPSS) version 20 **Study variables:** i) Age (years), ii) Gender (males v females), iii) Hypertension, iv) Diabetes, v) Serum Ca+, vi) Serum – K+, vii) Serum – Mg, viii) ECG changes.
Ethical considerations: Written ethical clearance and approval for conducting this research were obtained from Sudan Medical Specialization Board Ethical Committee. A written, informed consent was taken individually from all participants. Study data/information was used for the research purposes only. The participation was voluntary.

Results:

This study covered 66 participants receiving two sessions per week of regular hemodialysis at Ibn Sina hospital. The majority of the participants were aged between 20 and 60 years of age with only 15.14% aged above 60 years (Figure 1).

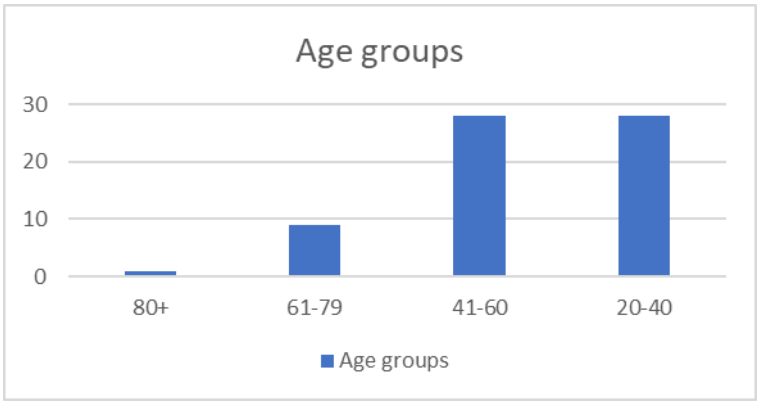

Figure 1: Age distribution amongst the study population

The study reported higher male gender percentage about 68% with male to female ratio about 2:1. Regarding educational status the study showed that 33.3% of the patients were primary school graduates and about 28.8% were secondary school graduates. The study also showed that 80% of the participants were unemployed. Concerning the Qtc prolongation, the study revealed about 69.7% of patients had prolonged Qtc at the time of study and only 30.3% were not prolonged not prolong (Figure 2).

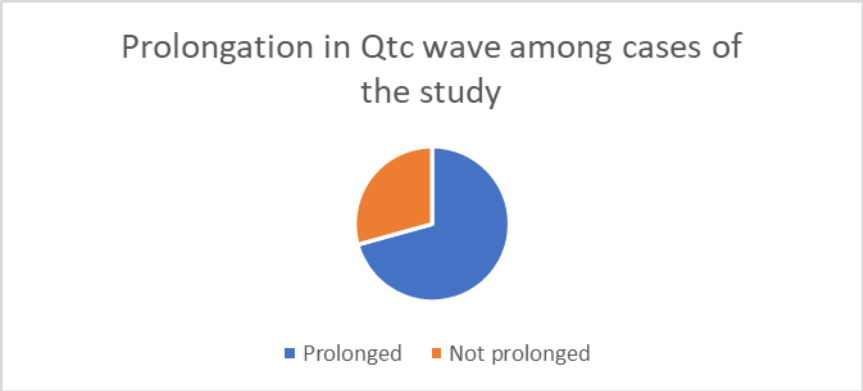

Figure 2: Prolongation in Qtc wave among cases of the study

The study illustrated no significant correlation between prolonged Qtc and the duration of hemodialysis with (P value 0.611) (Table 1).

Table 1: Correlation between duration of dialysis (in years) and prolonged Qt interval

	Years of Dialysis				
	Less than 1	1-5	6-10	11+	Total
Prolonged	1	25	12	8	46
Not prolonged	1	9	6	4	20
Total	2	34	18	12	66

Furthermore, our analysis revealed significant correlation between Qtc length readings before and after the dialysis with a P- value of <0.05 (Table.2) as well as some improvement in Qtc after dialysis in about 23.9% of participants.

Table 2: Correlation between Qtc length readings before and after dialysis

	After Dialysis			
		Not prolonged	Prolonged	Total
Before dialysis	Not Prolonged	12	8	20
	Prolonged	11	35	46
	Tota	23	43	46

A significant correlation between magnesium level and Qtc prolongation with P value <0.05 was also found. Furthermore, there was also a significant correlation between Qtc and calcium level with P-value of 0.044. No relationship was found between serum potassium and Qtc prolongation.

Discussion:

We found that about 70.3% of our participants had prolonged Qtc, while 29.7% didn't. These findings are consistent with Peng Liu et al (23). A 2019 study found an association between duration of dialysis and Qtc prolongation, these findings are not consistent with ours (1). Our findings in regards to the effects of dialysis

on Qt prolongation were consistent with Basturk Taner and colleagues (24).
An association between hypermagnesaemia and prolonged Qtc interval was noticed in our work, this is in agreement with the findings of 2015 study based in the USA (25).
Potassium level showed non-significant association, in agreement with SIDDHARTH G. findings (21).

Conclusion:
This study showed no significance between years of hemodialysis and Qtc prolongation. The study also showed significance Qtc prolongation after hemodialysis. Dialysis, per se, increased Qtc prolongation. Serum calcium and magnesium were found to be inversely associated with Qtc interval and risk of prolongation. The possibility of a correlation between Qtc prolongation and electrolyte imbalance/disturbance is raised here.

Recommendations:
1) Further studies on the topic.
2) Regular ECGs for all patients on hemodialysis.
3) Monitoring of patients on hemodialysis and management of any electrolyte imbalance.

The authors hereby declare no conflict of interest

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