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STATISTICAL ANALYSIS PLAN

A COMPARATIVE STUDY BETWEEN THE DYNAMIC ECG (HOLTER SYSTEM) FINDINGS OBTAINED BY QUORETECH'S QUOREONE SYSTEM WITH THOSE OBTAINED BY CARDIOS' CARDIOLIGHT RECORDER

PAE Version: 1 - 25-Feb-2022
Protocol Version: 3.0 – 10-Sep-2021

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Summary

1. INTRODUCTION

1.1. Rationale and Background

The 24-hour ambulatory electrocardiogram, performed by the Holder system, is a procedure whose objective is to find the correlation between symptoms and possible changes in the electrocardiogram in order to establish a cause-effect relationship[1-5]. In practice, a digital recorder is connected to a cable with electrodes at its ends, which are then applied to the thoracic surface. The objective is for the electrical signal emitted by the heart to be captured and recorded in at least three channels that correspond to the electrocardiographic leads[6]. Once captured, the signals recorded on a digital card are transferred to a computer that, by means of specific software, performs the analysis and issues a result that includes the maximum, minimum and mean heart rates, in addition to the total number of atrial and ventricular ectopic heart beats, total tachycardias and ST segment alterations and T waves. The interpretation of the electrocardiographic recordings is then carried out by a specialized technical analyst who confirms the data or corrects the information that is in disagreement. The following result is confirmed by a physician[6].

Current systems are limited to this type of analysis, but they suffer from some limitations. These are of a technical nature related to signal capture, the dependence on electrode cables, which often limit the mobility of patients and is associated with greater risks of interference in the recording channels (50/60 Hz electrical network, touching of clothing on the electrodes; electrode displacements, etc.)[1]. Depending on the intensity and duration of these alterations, there may be a need to repeat the examination.

With the advancement of technology, new signal capture systems have been developed. The possibility of applying the recorder directly to the thoracic surface eliminated the need for electrode cables. This fact not only improved the quality of the signs, but also allowed greater patient mobility, making the test better tolerated. The possibility of sending the recorded signals over the internet speeds up their interpretation. In addition, an analysis software previously trained by neural networks allows the editing of records more quickly by issuing a pre-report, facilitating the routine of the physician who will have less work to prepare the final report. With this approach, it is expected that the more exams the system analyzes, the better its performance should be, probably reaching almost the point of minimal medical interference in the final result.

In the study, which is now proposed to be carried out at the Cardiac Arrhythmias Outpatient Clinic of the Dante Pazzanese Institute of Cardiology (IDPC), Holter recordings will be performed in about 180 consecutive patients with the two systems simultaneously, the *QuoreOne* from Quoretech (system under test) and the *Cardiolight* from Cardios (conventional 24-hour Holter-system), a system that has been on the market for more than 30 years and is widely used in the country today. This approach will allow for the comparison of *QuoreOne*'s results with those of *Cardiolight*.

1.2. Objectives

Primary Objective:

To assess whether the detection of arrhythmias by *QuoreOne* is comparable to *Cardiolight*. Detection of the following arrhythmias will be compared: atrial fibrillation or atrial flutter, supraventricular tachycardia, ventricular tachycardia, polymorphic ventricular tachycardia or ventricular fibrillation; atrioventricular block and pauses.

Secondary Objective: Compare the 24-hour electrocardiographic recordings detected by both systems. The following will be included in the analysis: a) maximum, minimum and mean heart rates; b) total atrial and ventricular ectopic heart beats; c) episodes of supraventricular tachycardia, ventricular tachycardia, and pauses. In addition to these variables, the duration of the examination and the convenience of using both systems should also be compared.

2. STUDY METHODS

2.1. Study Design

This is a comparative, single-center study with consecutive inclusion of patients. Research participants will be included prospectively.

All exams will be performed at IDPC, the exams performed with the *Cardiolight* equipment will be stored both in the original file (.xcm) and in the final version of the report (.pdf). The exams performed with the *QuoreOne* equipment will be saved directly on the online report platform and in the final version of the report (.pdf). These files will be exported to an external hard drive and sent for tabbing. The parameters will be analyzed with anonymized data from the participants.

After the Holter devices are removed, the participant will be asked to answer a questionnaire about the convenience of use and functions of the *QuoreOne* device.

The Holter-type cardiac monitor is a portable ambulatory electrocardiography device. It aims to monitor the electrical activity of the heart over a prolonged period, usually twenty-four hours.

For this study, the *Cardiolight* recorder from the company Cardios, the predominant equipment in the medical practice of the IDPC, and the *QuoreOne* recorder, from Quoretech, will be used, which will be submitted to comparison.

The exams performed by the conventional system (*Cardiolight*, Cardios) will be analyzed and the reports released by physicians from the Electrophysiology Section of the IDPC. These tests will be implemented at the same time in the same patient and for the same duration. The physicians evaluating the results of one method will be the same as the physicians evaluating the results obtained by the other method, but these will be blinded to the patients' data, making it impossible to identify that the tests being evaluated are from the same patient.

2.2. Randomization

This is a comparative, single-center study, where all patients included consecutively and prospectively, will use both systems simultaneously, Quoretech's *QuoreOne* and Cardios' *Cardiolight*. In this way, it will not be necessary to use any randomization technique.

2.3. Sample Size

The sample size calculation of the study was established assuming the hypothesis of comparability of the *QuoreOne* device in relation to the conventional device. According to data from a previous study,[7] we have:

		Holter Any 6 (24 h)		
		No	At least 1	Total
Patch any 6 (24 h)	No	83	11	94
	Yes	2	**50**	**52**
	Total	85	**61**	146

Any arrhythmias (of the 6 types atrioventricular block, pause, polymorphic ventricular tachycardia, supraventricular tachycardia, ventricular tachycardia, or atrial fibrillation)

From the data in the table above, we obtain the following proportions:

		Holter Any 6 (24 h)		
		No	At least 1	Total
Patch any 6 (24 h)	No	0.5685	0.0753	0.6438
	Yes	0.0137	**0.3425**	**0.3562**
	Total	0,5822	**0.4178**	1.0000

Assuming that *QuoreOne* and Holter will agree to detect at least one arrhythmia event similar to that found between Patch and Holter in the reference study[7], a sample of 182 patients will have 80% power to show that the overall accuracy is greater than 85%, at a one-tailed significance level of 2.5%. (i.e., the lower limit of the 95% confidence interval (CI) should be above 85%). Therefore, this premise considers Holter as the "gold standard" test, and the accuracy of the *Quoreone* is evaluated in the detection of global arrhythmias (primary endpoint) and specific categories (secondary endpoints).

2.4. Interim Statistical Analysis and Interrupt Rules

Not applicable.

2.5. Timing of Final Analysis

All outcomes will be collectively analyzed after the last patient remains 24 hours with both systems simultaneously. The analyses will be initiated after all potential inconsistencies in the database have been resolved and the data is considered clean.

2.6. Moments of Evaluation of Results

The exams performed by the conventional system (*Cardiolight*, Cardios) and the *QuoreOne* system will be implemented at the same time in the same patient and for the same duration. The monitoring of the electrical activity of the heart during a period of approximately 24 hours will be done by the systems, which will record the records at times according to the custom of medical practice.

The parameters will be analyzed with anonymized data from the participants.

3. STATISTICAL PRINCIPLES

3.1. Confidence Intervals and p-Values

Two-tailed hypothesis tests with a significance level of 5% and confidence intervals of 95% will be used.

3.2. Protocol Compliance and Deviations

Number (and percentage) of participants with major and minor protocol deviations will be summarized with details of the type of deviation provided. Participants included in the full set of analysis will be used as the denominator to calculate the percentages. No formal statistical testing will be performed.

3.3. Analysis Populations

All individuals of both sexes, aged 18 years or older who use both systems simultaneously for 24 hours, present complete data in both examinations and have signed the consent form will be part of the Full Analysis Set (FAS).

4. STUDY POPULATION

4.1. Screening Data

Tables summarizing the disposition of patients will contain:

• The number of patients recruited;

• Number of patients with complete data from the two exams – % calculated from the total number of patients recruited;

• The number (%) of patients who withdrew from the study and the associated reasons (% calculated from the full set of analysis).

Unless otherwise specified, percentages will be calculated based on the number of patients in the full set of analysis.

4.2. Eligibility

All patients with simultaneous recordings performed from the date of approval of the protocol until the proposed number of patients is completed. The following inclusion and exclusion criteria will be considered:

Inclusion criteria

Patients aged ≥ 18 years, with indication for continuous 24-hour electrocardiographic monitoring by 24-hour Holter at the IDPC outpatient clinic, and who agree to participate in the study by signing the free and informed consent form (ICF).

Exclusion Criteria

Refusal to provide consent for the study.

4.3. Recruitment

All patients over 18 years of age who undergo Holter monitoring tests at the Electrophysiology and Cardiac Arrhythmias outpatient clinic of the Medical Section of Electrophysiology of the IDPC will be invited to participate in the study, and a prospective and consecutive recruitment of at least 182 patients with complete data from the two tests is expected.

4.4. Study Discontinuation/Follow-up

N/A.

4.5. Patient Baseline Characteristics

The baseline characteristics of the patients that will be analyzed descriptively will be the demographics and the underlying diseases. Frequency, percentage, and 95% CI, when appropriate, will be used to summarize the qualitative variables, and number of valid observations, mean, standard deviation (SD), median, interquartile range, and minimum and maximum values will be calculated for the quantitative variables.

5. ANALYSIS

5.1. Definition of Endpoints

Primary Endpoint

To compare the detection of arrhythmias between the two methods mentioned with regard to the set of the following arrhythmias: a) atrial fibrillation or atrial flutter; b) supraventricular tachycardia (≥ 3 beats); c) ventricular tachycardia (≥ 3 beats); d) polymorphic ventricular tachycardia or ventricular fibrillation; e) atrioventricular block (2nd degree Mobitz AVB I and II, 2:1 AVB and total AVB); and f) pauses (≥ 2.5 seconds).

Secondary Outcomes

- Comparison of the detection of each type of arrhythmia between the two devices;
- Comparison of the duration of the examination between the two devices;
- Comparison of mean, minimum, and maximum heart rate captured between the two devices;
- Comparison of the total atrial ectopic heart beats captured between the two devices;
- Comparison of the total number of ventricular ectopic heart beats captured between the two devices;
- Comparison of total episodes of supraventricular tachycardia, ventricular tachycardia, and pauses between the two devices;
- Evaluate the convenience of using the two registration systems.

5.2. Methods of analysis

All measures resulting from each of the two techniques will be summarized using the descriptive measures cited in Section 4.5.

Baseline characteristics

The baseline characteristics mentioned in Section 4.5 will be presented in descriptive analysis tables. The percentages will be calculated according to the number of participants for whom the data is available. When there are missing values, the denominator will be described in the table and no assumptions or imputation will be made.

Primary Endpoint

The comparison between the two methods in relation to the detection of arrhythmias will be evaluated by the accuracy of *QuoreOne* compared to Holter. The primary endpoint consists of the detection of any arrhythmia: a) atrial fibrillation or atrial flutter; b) supraventricular tachycardia (≥ 3 beats); c) ventricular tachycardia (≥ 3 beats); d) polymorphic ventricular tachycardia or ventricular fibrillation; e) atrioventricular block (2nd degree Mobitz AVB I and II, 2:1 AVB and total AVB); and f) pauses (≥ 2.5 seconds). Other diagnostic statistics: Sensitivity, specificity, positive and negative predictive values will also be presented always followed by 95% confidence intervals.

Secondary Outcomes

The individual categorical secondary endpoints (detection of each type of arrhythmia) will also be evaluated by diagnostic statistics (accuracy, sensitivity, specificity, positive and negative predictive values) with respective 95% confidence intervals.

The continuous secondary endpoints (mean, minimum and maximum heart rate, total atrial and ventricular ectopic heart beats, total episodes of supraventricular tachycardia, ventricular tachycardia and pauses) will be described by Bland-Altman plots accompanied by Lin and Pearson correlation coefficients.

Lists with the patients' reports will be made to evaluate the convenience of the systems. The Chi-square test or Fisher's exact test will be used to evaluate the proportion of patients who report greater comfort (comfort of the device) with *Quoreone* versus *Cardiolight*.

5.3. Missing Data

No imputation will be performed and only analysis of complete data will be performed.

5.4. Additional Analytics

The evaluation of agreement between the devices will also be performed from the Cohen Kappa statistic for the primary endpoint, and each of the secondary endpoints (arrhythmias criteria one by one).

5.5. Safety

There will be no safety analysis, as there is no intervention in this study.

5.6. Statistical Software

All analyses and summaries will be performed using SAS™, version 9.4 or higher. The R software (R Foundation) may also be used.

5.7. References

1 - Crawford MH, Bernstein SJ, Deedwania PC, et al. ACC/AHA Guidelines for Ambulatory Electrocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the Guidelines for Ambulatory Electrocardiography). Developed in collaboration with the North American Society for Pacing and Electrophysiology. J Am Coll Cardiol. 1999;34(3):912-948.

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3 - Summerton N, Mann S, Rigby A, Petkar S, Dhawan J. New-onset palpitations in general practice: assessing the discriminant value of items within the clinical history. Family practice 2001; 18:383-392

4 - RINGQVIST, I. et al. Diagnostic value of longterm ambulatory ECG in patients with syncope, dizziness or palpitations. Clinical Physiology 1989**;** 9:47-55.

5 - WEBER, Barbara E.; KAPOOR, Wishwa N. Evaluation and outcomes of patients with palpitations. Am J Med1996; 100:138-148.

6 - Lorga Filho A, Cintra FD, Lorga A et al. Recomendações da sociedade brasileira de arritmias cardíacas para serviços de Holter. Arquivos Brasileiros de Cardiologia 2013; 10:101-105.

7 - Barrett PM, Komatireddy R, Haaser S, Topol S, Sheard J, Encinas J, Fought AJ, Topol EJ. Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic monitoring. Am J Med. 2014 Jan;127(1):95.e11-7.

6. AMENDMENTS

Protocol		Amendments		
Version No.	Date	Amendment no.	Protocol Section	Summary of main changes

ADDITIONAL INFORMATION OF THE SERVICE