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Short Communication

Effect of artemisinin-piperaquine treatment on the electrocardiogram of malaria patients

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Abstract

Introduction: Concern regarding the cardiotoxicity of antimalarials has been renewed because of their potential to cause QT/QTc interval prolongation related to torsade de pointes (TdP). Artemisinin-piperaquine (AP) is considered an effective artemisinin-based combination therapy (ACT) for malaria. **Methods:** This study involved a retrospective analysis of clinical data of 93 hospitalized malaria patients who had received AP orally. Electrocardiograms (ECGs) were obtained at specific time points in the original study. **Results:** Some cases of QT prolongation were observed. However, no TdP was found. **Conclusions:** AP may cause QT interval prolongation in some malaria patients but may not lead to TdP.

Keywords: ECG. QT. Artemisinin-piperaquine. Malaria. Cambodia.

Malaria is an infectious disease caused by the parasite *Plasmodium*, which is spread via human-to-human or animal-to-human transmission by mosquitoes. According to the Malaria Report published by the WHO in 2017, there were approximately 216 million cases of malaria globally in 2016. Although global malaria incidence and mortality rates have fallen since 2010, some regions have seen increases since 2014. Indeed, the number of global malaria cases was higher by approximately 5 million in 2016 than in 2015. Malaria is an important public health challenge, and acknowledging the emerging malaria epidemic can increase the availability of treatment and other control mechanisms[1]. Malaria is prevalent in poor regions and developing countries, which find the costs of prevention, diagnosis, and treatment burdensome. Safe, effective, and widely available antimalarial drugs are needed.

Artemisinin-based combination therapy (ACT) is the recommended malaria treatment. Artemisinin (ART) is absorbed and excreted quickly *in vivo*. Piperaquine (PQ) is effective and better tolerated by patients than PQ phosphate. Additionally, treatment with PQ can save treatment time and costs. ART-PQ (AP) was confirmed to be an effective and safe ACT for malaria, especially for falciparum malaria[2]. Mass drug administration (MDA) with AP can effectively reduce malaria prevalence, and no serious adverse reactions have been reported[3].

Prolongation of ventricular repolarization can cause subsequent prolongation of the effective refractory period, and QT interval prolongation (QTL) is reflected in electrocardiograms (ECGs)[4]. TdP is a type of polymorphic ventricular arrhythmia associated with QTL. During the development of TdP, the QTL before the sudden appearance of rapid and disorganized heart contractions. Transient TdP can cause clinical symptoms such as dizziness and loss of consciousness, and sustained TdP can lead to death. Although not all QTL will develop into TdP, they are commonly used to identify drugs that may cause TdP[5]. As the QT interval varies with heart rate, QTc is used to evaluate the cardiotoxicity of drugs. Drug-induced QT/QTc interval prolongation could increase the risk of TdP, which has garnered renewed attention due to the cardiotoxicity of medicines, especially antimalarials[6]. The efficacy and drug resistance of AP in malaria treatment have been studied, but there is a paucity of reports on cardiac safety evaluations. The aim of this study was to conduct a detailed analysis of ECGs of malaria patients who were treated with AP, to assess the cardiotoxicity of this drug combination.

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This study was based on the "Agreement of Cambodia-China Fast Malaria Control Co-operation" and "National Ethics Committee for Health Research (No. 03G/03NECHR)" signed by Guangzhou University of Chinese Medicine, China, and the Ministry of Health, Kingdom of Cambodia. The original clinical study described the therapeutic efficacy and safety of AP, DHP, and AL treatments for malaria patients. The clinical trial registry number was 2005L01041. After reviewing the medical history, the records of 93 malaria patients who were treated with AP in Pursat Hospital in Cambodia from 2003 to 2005 were collected. All patients were diagnosed with malaria and treated with AP. Malaria cases are defined as patients with clinically diagnosed or laboratory-verified malaria. A person suffering from malaria-like symptoms with a history of living in or traveling to an area experiencing a malaria epidemic can be clinically diagnosed as a malaria case. Laboratory-verified cases are defined as any positive result in laboratory tests consisting of rapid diagnostic tests (RDTs) and microscopy. Inclusion criteria were: (1) patients with malaria symptoms, (2) presence of *Plasmodium falciparum* in peripheral blood smears under the microscope, and (3) no antimalarial medications taken in the 7 days before enrollment. Exclusion criteria were: (1) pregnant or breastfeeding women, (2) patients younger than 7 years or older than 65 years, (3) non-malarial febrile illness, (4) patients who had taken antimalarial medicine in the past 7 days, and (4) patients with a history of allergies to ART, PQ or similar drugs. The research process and patient recruitment are shown in **Figure 1**. A total of 91 patients completed treatment and clinical observation. After the data were tested for normality and homogeneity of variance, the rank sum test and analysis of variance (Stata 13.0) were used to analyze the data. P-values <0.05 were indicative of statistical significance.

ECGs were obtained at three time points: before treatment, 4 hours after the first dose of medicine (4h-1st dose), and 4 hours after the second dose of medicine (4h-2nd dose). All ECG traces were sent to the First Affiliated Hospital of Guangzhou University of Chinese Medicine for blinded manual adjudication. The ECG indicators included the PR interval, QRS complex, RR interval, and QT interval. QTcF, QTcB and ΔQTc were calculated. QT intervals >30 ms were defined as moderately prolonged, whereas those >60 ms were defined as severely prolonged. ECG results were showed in **Table 1.**

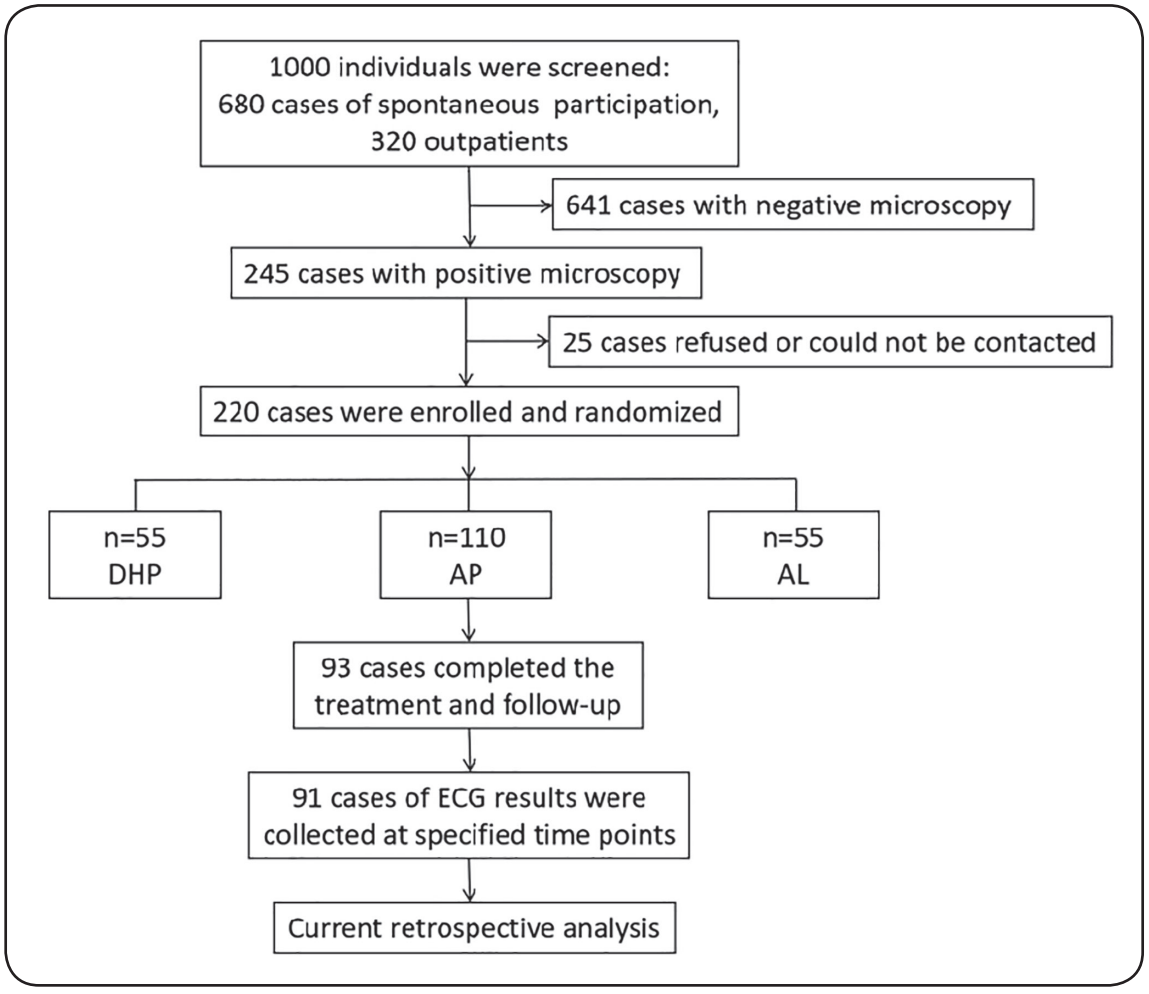

FIGURE 1: Patient selection flow chart of the original clinical study and the current study.

TABLE 1: ECG results before and after AP treatment.

Characteristics	Frequency (n = 93)	Percentage (%)
Gender		
Male	69	74.2
Female	24	25.8
Age (years)		
≤20	46	49.5
21-30	18	19.4
31-40	16	17.2
41-50	11	11.8
>50	2	2.2
Symptoms		
Fever	91	97.8
Headaches	93	100
Body aches	38	40.9
Malaise	80	86.0
Vomiting	41	44.1
Dyspnea	3	3.2
Convulsions	1	1.1
Diminished consciousness	1	1.1
Other*	22	23.7
Characteristics	**Mean**	**SD**
Weight (kg)	46.02	12.59
Body temperature (°C)	38.24	1.19
Fever recovery time (h)	28.27	19.05
Plasmodium removal time (h)	72.98	39.53
QTcF-Before (ms)	389.67	24.83
QTcF-4h-1st dose (ms)	383.08	26.28
QTcF-4h-2nd dose (ms)	383.30	24.09
QTcB-Before (ms)	421.21	31.93
QTcB-4h-1st dose (ms)	401.54	32.56
QTcB-4h-2nd dose (ms)	396.70	29.78
Characteristics	**4h-1st dose**	**4h-2nd dose**
Maximum QTcF prolongation (ms)	58.61	72.18
Maximum QTcB prolongation (ms)	63.36	74.81
QTcF prolongation	38(41.30%)	37(40.22%)
QTcF shortening	54 (58.70%)	55 (59.78%)
QTcB prolongation	24 (26.09%)	21(22.83%)
QTcB shortening	67(72.83%)	71(77.17%)
ΔQTcF > 30 ms	8(8.70%)	12(13.04%)
ΔQTcF > 60 ms	0	1(1.09%)
ΔQTcB > 30 ms	4(4.35%)	3(3.26%)
ΔQTcB > 60 ms	1(1.09%)	3(3.26%)

*mild cough, 1 case; palpitation, 4 cases; nausea, 11 cases; abdominal pain, 5 cases; dizziness, 5 cases; diarrhea, 3 cases. Fever recovery time refers to the time from the start of treatment to the return of body temperature to normal (≤37.3 °C). Seventy-five patients had a fever. The 18 patients who did not have a fever were excluded from this index. Plasmodium removal time refers to the time from the start of treatment to the observation of negative blood smears. All patients had positive smears at enrollment, and blood smears for 81 patients were observed to be negative during hospitalization. The other 12 patients reverted to negative smears at follow-up, so the removal time of these patients could not be accurately calculated.

Abbreviations: 4h-1st dose, 4 hours after the first dose; 4h-2nd dose, 4 hours after the second dose. ΔQTc was defined as the difference in QTc before and 4 hours after each medication. ΔQTc >30 ms was defined as moderate prolongation, and that >60 ms was defined as severe prolongation.

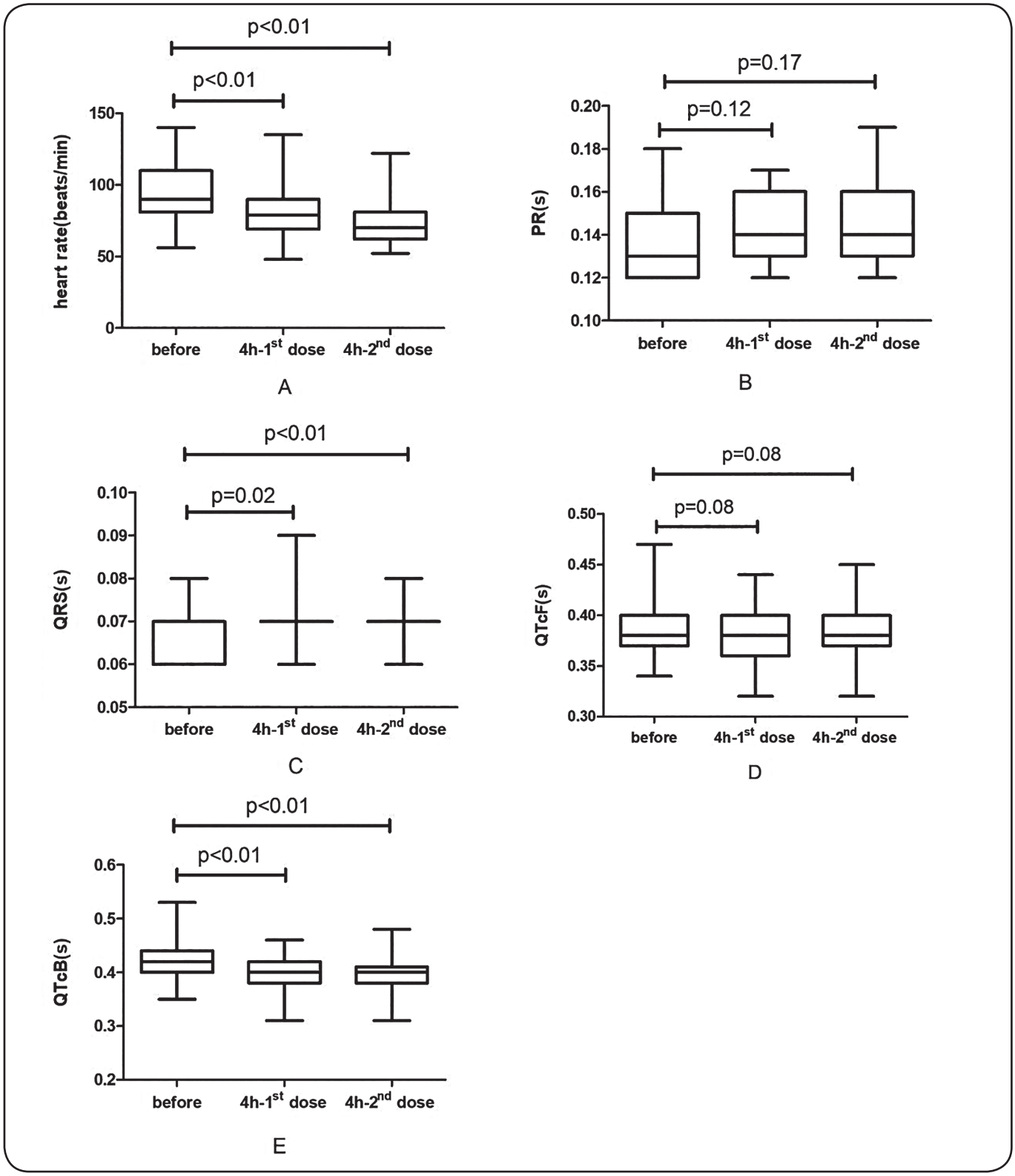

FIGURE 2: Comparison of ECG result before and after AP treatment. **Abbreviations:** before, before medication; 4h-1st dose, 4 hours after the first dose; 4h-2nd dose, 4 hours after the second dose.

QTcF showed no significant difference between the time points before and after treatment ($p = 0.08$; **Figure 2-D**). QTcB was shortened at both 4h-1st dose and 4h-2nd dose ($p < 0.01$; **Figure 2-E**). The heart rate was decreased at 4h-1st dose and 4h-2nd dose ($p < 0.01$; **Figure 2-A**). There was no significant difference in the PR interval before and after treatment (**Figure 2-B**). The QRS duration was longer at 4h-1st dose ($p = 0.02$) and 4h-2nd dose ($p < 0.01$; **Figure 2-C**). No TdP or other qualitative ECG abnormalities were recorded in this study.

The outward current of potassium ions is the main mechanism of cardiac ventricular myocyte repolarization. The delayed rectifier current of potassium ions (I_k) is one of the most important outward currents among rapid and slow currents[7]. The human potassium ion channel subunit encoded on chromosome 7 (by the ether-a-go-go-related gene, hERG) affects this current. Mutation of hERG can cause long QT syndrome, which may lead to TdP and sudden death[8]. The U.S. Food and Drug Administration found that QTc interval prolongation over 60 ms was closely related to an increased risk of TdP. QTc prolongation caused by antimalarials has been included in antimalarial drug safety assessments[6]. Although it has been reported that *Plasmodium falciparum* can be isolated in cardiac microvessels, significant myocardial dysfunction or arrhythmia in severe malaria cases is very rare. Thus, ECG changes caused by *Plasmodium* can essentially be ignored[9]. When the core temperature increases by 1°C during a fever, the heart rate increases by 8.5 beat per minute (bpm). Heart rate changes are related to changes in the QTc interval. Therefore, before analyzing the effects of antimalarials on the QT interval, the data should be corrected using the appropriate formulae[4].

ART has a short half-life and can be rapidly metabolized in humans. However, PQ is a fat-soluble substance that undergoes slower metabolism, with a time to maximum concentration of approximately 4–5 hours[10], which is related to the long-term efficacy of AP. PQ is also the main component that causes QTL[11]. Here, QTL was observed in some individuals after treatment; however, as there were no clinical manifestations or ECG features of arrhythmia, this prolongation had no clinical significance[12]. Furthermore, QTL did not worsen TdP or any other type of arrhythmia, possibly because the drugs were administered at safe doses.

This study was based on a historical study of malaria treatment, so some limitations exist. First, due to the limited medical treatment available at local hospitals at the time of data collection, the concentration of ions related to cardiac currents could not be monitored; therefore, the mechanism of AP-induced QTL could not be further analyzed. Second, all individuals enrolled were malaria patients, so the effect of malaria on the QT interval could not be completely ruled out. Subsequent studies should assess the relationship between AP and QTL in healthy individuals. Third, males are the main people who participate in field work and are more likely to be bitten by mosquitoes, the risk of malaria was greater. Therefore, here, more male patients were enrolled, leading to a gender bias (74.19% male, 25.81% female). Female gender is one of the factors known to cause QTL, limiting the scope of this study. Fourth, considering the degree of patient compliance, ECGs were not reviewed during the follow-up period. Fifth, many cases of QTL after AP treatment were found in this study, even if not statistically significant. This may have been due to the small sample size. Sixth, patients with a history of heart disease were excluded from the study to avoid any unnecessary serious events. Thus, the results of this study cannot be directly extrapolated to all malaria patients, especially those with a history of heart disease. Many risk factors still need to be considered when patients suffer from QTL after taking AP. Larger studies involving healthy subjects and malaria patients should be performed to obtain conclusions about the cardiac safety of AP. AP can cause QTL in some malaria patients, but no arrhythmias occurred in the subjects of this study. Therefore, AP is unlikely to have significant cardiotoxicity when used within a safe dose range and can be safely utilized in the treatment of malaria. However, there is a need for further evaluation of the cardiotoxicity of AP in people with a risk of QTL or arrhythmia.

Acknowledgments

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Conflict of Interest

The authors declare no conflicts of interest.

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