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TABLE OF CONTENT

Original Article

Risk Factors of Prolonged QTc Interval in Patients with Drugs-Resistant Tuberculosis

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Abstract

Background*: Drug-Resistant Tuberculosis (DRTB) is still one of the biggest health problems worldwide. In 2016, WHO published new guidelines for DRTB management using 7 second-line drugs that only required 9-11 months of treatment with a higher success rate. Unfortunately, one of the side effects was the possibility of a prolonged QT-c interval on electrocardiography. However, to date there have been no known factors which increased the risk of QTc prolongation in DRTB patients.*

Methods: *This was a retrospective cohort study that analyzed the medical records of 50 DRTB patients who underwent treatment from August 2017 to August 2020 at the DRTB Clinic of Adam Malik Hospital Medan. Statistical analysis was performed using logistic regression to determine the factors which increased the risk of QTc prolongation in DRTB patients.*

Results: *Of the 50 study samples consisting of 40 MDR TB patients, 9 pre-XDR TB patients and 1 XDR TB patient, 14 (28%) subjects were found to have QTc prolongation. There were no correlation between the regimen type (*P *= 0.51), age (*P *= 0.40), sex (*P *= 0.74), nutritional status (*P *= 0.35) and comorbid diseases (*P *= 0.31) on the prolongation of QTc interval. Patients receiving clofazimine had a greater percentage (78.6% vs 21.4%) to experience prolonged QTc interval, although not statistically significant (*P *= 0.41).*

Conclusion: *Treatment regimen, age, sex, nutritional status and comorbid disease were not associated with prolonged QTc interval in DRTB.*
(J Respirol Indones 2022; 42(1): 52–7)

Keywords: *Regimen, prolonged-QTc, tuberculosis, resistant, electrocardiography*

Faktor Risiko Pemanjangan Interval QTc pada Pasien Tuberkulosis Resistan Obat

Abstrak

Latar Belakang: *Tuberkulosis Resisten Obat (TBRO) masih menjadi salah satu masalah kesehatan terbesar di dunia. Pada tahun 2016, WHO menerbitkan pedoman baru untuk manajemen TBRO menggunakan 7 obat lini kedua yang hanya membutuhkan 9-11 bulan pengobatan dengan tingkat keberhasilan yang lebih tinggi. Sayangnya, salah satu efek sampingnya adalah kemungkinan pemanjangan interval QT-c pada elektrokardiografi. Meski demikian, sampai saat ini belum ada faktor yang diketahui meningkatkan risiko pemanjangan QTc pada pasien TBRO.*

Metode: *Penelitian ini merupakan studi kohort retrospektif yang menganalisis rekam medis 50 pasien TBRO yang menjalani pengobatan sejak Agustus 2017 sampai Agustus 2020 di Klinik TBRO RS Adam Malik Medan. Analisis statistik dilakukan menggunakan regresi logistik untuk mengetahui faktor-faktor yang meningkatkan risiko pemanjangan interval QTc pada pasien TBRO.*

Hasil: *Dari 50 sampel penelitian yang terdiri dari 40 pasien TB MDR, 9 pasien TB pre-XDR dan 1 pasien TB XDR, terdapat 14 (28%) subjek yang mengalami pemanjangan interval QTc. Tidak ada hubungan antara jenis regimen (*P *= 0,51), usia (*P *= 0,40), jenis kelamin (*P *= 0,74), status gizi (*P *= 0,35) dan penyakit penyerta (*P *= 0,31) terhadap pemanjangan interval QTc. Pasien yang menerima clofazimin memiliki persentase yang lebih besar (78,6% vs 21,4%) untuk mengalami pemanjangan interval QTc, meskipun tidak bermakna secara statistik (*P *= 0,41).*

Kesimpulan: *Regimen pengobatan, umur, jenis kelamin, status gizi dan penyakit komorbid tidak berhubungan dengan pemanjangan interval QTc pada TBRO.* ***(J Respirol Indones 2022; 42(1): 52–7)***

Kata kunci*: regimen, interval QTc, tuberkulosis, resisten, elektrokardiografi*

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INTRODUCTION

Tuberculosis (TB) is still one of the biggest health problems worldwide. Currently, the problem related to TB as a burden in the health sector is the high number of TB strains which are resistant to available TB drugs. Global TB Report 2020 by WHO stated that Indonesia had the second highest number of TB patients throughout the world.[1]

The success rate of TB treatment without complications in several country was actually quite good, reaching 86%. Unfortunately, this number has dropped dramatically in MDR TB cases as the success rate was only around 48%.[2] Moreover, in the case of XDR TB, the treatment success rate was very low, which was only 28%. Not to mention about the duration of treatment that reached 18–24 months, resulting in a greater number of failures and withdrawals.[3]

In 2016, WHO published new guideline for the management of drug resistant TB (DRTB). This guideline began to introduce a mixture of new treatments in the form of short-term regimen. This regimen used a combination of 7 second-line anti-tuberculosis drugs which only required 9–11 months of treatment with a higher treatment success rate than the previous conventional regimen.[4] Afterwards, in 2019, WHO introduced a fully oral regimen resulted in even better success rate.[5]

Unfortunately, one of the side effects that must be considered regarding the use of this regimen was the possibility of heart rhythm disturbances in the form of prolonged QTc interval (PQTcI) on electrocardiography. If it was not quickly identified, and thus not managed properly, this PQTcI would produce more serious adverse effects that might lead to death. The PQTcI reflects the delay in myocardial repolarization which is a predisposition of a rapid and chaotic heartbeat. This rapid heartbeat might trigger a sudden faint in patient. This polymorphic ventricular tachycardia is called torsades de pointes (TdP). Although usually self-limited, TdP may degenerate into ventricular fibrillation and cause syncope or even sudden death. In general, the QTc interval of more than 500ms is associated with an increased risk of fatal PQTcI.[6–10]

Several studies stated that PQTcI were reported to occur in 15–26% patients, but the exact number was still inconclusive.[10,11] More importantly, the data on the prevalence of PQTcI among DRTB patients in Indonesia was still not available. This study aimed to provide the number of DRTB patients who experienced PQTcI during treatment.

However, to date there have been no known factors that increase the risk of PQTcI in DRTB patients. Therefore, researchers were interested to identify factors that influenced the PQTcI in order to anticipate the possible side effects of heart rhythm disturbances.

METHODS

This was a retrospective cohort study that analyzed the medical records of 50 DRTB patients calculated by formula to estimate the proportion of population with specified relative precision. Study subjects were patients who underwent treatment from August 2017 to August 2020 at the DRTB Clinic RSUP H Adam Malik Medan. For this reason, a medical record review was carried out in order to follow the treatment course of DRTB patients from the beginning to the end of treatment with a focus on monitoring the QTc interval.

Electrocardiograph (ECG) was performed before treatment (baseline) and every month for the first 6 months of treatment. Assessment to determine the QTcI in this study was conducted in the fourth month. This was because data from previous studies stated that the highest incidence of prolonged QTc occurred in the first 4 months of treatment. Electrocardiograph interpretation was performed by certified cardiologist.

Ethical clearance was obtained from the Ethical Committee of Health Research Universitas Sumatera Utara. Statistical analysis was performed using logistic regression to determine the factors that might increase the risk of PQTcI in DRTB patients.

RESULTS

As many as fifty patients became the subjects of this study. Thirty-four patients (68%) were male. The majority of subjects were in the range of 30 to 59 years.

Table 1. Demographic characteristics of subjects

Characteristic		n	%
Sex	Male	34	68
	Female	16	32
Age	<30 years old	10	20
	30–59 years old	34	68
	≥60 years old	6	12
	Underweight	12	24
Nutritional status	Normoweight	36	72
	Overweight	2	4
Comorbid	Without comorbid	30	60
	DM	16	32
	HIV	4	8

This study was aim to determine factors that might induce PQTcI in DRTB patients. Therefore, all subjects underwent ECG examination every month. Assessment of the ECG results was performed by a certified cardiologist, in which QTc interval ≥500 ms was declared as prolonged. In this study, 14 subjects (28%) had PQTcI. The characteristics of subjects based on clinical appearance and ECG results can be seen in Table 2.

Table 2. Clinical characteristics of subjects

Characteristics		n	%
Prolonged QTcI	Yes	14	28
	No	36	72
Type of regimen	STR injection	19	38
	LTR oral	31	62
Diagnosis	MDR	40	80
	PreXDR	9	18
	XDR	1	2

STR Injection: Km – Mfx – Eto – Cfz – H(dt) – E – Z

LTR oral: Lfx – Bdq – Lzd – Cfz – Cs or Lfx – Bdq – Lzd – Cs – E

Km (Kanamycin), Mfx (Moxifloxacin), Eto (Etionamid), Cfz (Clofazimin), H(Isoniazid), E (etambutol), Z (Pirazinamid), Lfx (Levofloxacin), Bdq (Bedaquilin), Lzd (Linezolid), Cs (Cycloserine)

Statistical analysis was carried out to determine whether there was a correlation between clinical characteristics, treatment regimen and PQTcI, with the results as shown in Table 3.

Table 3 shows that there were no significant correlation between sex, age, nutritional status, and comorbidity to PQTcI in DRTB patients (P >0.05). There were also no association between the type of treatment regimen and PQTcI (P >0.05). However, it was obvious that of the 14 subjects experiencing PQTcI, 12 subjects received a regimen containing Clofazimine. Thus, the use of Clofazimine may increase the risk of PQTcI among DRTB patients.

Table 3 Factors associated with PQTcI

Characteristic		Prolonged		Normal		*P* value
		n	%	n	%	
Sex	Male	10	71.4	24	66.7	0.74
	Female	4	28.6	12	33.3	
Age	<30 years old	3	21.4	7	19.4	
	30–59 years old	8	57.1	26	72.2	0.407
	≥60 years old	3	21.4	3	8.3	
Nutritional status	Underweight	5	35.7	7	19.4	
	Normoweight	9	64.3	27	75.0	0.35
	Overweight	0	0.0	2	5.6	
Comorbid	Without comorbid	8	57.1	22	61.1	
	DM	6	42.9	10	27.8	0.31
	HIV	0	0.0	4	11.1	
Regimen	STR Injection	7	50.0	12	33.3	0.27
	LTR oral	7	50.0	24	66.7	
Mfx use	With Mfx	7	50.0	13	36.1	0.36
	Without Mfx	7	50.0	23	63.9	
Cfz use	With Cfz	12	85.7	25	69.4	0.23
	Without Cfz	2	14.3	11	30.5	
Bdq use	With Bdq	7	50.0	24	66.7	0.27
	Without Bdq	7	50.0	12	33.3	

DISCUSSION

Treatment regimens of DRTB continue to evolve over time. In 2016 WHO introduced a short-term regimen of 9–11 months with satisfying success rate.[4,12] Later in 2019, WHO introduced a full oral regimen which was declared to have a higher success rate.[5,13] Unfortunately, both the 2016 and the 2019 regimens contained a combination of several drugs that could cause PQTcI, including Bedaquiline, Delamanid, Clofazimine and Moxifloxacin.[6,7,14,15] In some cases, the PQTcI could be very severe and led to mortality.[9]

The QT interval is an ECG measure that represents the flow of ions through ventricular myocytes cell membrane mediated by specialized protein channels. When these channels do not work properly, they may disrupt normal heart rhythms and put patients at risk of life-threatening arrhythmias.[10,16]

This study aimed to identify factors associated with PQTcI in DRTB patients during treatment. Subjects of this study were grouped according to the type of treatment regimen they received. A total of 19 subjects received the WHO 2016 injectable short-term regimen/STR which consisted of Km - Mfx - Eto - Cfz - H (dt) - E – Z, meanwhile 31 subjects received the WHO 2019 full oral regimen, consisting of Lfx - Bdq - Lzd - Cs, with or without clofazimine (Cfz). Patients with QTc interval ≥500ms were declared to have a prolongation of QTc interval, both with and without clinical symptoms of cardiovascular disorders.[16]

Based on table 2, as many as 28% of subjects experienced PQTcI. In other words, nearly one-third of all DRTB patients experienced PQTcI during treatment. This finding was not much different from the previous studies which stated that the prevalence of PQTcI in DRTB patients ranged from 15–26%.[10,11]

Drug-associated QT prolongation is assumed to be caused by restraint of the rapid components and deferred rectifier potassium current. This restraint causes a prolongation of the length of the ventricular activity potential, leading to excessive sodium convergence or diminished potassium efflux. This induces a positive charge in the cell which can draw out the repolarization stage. This prolongation of the repolarization stage frequently causes a wavering of the layer expected known as ahead of schedule after depolarization. Repolarization stage stretching results in a drawn-out QT span on the ECG.[16,17]

Several studies have identified second-line antituberculosis drugs that could increase the risk of PQTcI. The drugs most reported to induce PQTcI were bedaquiline, delamanid, moxifloxacin or levofloxacin, and clofazimine.[10,16] Bedaquiline and delamanid produced metabolites M2 and DM6705 subsequently, causing QTc prolongation related to the inhibitory effect on the rapidly activating delayed rectifying potassium channels in myocardial tissue. The long terminal half-lives of M2 and DM6705 lead to a delayed effect of maximum QTc after 5–8 weeks of delamanid and 24 weeks of bedaquiline.[18] Moxifloxacin causes a slight prolongation of QTc by reversible and dose-dependent blockade of the rapidly activating delayed rectifying potassium channel. Moxifloxacin is more likely to cause prolonged QTc than the other fluoroquinolones. The risk of PQTcI with moxifloxacin is greater when electrolyte abnormalities occur. Clofazimine induces a PQTcI in a dose-dependent pattern.[19]

This study found that there were no significant difference in the incidence of PQTcI between subjects receiving bedaquilin, moxifloxacin or clofazimine regimens (P >0.05). However, of the 14 subjects receiving clofazimine, 12 (85.7%) subjects had PQTcI. This finding was much higher than that of bedaquiline and moxifloxacin where PQTcI was found in 50% of subjects. Thus, this study found that clofazimine was the DRTB drug most at risk for PQTcI. Another studies also stated that the use of DRTB drugs such as bedaquiline and moxifloxacin increased the risk of PQTcI when combined with clofazimine.[16]

However, there were some results that contradicted the findings of this study. Sanne, et al. stated that the incidence of PQTcI after clofazimine administration was fluctuating and influenced by

circadian rhythm, thus did not significantly cause PQTcI.[20] Another study stated that the effect of PQTcI due to clofazimine was related to the dose of the drug given, and it would return to normal after the drug was discontinued.[19]

This study found that there were no statistically significant correlation between sex (*P*=0.74), age (*P*=0.407), nutritional status (*P*=0.35) and comorbidities (*P*=0.31) with the incidence of PQTcI. Another study pointed out that patients aged >68 years and female sex could increase the risk of PQTcI which had the potential to cause Torsade de Pointes.[21]Further studies are needed to identify other factors associated with PQTcI such as electrolyte imbalance, dose of drug used and plasma drug concentration.

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CONCLUSION

The prolongation of QTc was found in 28% of DRTB patients. Drug-resistant TB patients who received a treatment regimen containing clofazimine were at greater risk of PQTcI although it was not statistically significant. There were no correlation between the treatment regimen, sex, age, nutritional status or comorbidities with PQTcI in DRTB patients. Regular monitoring of QTcI should be mandatory particularly in DRTB patients receiving regimens containing Clofazimine.

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