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Positive Bias in the Prolonged QT Interval in Epilepsy is Related to the Calculation Method Rather Than Specific Anti-seizure Medications

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Abstract

Objective: Previous studies have shown conflicting results regarding the significantly prolonged QT interval in epilepsy, which could be attributed to the method of calculating the corrected QT (QTc). This study aimed to investigate the impact of the method on the calculation of QTc by determining the agreement between these methods using the Bland-Altman plot.

Methods: This cross-sectional study included 86 patients of both sexes aged <18 years. The patients were categorized into group 1 (new cases, untreated epilepsy); group 2 (sodium valproate treatment); and group 3 (levetiracetam treatment). The QTc interval of each participant was calculated using 10 different methods. Bias was assessed using Bland-Altman plot analysis.

Results: The mean±standard error of QTc was within the normal range and did not show significant differences between groups 2, 3, and 1, despite the detection of significant prolonged QTc in the number of patients in each group. Bland-Altman analysis showed significant disagreement between methods with positive mean bias when using Bazett's formula compared with other formulas.

Conclusion: Prolonged QTc interval was negligible in treated or untreated epileptic patients, and the overestimation of prolonged QTc was related to the calculation method used for overestimation of QTc, and a positive bias was related to the use of Bazett's formula compared with others.

Keywords: Epilepsy, anti-seizure medicines, QT-interval, Bland-Altman analysis

INTRODUCTION

Variable effects of epilepsy or its therapeutic agents showed variable effects on the heart. Epileptic patients, particularly those using carbamazepine and sodium valproate, were at risk of developing cardiac arrhythmias.[1] Evidence of ventricular repolarization, as shown by the prolongation of the QT period in the electrocardiogram (ECG) record, was observed during the interictal period in epilepsy patients.[2] QT interval, which is corrected QT (QTc) by using Bazett's formula, has been reported to be prolonged with carbamazepine, sodium valproate, and levetiracetam in epileptic patients.[3] Lamotrigine in different doses produced a non-significant decrease in the QTc interval estimated by using the Framingham equation.[4] In healthy subjects, gabapentin enalapril at higher doses did not produce a significant effect on the QTc interval estimated by using Fridericia's equation,[5] as did topiramate, carbamazepine, or sodium valproate as monotherapy, which did not produce effects on the QTc interval calculated by Fridericia's equation in epileptic children.[6] The variability in the effects of anti-seizure medicines (ASMs) may be related to the different methods of calculating the QTc interval. Several methods are used to calculate the QTc interval, including Bazett's, Fridericia's, Hodges', Framingham's, and other equations. In addition, the accuracy of the QT-nomogram is varied with each formula, as it has been found that the application of Rautaharju's formula [which used a cutoff value of 477 milliseconds (ms)] is superior to Bazett's or Fridericia's formulas.[7,8] Another study proposed a new formula derived from Bazett's, Hodges's, Fridericia's, and Framingham's formulas for calculating the QTc interval at a heart rate between 40 and 140 beats per minute, which showed agreement with Hodges's but not with other formulas by using Bland-Altman analysis.[9] Therefore, it is necessary to include the specifications of each formula in the assessment of the cardiac effects of ASMs, as the estimation of QTc by one method could be within normal limits, while using the other method will be significantly prolonged. This study aimed to detect the negative or positive bias by applying Bland-Altman analysis in calculating the QTc interval in epileptic patients treated with sodium valproate or levetiracetam compared with non-treated patients by applying different methods of calculation.

METHODS

Study Design

This cross-sectional study was conducted at the University of Diyala Faculty of Medicine, in 2023. The Institutional Scientific Committee of the University of Diyala Faculty of Medicine, approved this study according to the Helsinki guidelines (decision no: 243, date: 21.05.2024). The participants or their proxy were informed that the study would not interfere with their management, and they requested ECGs to document the effects of ASMs on the heart, specifically on ventricular repolarization represented by measuring the duration of the QT interval in ms.

Data Collection

Epileptic patients were recruited from public health centers who attended the medical centers for management or follow-up. Eligible patients included both sexes that were 18 years old. The criteria for inclusion were newly diagnosed epileptic patients (at the time of entry, they were not using treatment) and those treated with sodium valproate or levetiracetam for at least 3 months as part of a monotherapy schedule. Patients with cardiovascular diseases, pregnant women, and those using antiarrhythmic drugs or drugs that could potentially affect the heart rate or the conduction of impulses treated with more than one ASM were excluded. A total of 86 participants were recruited, and they were divided into the following groups:

Group 1: Newly diagnosed epilepsy (n=22; 10 females and 12 males),

Group 2: Epilepsy patients treated with a variable dosage schedule of sodium valproate (n=40; 13 females and 27 males),

Group 3: Epileptic patients treated with a variable dosage schedule of levetiracetam (n=24; 14 females and 10 males).

Definition of Pathological Conditions

The heart rate, P-R period, R-R interval, and QTm were measured manually by two independent physicians. A 12-standard lead ECG record was adjusted to 10 mm/mV, and the record speed was 25 mm/min. An ECG record strip with sinus rhythm was included in the study; abnormal rhythms were excluded from the study. The ECG strips were then scanned, and the scanned image was magnified using a PC windows photo viewer to zoom. The durations of small and large squares in the ECG records is 40 ms and 200 ms, respectively. The heart rate (which is equal to 300 divided by the number of large squares between two consecutive R waves), PR interval (which was measured from the beginning of the P-wave to the beginning of the QRS complex wave), and QTm (which is measured from the beginning of the QRS complex wave to the end of the T-wave; the average of 5 measurements were considered).

MAIN POINTS

- Anti-seizure medicines (ASMs) are safe and have minimal effects on ventricular repolarization.
- There are many methods for calculating the corrected QT (QTc) interval, but these methods did not show an agreement.
- The use of one method will show that one ASM significantly prolongs the QTc, while another method will show no significant effects.
- It is necessary to use the same calculation method for QTc when reporting the effects of ASMs on QTc.

The QTc interval was calculated using 10 different formulas as follows;

$QTc=QT/\sqrt{RR}$ (Bazett).[10]

$QTc=QT/RR^{1/3}$ (Fridericia).[11]

$QTc=QT+0.154\times(1-RR)$ (Framingham).[12]

$QTc=QT+0.00175\times(HR-60)$ (Hodges).[13]

$QTc=QT+0.24251-0.434\times e^{-0.0097\times HR}$ [Rautaharju (1)].[14]

$QTc=QT\times(120+-HR)/180$ (Rautaharju-2).[7]

$QT+0.205\times(1-RR)$ (Schlamowitz).[15]

$QTc=QTc=QT/RR^{0.413}$ (Dmitrienko).[16]

$QTc=QT-0.04462+0.664\times e^{-2.7\times RR}$ (Sarma).[17]

$QTc=QT/\log_{10}[10\times(RR+0.07)]\times\log 10\ (10.7)$ (Ashman).[18]

The cutoff values of QTc as a pathologically prolonged interval in children and adolescents are 455 ms (female) and 440 ms (male).[19]

Statistical Analysis

The results are expressed as a number, percentage, minimum-maximum value, median (25^{th}-75^{th} percentiles), 95% confidence interval, and mean±standard error. The results were analyzed using the Statistical Package for Social Sciences (version 24, IBM-compatible cooperation, USA). The data on the participants' characteristics were analyzed using Fisher's exact probability test (sex, residency, family history of epilepsy) and the independent Kruskal-Wallis test (age and duration of epilepsy). A two-paired one-way analysis of variance followed by the lysergic acid diethylamide test was used to determine significant differences between treated groups and new cases (the untreated group) of epilepsy. The positive and negative bias in the calculation of QTc using different formulas was assessed by using Bland-Altman analysis with one sample t-test applied to measure the difference in the QTc value and 95% confidence interval between each formula and other formulas. Statistical analysis was not applicable to no-observation data (zero-value) in the characteristics of the participants. A p value of less than 0.05 indicates the lower limit of significance.

RESULTS

The characteristics of the participants are displayed in Table 1. The distribution of sexes (p=350), age (p=0.222), residence (p=0.343), family history of epilepsy (p=0.578), and duration of epilepsy (p=0.776 between groups 1 and 3) were not significantly different. Of the participants, 19.1% (19 out of 86) had a positive family history, whereas 4.7% (4 out of 86) had a history of head injuries.

Figure 1 shows a positive correlation between QTm and R-R interval, and one participant in group 2 had a QTm of 640 ms.

The correlation coefficients were 0.559 (p=0.007), 0.469 (p=0.002), and 0.309 (p=0.142) for groups 1, 2, and 3, respectively. The correlation coefficient tended to decline in treated patients compared with untreated patients. The nomogram showed that the QTm of the participants with respect to their heart rate was within the normal limit, except for one participant in group 2, who was above the border line of the nomogram (Figure 2). This result indicates that QTm interval measurements were within normal limits for both untreated and treated patients of whatever medicines. Table 2 shows that there were non-significant differences between groups 1 and 2 or 3 in heart rate, P-R period, R-R interval, and QTm measurements. Furthermore, the QTc interval determined using the 10 formulas was not significantly different between the groups. The mean value of QTc calculated using Bazett's formula was higher than the corresponding values of QTc determined using other formulas in each group. Table 3 shows that significant prolonged QTc using Bazett's formula was observed in 3 participants in group 1 and 6 participants in group 2. Furthermore, the detection of a significantly prolonged QTc interval varied according to the calculation formula used. Accordingly, the significantly prolonged QTc in each studied group was related to the method for calculating the QTc interval.

As shown in Table 4, the Bland-Altman analysis showed significant bias (disagreement) in the value of QTc when calculated using different formulas. Disagreements between Bazeet and other methods were observed in all groups. The application of the Fridericia method was in agreement with other methods, including the Framingham, Hodges, and Rautanarju-2 methods only in untreated patients (group 1) and with the Hodges method in group 3. The Framingham method agreed with Hodges and Rautanarju-2 in calculating QTc for groups 1 and 3. The Hodges method agreed with the Dmitrienko method in group 3. Agreement in calculating the QTc interval was observed in the interplay comparison between the Rautaharju (1), Schlamowitz, Dmitrienko, Sarma, and Ashman methods. These findings indicate that there is no reliable method for calculating the QTc interval in epileptic patients.

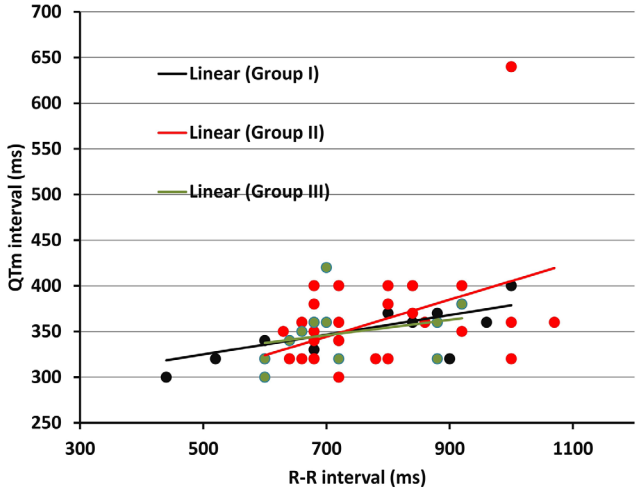

Figure 1. Relationship between R-R interval and measured QT interval (QTm) in epileptic patients Group 1: new cases; group 2: treated with sodium valproate; group 3: treated with levetiracetam
ms: Milliseconds

Table 1. The characteristics of the participants

Variables	Group 1	Group 2	Group 3	p value
Sex (male:female)	12:10	27:13	10:14	0.350
Age	14 (9, 15.5)	12 (8.3, 15.8)	14 (9, 18.8)	0.222
Residency				
Urban	18	33	22	0.343
Rural	4	7	2	
Family history of epilepsy	4	9	6	0.578
History of head injury	1	3	0	NA
The type of epilepsy				
Idiopathic generalized epilepsy	16	35	20	
Absence (petit mal) seizures	2	5	2	NA
Focal epilepsy	4	0	2	
Duration of epilepsy	-	2.5 (2, 3)	2.5 (1, 5.3)	0.776
History of status epilepticus	0	4	0	NA
Oral dosage regimen of antiepileptic (mg/day)	-	400 (400, 400)	1000 (500, 1000)	NA

The results are expressed as numbers and medians (25^{th}-75^{th} percentiles). The p value was calculated using an independent-samples Kruskal-Wallis test for age (between groups 1, 2, and 3) and duration of epilepsy (between groups 1 and 2) and by Fisher's exact probability test for other variables. NA: Not applicable because there are no observation data (zero value). The differences between groups 1 and 2 were not statistically analyzed because of the difference in the strength of antiepileptics

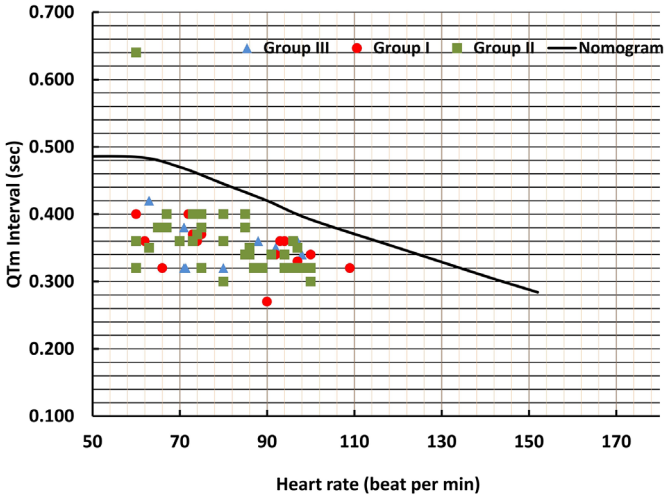

Figure 2. Nomogram of the relationship between heart rate and measured QT interval (QTm) in patients with epilepsy. Group 1: new cases; group 2: treated with sodium valproate; group 3: treated with levetiracetam

Table 2. Calculated QT interval ms using different formulas in patients with epilepsy

Variable	Group 1	Group 2	Group 3	p value
RR-interval ms	746±31 (440-1000)	768±20 (600-1070)	738±24 (600-920)	*0.537; †0.833
Heart rate bpm	83±3 (60-109)	82±2 (60-100)	84±3 (63-100)	*0.769; †0.802
QTm	351±6 (300-400)	358±9 (300-640)	349±6 (300-420)	*0.567; †0.865
Bazett-QTc	411±7 (337-485)	410±8 (320-640)	409±8 (341-502)	*0.966; †0.890
Fridericia, QTc	389±6 (331-445)	392±8 (320-640)	388±7 (334-473)	*0.836; †0.883
Framingham-QTc	390±5 (335-449)	394±8 (320-640)	389±6 (338-466)	*0.743; †0.927
Hodges-QTc	392±6 (331-435)	396±8 (320-640)	391±5 (339-425)	*0.640; †0.955
Rautaharju (1)-QTc	398±6 (334-443)	403±7 (320-640)	398±5 (345-433)	*0.643; †0.981
Rautaharju (2)-QTc	395±6 (331-444)	399±8 (320-640)	394±6 (340-434)	*0.674; †0.940
Schlamowitz-QTc	404±6 (341-466)	406±8 (320-640)	403±7 (345-482)	*0.841; †0.963
Dmitrienko, QTc	399±6 (334-469)	400±8 (320-640)	398±7 (337-487)	*0.929; †0.888
Sarma, QTc	402±7 (334-461)	402±8 (320-640)	399±7 (337-476)	*0.976; †0.818
Ashman, QTc	401±4 (334-471)	401±8 (320-640)	399±8 (337-488)	*0.984; †0.855

The results are presented as mean±SE (minimum-maximum). P values were calculated using a one-way, two-tailed analysis of variance with a post-hoc LSD test. *Compared between groups 1 and 2;†compared between groups 1 and 3. Group 1: New patients; group 2: patients treated with sodium valproate; group 3: patients treated with levetiracetam.
ms: Milliseconds, bpm: Beats per minute, QTc: Corrected QT, LSD: Lysergic acid diethylamide, SE: Standard error

Table 3. Distribution of participants with QTc intervals (≥440 ms for males and ≥550 ms for females) in epileptic patients

Formulas	Group 1 (n=22)	Group 2 (n=40)	Group 3 (n=24)
Bazett	3 (13.6)	6 (15%)	2 (8.3)
Fridericia	0 (0.0)	3 (7.5)	2 (8.3)
Framingham	0 (0.0)	2 (5)	2 (8.3)
Hodges	0 (0.0)	2 (5)	0 (0.0)
Rautaharju (1)	0 (0.0)	2 (5)	0 (0.0)
Rautaharju (2)	0 (0.0)	3 (7.5)	0 (0.0)
Schlamowitz	1 (4.5)	5 (12.5)	2 (8.3)
Dmitrienko	1 (4.5)	3 (7.5)	2 (8.3)
Sarma	1 (4.5)	3 (7.5)	2 (8.3)
Ashman	1 (4.5)	3 (7.5)	2 (8.3)

Group 1: New patients; group 2: patients treated with sodium valproate; group 3: patients treated with levetiracetam.
QTc: Corrected QT, ms: Milliseconds

Table 4. Bias in calculating the QTc interval by using Bland-Altman analysis for the agreement in between formulas in patients with epilepsy

Methods agreement	Group 1 (n=22)		Group 2 (n=40)		Group 3 (n=24)	
	Mean difference (95% CI)	p value	Mean difference (95% CI)	p value	Mean difference (95% CI)	p value
Bazett, Fridericia	21.3 (14.9, 27.7)	<0.001	18.5 (15.1, 22.0)	<0.001	21.3 (16.7, 25.8)	<0.001
Bazett-Framingham	20.3 (12.8, 27.8)	<0.001	16.5 (13.0, 19.9)	<0.001	19.5 (14.4, 24.6)	<0.001
Bazett-Hodges	19.1 (9.4, 28.9)	0.001	14.0 (10.1, 17.8)	<0.001	18.0 (9.2, 26.7)	<0.001
Bazett-Rautaharju (1)	12.7 (3.4, 22)	0.010	7.6 (4.1, 11.0)	<0.001	11.2 (2.1, 20.3)	0.018
Bazett-Rautaharju (2)	15.7 (5.7, 25.7)	0.004	10.9 (7.6, 14.2)	<0.001	14.8 (5.8, 23.7)	0.002
Bazett-Schlamowitz	7.4 (2.8, 11.9)	0.003	4.6 (2.8, 6.4)	<0.001	6.1 (3.1, 9.1)	<0.001
Bazett, Dmitrienko	11.3 (7.8-14.7)	<0.001	9.8 (8.0, 11.6)	<0.001	11.2 (8.8, 13.6)	<0.001
Bazett, Sarma	8.8 (6.1, 11.5)	<0.001	8.7 (6.8, 10.6)	<0.001	9.8 (7.0, 12.7)	<0.001
Bazett, Ashman	9.6 (7.4, 11.8)	<0.001	9.0 (7.5, 10.5)	<0.001	10.2 (8.5, 10.5)	<0.001
Fridericia, Framingham	-0.86 (-2.32, 0.59)	**0.233**	-2.0 (-3.0, -1.1)	<0.001	-1.6 (-3, -0.2)	0.006
Fridericia, Hodges	-2.1 (-7.7, 3.4)	**0.430**	-4.6 (-7.5, -1.6)	0.004	-3.3 (-10.3, 3.7)	**0.221**
Fridericia, Rautaharju (1)	-8.6 (-14.0, -3.0)	0.005	-7.7 (-10.3, -5.1)	<0.001	-10.3 (-17.9, -2.6)	0.002
Fridericia-Rautaharju (2)	-5.59 (-11.7, 0.5)	0.069	-10.9 (-14.3, -7.6)	<0.001	-6.5 (-13.8, 0.8)	0.026
Fridericia, Schlamowitz, Switzerland	-14.1 (-16.8, -11,4)	<0.001	-14.0 (-16.5, -11.4)	<0.001	-15.3 (18.0, -12.6)	<0.001
Fridericia, Dmitrienko	-10.0 (-13.0, -7.0)	<0.001	-8.72 (-10.4, -7.1)	<0.001	-10.0 (-12.2, -7.8)	<0.001
Fridericia, Sarma	-12.3 (-19.2, -5.5)	0.001	-9.8 (-12.8, -6.7)	<0.001	-11.4 (-15.8, -7.1)	<0.001
Fridericia-Ashman	-11.6 (-16.0, -7.1)	<0.001	-9.6 (-11.6, -7.5)	<0.001	-11.1 (-13.8, -8.3)	<0.001
Framingham-Hodges	-1.3 (-6.0, 3.4)	**0.579**	-2.5 (-5.0, -0.03)	0.047	-1.7 (-7.8, 4.3)	**0.566**
Framingham-Rautaharju (1)	-7.8 (-12.7,-2.9)	0.003	-8.9 (-11.7, -6.1)	<0.001	-8.7 (-15.3, -2.0)	0.013
Framingham-Rautaharju (2)	-4.7 (-10.08, 0.63)	**0.080**	-5.7 (-8.0, -3.4)	<0.001	-4.9 (-11.4, 1.6)	**0.133**
Framingham-Schramowitz	-13.2 -16.4, -10.0)	<0.001	-11.9 (-14.0, 9.8)	<0.001	-13.8 (-18.2, -11.3)	<0.001
Framingham, Dmitrienko	-9.1 (-13.2, -5.1)	<0.001	-6.7 (-8.5, -4.9)	<0.001	-8.4 (-11.3, -5.6)	<0.001
Framingham, Sarma	-11.5 (-19.3, -3.6)	0.006	-7.72 (-10.5. -5.0)	<0.001	-9.8 (-13.8, -5.8)	<0.001
Framingham, Ashman	-10.7 (-16.3, -5.2)	<0.001	-7.5 (-9.6, -5.4)	<0.001	-9.5 (-12.7, -6.3)	<0.001
Hodges-Rautaharju (1)	-6.5 (-7.5, -5.5)	<0.001	-6. 4 (-7.2, -5.5)	<0.001	-7.0 (-7.8, -6.1)	<0.001
Hodges-Rautaharju (2)	-3.5 (-4.8, -2.1)	<0.001	-3.2 (-4.2, -2.1)	<0.001	-3.2 (-4.6, -1.9)	<0.001
Hodges-Schlamowitz	-12.0 (-17.9, -6.1)	<0.001	-9.4 (-12.1, -6.7)	<0.001	-12.0 (-18.6, -5.5)	0.001
Hodges, Dmitrienko	-7.9 (-14.9, -0.8)	0.030	-4.2 (-7,1, -1.2)	0.007	-6.7 (-14.3, 0.9)	**0.079**
Hodges-Sarma	-10.2 (-21.0, 0.2)	0.054	-5.2 (-7.9, -2.5)	<0.001	8.12 (14.9, 1.3)	0.021
Hodges-Ashman	-9.5 (-17.9, -1.1)	0.029	-5.0 (-8.0, -2.0)	0.002	-7.8 (-15.4, -0.1)	**0.046**
Rautaharju (1)-Rautaharju (2)	3.0 (1.8, 4.3)	<0.001	3.2 (2.0, 4.4)	<0.001	3.8 (2.4, 5.1)	**<0.001**
Rautaharju (1)-Schlamowitz	-5.45 (-11.09, 0.18)	0.057	-3.0 (-5.4, -0.7)	0.013	-5.1 (-12.1, 1.9)	**0.146**
Rautaharju (1)-Dmitrienko	-1.4 (-8.2, 5.5)	**0.683**	2.2 (-0.7, 5.1)	**0.135**	0.3 (-7.8, 8.3)	**0.950**
Rautaharju (1)-Sarma	-3.7 (-13.9, 6.5)	**0.462**	1.2 (-1.3, 3.7)	**0.344**	-1.2 (-8.0, 6.0)	**0.739**
Rautaharju (1)-Ashman	-3.0 (-11.2, 5.2)	**0.462**	1.4 (-1.5, 4.3)	**0.343**	-0.8 (-9.0, 7.3)	**0.835**
Rautaharju (2)-Schlamowitz	-8.5 (-14.9-, -2.1)	0.011	-6.2 (-8.6, -3.8)	<0.001	-8.8 (-15.8, -1.9)	0.015
Rautaharju (2)-Dmitrienko	-4.4 (-11.9, 3.05)	**0.233**	-1.0 (-3.4, 1.4)	**0.404**	-3.5 (-11.3, 4.3)	**0.364**
Rautaharju (2)-Sarma	-6.7 (-17.8, 4.3)	**0.219**	-2.0 (-4.7, 0.63)	**0.132**	-4.9 (-12.3, 2.4)	**0.179**
Rautaharju (2)-Ashman	-6.0 (-14.9, 2.9)	<0.001	-1.8 (-4.3, 0.7)	**0.144**	-4.6 (-12.5, 3.4)	**0.245**
Schlamowitz, Dmitrienko	4.1 (2.4, 5.8)	<0.001	5.2 (3.3, 7.1)	<0.001	5.3 (3.6, 7.1)	<0.001
Schlamowitz-Sarma	1.8 (-3.6, 7.1)	**0.497**	4.2 (2.2, 6.2)	<0.001	3.9 (2.0, 5.8)	<0.001
Schlamowitz, Ashman	2.5 (-0.5, 5.5)	0.497	4.4 (2.6, 6.2)	<0.001	4.3 (2.6, 5.9)	<0.001
Dmitrienko-Sarma	-2.1 (-6.6, 2.0)	**0.277**	-1.0 (-2.9, 0.9)	**0.285**	-1.1 (-4.4, 1.6)	**0.342**
Dmitrienko, Ashman	-1.6 (-3.2, 0.03)	**0.054**	-0.8 (-1.3, -0.4)	0.001	-1.1 (-1.8, -0.4)	0.003
Sarma-Ashman	0.7 (-2.1, 3.5)	**0.597**	0.2 (-1.4, 1.8)	**0.800**	0.3 (-2.2, 2.9)	**0.727**

The p values were calculated using a sample t-test. Group 1: new cases; group 2: patients treated with sodium valproate; group 3: patients treated with levetiracetam. The bold cell exhibited a non-significant difference, indicating agreement.
QTc: Corrected QT, CI: Confidence interval

DISCUSSION

The results showed that significant disagreement between the methods used in calculating QTc interval was the cause of prolonged QTc interval detection in epilepsy patients without treatment or treated with sodium valproate or levetiracetam. The study findings are unaffected by the participant characteristics because no significant differences in the individuals' distinguishing characteristics. The results of this study showed that prolonged QTc intervals were observed between 0-13.6%, 5-15%, and 0-8.3% in groups 1, 2, and 3, respectively. The variability in these percentages is related to the methods of calculating the QTc interval. Bazett's method overestimated the QTc interval compared with the other methods. It has been found that a significantly prolonged QTc interval, which was calculated using Bazett's method, was 454 ms (mean) in epileptic children <2 years of age.[20] Therefore, using Fridericia's or Framingham's methods will result in a decrease in the mean value of QTc by 21.3 and 20.3 ms, respectively; i.e., the QTc interval is within the normal range.

In adults, the QTc interval calculated using Fridericia's formula was 441.2±56.6 ms in patients treated with levetiracetam, which is significantly higher than the cutoff value of QTc [21], which is higher than the QTc interval calculated using Dmitrienko's, Sarma's, or Ashman's methods. Therefore, the calculation method is critical for identifying patients at risk of developing prolonged QTc intervals. Gervasi et al.[22] showed a significant correlation between heart rate and QTc interval using Bazett's and Framingham's methods, but not Fridercia's method. Furthermore, there is a difference in the QTc values estimated by Bazett's (469 ms), Hodges's (361 ms), Framingham's (458 ms), and Fridericia's (451 ms) indices, which agrees with the findings of this study.[22] Another study tested nine formulas by using Person's correlation test between two formulas of the following: Bazett's, Fridericia's, Hodges's, Sarma's, Lecocq's, Rautaharju's, Framingham's (Sagie's), Arrowood's, and Malik's formulas and found that the detection of prolonged QT intervals depended on the estimation method of calculation.[23] Another study reported significant errors in the assessment of drug-induced prolonged QTc interval, particularly with Bazett's and Fridericia's methods, but the study did not mention the magnitude of bias for these formulas.[24] The positive bias found using Bazett's method in this study is consistent with others who reported false positive results for prolonged QTc intervals calculated using Bazett's method in children, and those authors recommended using Fridericia's method.[25]

The present study showed that the mean difference in QTc between Bazett's and Fridericia's methods was 21.3 ms, which indicates that this method is preferable for calculating QTc in children. The wide mean differences in the calculated QTc interval between Bazett's and Fridericia, Framingham, or Hodges's formulas allow these formulas to replace Bazett's formula in the calculation of the QTc interval.[26] The strength of this study is using the Bland-Altman plot analysis, which detects the magnitude of positive bias and an agreement between Friedericia's-Framingham's (+1 ms) and Fridericia's-Hodges's (+2.2 ms). Furthermore, this study revealed that epilepsy per se is not associated with prolonged QTc interval, whereas sodium valproate and levetiracetam significantly prolonged QTc interval in epileptic patients by up to 7.5% and 8.3%, respectively.

Study Limitations

One important limitation of this study is the small sample size, which is difficult to overcome because the study was conducted on specific patients aged 18 years.

CONCLUSION

This study highlights the need to use a proper formula for calculating the QTc interval, particularly for the assessment of drugs in epilepsy, by using Bland-Altman plot analysis. Friedericeria, Framingham, and Hodges formulas showed agreement regarding QTc, and ASMs induced significant prolonged QTc in a small percentage.

Ethics

Ethics Committee Approval: This cross-sectional study was conducted at the University of Diyala Faculty of Medicine, in 2023. The Institutional Scientific Committee of the University of Diyala Faculty of Medicine, approved this study according to the Helsinki guidelines (decision no: 243, date: 21.05.2024).

Informed Consent: It is verbal. Written consent not applicable.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.S.A., Concept: M.S.A., Design: M.S.A., Data Collection or Processing: A.K.A., Analysis or Interpretation: M.S.A., Literature Search: M.S.A., A.K.A., Writing: M.S.A., A.K.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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