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ORIGINAL ARTICLE

ANALYSIS OF DRUGS EFFECTS ON QTc INTERVAL PROLONGATION IN CRITICALLY ILL PATIENTS IN INTENSIVE CARE UNITS

ANALIZA DEJSTVA LEKOVA NA PRODUŽENJE QTc INTERVALA KOD KRITIČNO OBOLELIH PACIJENATA U JEDINICAMA INTENZIVNOG LEČENJA

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Abstract

Introduction: The QTc interval is considered extended if its duration is longer than 460 ms for men, or 470 ms for women. Its prolongation is an often-underdiagnosed condition with a higher prevalence than clinicians realize. Numerous drugs can prolong the QTc interval.
Aim: The aim of this study was to analyze the impact of drug interactions on prolonging the QTc interval in critically ill patients.
Material and methods: This is a cross-sectional observational study with retrospective data collection of adult patients admitted to one of the three intensive care units (ICU) of the Clinical Hospital Center “Bezanijska kosa” from April to September 2022. To identify risk factors for the development of a prolonged QTc interval, patient variables were compared between patients with prolonged and those with normal QTc intervals.
Results: A number of 166 patients of average age 70.7 ± 12.2 years were included in the study of whom 45.2% were women. The overall prevalence of QTc prolongation was 42.8% (71/166; 95% CI = 35.1% - 50.7%). When analyzed by gender, the prevalence was 50.5% (95% CI = 39.9% - 61.2%) in men and 33.3% (95% CI = 22.9% - 45.2%) in women. The difference between men and women was not statistically significant (p = 0.12). During their stay in the ICU, 32 patients (19.3%, 95% CI = 13.6% - 26.1%) were prescribed two drugs known to be associated with QTc interval prolongation. Among patients with prolonged QTc intervals, 27 out of 32 (84.4%, 95% CI = 67.2% - 94.7%) received these drugs, compared to 5 out of 32 patients (15.6%, 95% CI = 5.3% - 32.8%) with normal QTc interval duration who received the same drugs.
Conclusion: The study showed a high prevalence of prolonged QTc interval in critically ill patients and pointed to the most likely existence of a higher risk of its prolongation when drugs whose interaction can lead to its prolongation are used at the same time.

Keywords:
QTc interval,
intensive care units,
drugs interactions

The authors declare no conflicts of interest.

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Sažetak

Uvod: QTc interval se smatra produženim ukoliko je njegovo trajanje duže od 460 ms kod muškaraca, odnosno 470 ms kod žena. Produženje QTc intervala predstavlja stanje koje se često ne dijagnostikuje i čija je prevalencija verovatno veća nego što kliničari misle. Mnogi lekovi mogu da produže QTc interval, samostalno ili u interakciji sa drugim lekovima.
Cilj: Cilj ovog rada bio je da analizira uticaj interakcije lekova na produženje QTc intervala kod kritično obolelih pacijenata.
Materijal i metode: U pitanju je opservaciona studija preseka sa retrospektivnim prikupljanjem podataka adultnih pacijenata primljenih u neku od tri jedinice intenzivnog lečenja Kliničko-bolničkog centra (KBC) „Bežanijska kosa" u periodu od aprila do septembra 2022. godine. U cilju identifikacije faktora rizika za nastanak produženog QTc intervala, poređene su varijable između pacijenata sa produženim QTc i onih sa normalnim QTc intervalom.
Rezultati: U studiju je bilo uključeno 166 pacijenata prosečne starosti 70,7 ± 12 godina, od kojih su 45,2% bile žene. Prevalencija produženja QTc intervala bila je 71/166, tj. 42,8%(95% CI = 35,1 - 50,7%), 50,5% (95% CI = 39,9% - 61,2%) među muškarcima i 33,3% (95% CI = 22,9% - 45,2%) među ženama (p = 0,12). Tokom boravka u jedinici intenzivnog lečenja (JIL), 32 pacijenata je imalo preskripciju 2 leka za koje je poznato da su povezani sa produženjem QTc intervala (19,3%, 95% CI = 13,6 - 26,1%). Među pacijentima sa produženim QTc intervalom, 27/32 (84,4%, 95% CI = 67,2% - 94,7%) primalo je lekove koji su povezani sa produženjem QTc interval, dok je 5/32 sa normalnim QTc intervalom (15,6%, 95% CI = 5,3 - 32,8%) primalo lekove koji su povezani sa produženjem QTc intervala.
Zaključak: Naša studija je pokazala visoku prevalenciju produženog QTc intervala kod kritično obolelih pacjijenata i ukazala na najverovatnije postojanje većeg rizika od produženja QTc intevala kada se istovremeno koriste lekovi čija interakcija može dovesti do njegovog produženja.

Ključne reči:
QTc interval,
jedinice intenzivnog lečenja,
interakcije lekova

Introduction

The QT interval is a measurement used in electrocardiography (ECG) that represents the total time taken for the ventricles of the heart to depolarize and then repolarize. It is measured from the beginning of the Q wave (the start of the QRS complex) to the end of the T wave on an ECG. The duration of the QT interval can be influenced by the heart rate; therefore, it is often corrected for heart rate using various formulas, with Bazett's formula being the most commonly used. The corrected QT interval (QTc) is calculated as the QT interval divided by the square root of the R-R interval (the time between two successive R waves), and it allows for comparison across different heart rates (1).

A QTc is considered long when it is greater than 460 ms in males and 470 ms in females. The length of the QTc interval depends on sodium channels responsible for depolarization, input-rectifying potassium channels (Kir) and voltage-gated potassium channels responsible for repolarization (2).

Causes of QTc prolongation

Prolonged QTc interval can be congenital (mutation of genes for proteins that form Kir, Kr, Ks, Na and L-Ca channels) or acquired due to various electrolyte disorders (especially hypocalcemia, hypomagnesemia and hypokalemia), and can also develop during acute myocardial infarction. The QT interval can be extended by numerous pharmacological preparations (mainly Kir blockade) (2-4).

Risk factors for QTc prolongation

Prolongation of the QTc interval is also associated with certain risk factors such as the patient's age (patients older than 65 years), female sex, bradycardia, heart disease and the use of diuretics (2).

No drug that prolongs the QT interval should increase the QTc above 500 ms (i.e. 550 ms if there is a branch block). If this rule is followed, the risk of ventricular arrhythmia is significantly reduced (3).

It is important to note that QTc prolongation can lead to sudden cardiac death and increase the risk of dangerous *torsades de pointes*. Thus, the prolongation of the QTc interval is linked to an increased risk of extended hospital stays and mortality (5, 6).

QTc prolongation is an often-underdiagnosed condition with a higher prevalence than clinicians realize (6).

Numerous drugs can prolong the QTc interval, either independently or in interaction with other drugs, therefore, the aim of this work is to analyze the influence of drug interaction on the prolongation of the QTc interval in critically ill patients, i.e. patients with conditions that further increase the risk of this phenomenon and the consequences he carries.

Materials and methods

Study design

It is a cross-sectional observational study with retrospective data collection of adult patients admitted to one of three intensive care units of the Clinical Hospital Center "Bezanijska kosa" from April to September 2022.

The data of patients older than 18 years, of both sexes, were analyzed. Exclusion criteria encompassed patients with left bundle branch block or other conduction abnormalities hindering the measurement of QTc interval, individuals with implanted pacemakers, as well as those admitted for less than 48 hours for standard post-procedural monitoring or following elective surgical procedures.

Data was collected from the medical histories of patients stored in the hospital's archive. These records included comprehensive patient histories, demographic information, clinical history, medication lists, laboratory results, and ECG records.

The ECG records of all patients were reviewed and the QTc interval was determined using the Bazett method (1). The QTc prolongation was characterized by a measurement exceeding 460 milliseconds for men and 470 milliseconds for women.

The following steps were taken to gather data on the use of these drugs: for each patient, the detailed medical histories stored in the hospital's archive were reviewed. These histories included comprehensive lists of medications that the patients were taking during their stay in the ICU. The medication lists from the patients' histories were cross-referenced with the predefined list of drugs known to prolong the QTc interval. This list included medications recognized in medical guidelines and literature having the potential to extend the QTc interval. For each patient identified as using one or more drugs from the predefined list, adequate data was extracted and recorded.

For each patient, data was collected on sex, age, use of drugs suspected of prolonging QTc interval, the type ICU in which they were hospitalized (coronary, internist or surgical intensive care unit), any emergency surgical procedure performed by admission, diagnosis on admission (myocardial infarction, heart failure, diabetes, nephropathy or other), systolic, diastolic and mean arterial pressure values, as well as measured laboratory values of sodium and potassium in the serum.

Statistical analysis

Patient characteristics were depicted as absolute or relative frequencies or as mean values with standard deviations. Population proportions were accompanied by 95% binomial confidence intervals (CI). Proportions were compared using the Chi-square test, while arithmetic means were compared using Student's t-test. To discern risk factors for QTc prolongation, patient variables were compared between those with prolonged QTc intervals and those with normal QTc intervals. Variables with a p-value below 0.10 were incorporated into a multivariate logistic regression analysis model. To assess the risk of QTc prolongation linked to drug interactions, logistic regression was employed, adjusting for established risk factors such as age, sex, heart failure, and hypokalemia. Multivariate analysis outcomes are reported as odds ratios (O.R.) with corresponding 95% confidence intervals. Statistical analysis was conducted using EZR (The R Foundation for Statistical Computing).

Results

Patient characteristics

The study included 166 patients with an average age of 70.7 ± 12 years, of whom 45.2% were women. Emergency surgery was performed in 41 patients (24.7%). On admission, 25 patients had diabetes mellitus (15.1%), 6 patients had nephropathy (3.6%), 13 patients had heart failure (7.8%) and 16 patients had myocardial infarction (9.6%) (**table 1**).

Table 1. Characteristics of the studied population.

Age, years	70.7 ± 12	
Females (n, %)	75	45.2
Emergency surgery (n, %)	41	24.7
Diabetes mellitus (n, %)	25	15.1
Nephropathy (n, %)	6	3.6
Heart failure (n, %)	13	7.8
Myocardial infarction (n, %)	16	9.6

Prevalence of QTc Prolongation and QTc Interval Duration

The prevalence of QTc prolongation was 71/166, i.e. 42.8% (95% CI = 35.1% - 50.7%), 50.5% (95% CI = 39.9% - 61.2%) among men and 33.3% (95% CI = 22.9% - 45.2%) among women (p = 0.12).

The prevalence of QTc values over 500 ms was 55.5% (95% CI = 45.7% - 65.1%), 32.4% (95% CI = 23.7% - 42.1%) among men and 23.1% (95% CI = 15.6% - 32.2%) among women.

Arithmetic mean duration of QTc interval among patients with its prolongation was 520 ± 45.4 ms (range 462 to 694 ms), 518 ± 48.4 ms among men and 523 ± 41 ms among women (p = 0.59). In patients without prolongation of the QTc interval, the arithmetic mean of its duration was 432 ± 25.8 ms.

Compared with the normal duration of QTc interval, patients with prolonged QTc interval in ICU are older, have higher heart rate and higher body temperature.

Patients with a prolonged QTc interval had more frequent diagnoses of myocardial infarction, heart failure, diabetes mellitus and nephropathy, but no statistically significant association was shown compared to the group of patients with a normal QTc interval duration (p = 0.31) (**table 2**).

Table 2. Characteristics of patients in groups with normal and prolonged QTc interval.

Characteristics of patients	Normal QTc	Prolonged QTc	p
Age (years)	67.7 ± 12.5	72.3 ± 11.4	0.12
Female	31 (41.3%)	44 (58.7%)	0.31
Emergency surgery	17 (41.5%)	24 (58.5%)	0.31
Systolic blood pressure (mmHg)	123.9 ± 16.4	121.5 ± 21.9	0.48
Diastolic blood pressure (mmHg)	78.8 ± 10.4	78.2 ± 14.5	0.76
Heart rate	79.8 ± 25.2	87.6 ± 25.4	0.06
Body temperature (^{0}C)	36 - 37.5	36 - 38.5	0.2
Sodium (mmol/L)	138.9 ± 6.2	137.7 ± 8.2	0.33
Potassium (mmol/L)	4.37 ± 0.77	4.27 ± 0.86	0.44

Drug Prescriptions and QTc Prolongation

During their intensive care unit (ICU) stay, 32 patients were prescribed 2 drugs known to be associated with QTc prolongation (19.3%, 95% CI = 13.6% - 26.1%). Among patients with prolonged QTc interval, 27/32 (84.4%, 95% CI = 67.2% - 94.7%) received drugs associated with QTc prolongation while 5/32 with normal QTc interval (15.6%, 95% CI = 5.3% - 32.8%) received drugs associated with QTc prolongation (p = 0.47) (**figure 1**).

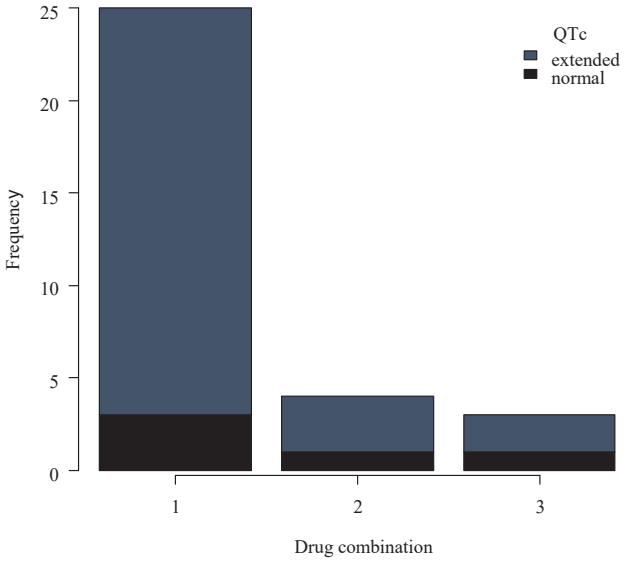

Figure 1. Frequency of QTc interval prolongation in patients who used combinations of drugs that lead to QTc interval prolongation.
Drugs combination:
1. amiodarone and furosemide
2. amiodarone and levofloxacin
3. amiodarone and azithromicin.

Logistic Regression Analysis for QTc Prolongation Risk

In order to examine the risk of prolongation of the QTc interval for each of the interactions between the two drugs, logistic regression was performed to estimate the O.R. for each of the interactions. Interactions most likely to have a higher risk of QTc prolongation are interactions of amiodarone with furosemide (O.R. 6.727), levofloxacin (O.R. 1.535) and azithromycin (O.R. 1.931) (**table 3**).

Table 3. The risk of QTc prolongation associated with the use of drugs that prolong the QTc interval adjusted for age, sex, hypokalemia and heart failure.

Drugs that prolong the QTc interval	O.R.	95% CI		p
Amiodarone and furosemide	6.727	1.070	42.298	0.042
Amiodarone and levofloxacin	1.535	0.52	45.721	0.805
Amiodarone and azithromycin	1.931	0.91	41.090	0.673

Discussion

In this pilot study, the relationship between the use of potentially proarrhythmogenic drugs and QTc prolongation was examined in patients treated in intensive care units of a tertiary care hospital (coronary unit, surgical intensive care unit, level 3 intensive care unit, and internist intensive care unit). The aim of the study was to analyze the influence of drug interactions on the prolongation of the QTc interval in critically ill patients, focusing on those with conditions that further increase the risk of this phenomenon and its associated consequences.

According to the results, over a third of patients admitted to the intensive care units of the Clinical Hospital Center "Bezanijska kosa" had a prolongation of the QTc interval. Among the patients included in the study, a probable association of prolongation of the QTc interval with drugs described in the literature such as amiodarone and furosemide was observed (7).

The mechanism of action of amiodarone involves the blockade of Kir leading to prolongation of the action potential (AP). It is known that drugs that prolong the cardiac action potential (which is clinically detected as prolongation of the QTc interval) can also have paradoxical proarrhythmic effects. This particularly occurs in patients taking other drugs that prolong QTc interval, in patients with electrolyte disturbances involved in repolarization (hypokalemia) or in people with hereditary prolongation of the QTc interval (Romano-Ward syndrome) (8).

Amiodarone prolongs the refractory period to a greater extent in slow arrhythmias compared to fast ones (4). That is why in this study heart rate was considered in all patients. However, a statistical association of a slower heart rate with a higher risk of QTc prolongation was not demonstrated.

The use of furosemide is characterized by a loss of potassium that leads to hypokalemia which enhances the effect of amiodarone on prolonging the QTc interval (8). Macrolide antibiotics such as erythromycin can block voltage-gated potassium channels and thus prolong the QTc interval (4). Consequently, within the study, the odds ratio (O.R.) for QTc interval prolongation associated with

the concurrent use of azithromycin and amiodarone was computed. However, likely attributable to the limited number of patients receiving this drug combination in the sample, no statistically significant association was observed.

Patients admitted to the ICU are predisposed to QTc prolongation due to heightened susceptibility to conditions like hypokalemia, hypomagnesemia, and increased instances of atrial fibrillation conversion to sinus rhythm (9, 10).

Other studies showed a prevalence of QTc prolongation of 28 to 30% among patients who were also treated in the ICU, which is less compared to this study group (6, 11).

In this investigation, elderly patients exhibited an elevated risk of QTc interval prolongation, consistent with findings in the literature where advanced age is recognized as an independent risk factor (12-14). Also, it was shown that patients with prolonged QTc interval had a higher frequency of heart failure, myocardial infarction, diabetes and nephropathy, but no statistically significant association was shown in comparison to the group with normal QTc interval duration.

The data did not show an association between female gender and QTc prolongation as shown in other studies (15, 16).

One limitation of the study is the inclusion of patients from different intensive care units. While this diversity of patients is a strength, it also represents a limitation because the prevalence was not compared, alongside risk factors, and causes of QT interval prolongation between these units. The small number of patients in each unit restricted the ability to perform such comparisons, which could provide more detailed insights into the differences between the units. Additionally, the relatively small sample size limits the power of the statistical analyses and the generalizability of these findings.

The study underscores the necessity for systematic monitoring of the QTc interval in high-risk patients within intensive care units. The findings suggest that careful consideration should be given to drug interactions that may prolong the QTc interval, particularly in patients with existing risk factors such as advanced age or electrolyte imbalances. Clinicians should regularly monitor QTc intervals and manage electrolyte levels to mitigate the risk of potentially life-threatening arrhythmias. Furthermore, the results indicate the need for expanded research with larger patient samples to validate these findings and improve clinical guidelines for managing QTc prolongation in critically ill patients.

Conclusion

This study demonstrates a high prevalence of prolonged QTc interval among critically ill patients, emphasizing the need for careful monitoring of QTc interval to mitigate the risk of drug-induced arrhythmias.

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