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Double sequence external defibrillation:
A randomized controlled trial in
patients with atrial fibrillation
refractory to DC cardioversion

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Background information and Significance

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice. Patients are at increased risk for death, heart failure, hospitalization, and thromboembolic events [1-3]. In one study by Go et al., it was shown that the overall prevalence of AF was 1%; ranging from 0.1% among adults less than 55 years of age to 9% in those ≥ 80 years of age [4]. The restoration (cardioversion) of sinus rhythm is performed in many patients with AF to improve symptoms. Therefore, some physicians attempt to restore sinus rhythm ('rhythm control' strategy) in patients with AF, either using drugs ('pharmacological cardioversion') or by direct current (DC) shocks ('electrical cardioversion'). Electrical cardioversion requires admission to the hospital, a short-acting anesthetic and a direct current shock. Sometimes repeated cardioversions are required if a patient spontaneously reverts to AF. There are two important reasons why cardioversion might be useful. Firstly, successful restoration of sinus rhythm may reduce the risk of embolic complications, thereby obviating the need for long term anticoagulation, with its attendant risks [5]. Secondly, observational studies have shown that after successful restoration of sinus rhythm, left ventricular function improves [6], atrial and ventricular function normalizes [7], and that after restoration of atrial contractility, left ventricular ejection fraction and maximal exercise capacity both improve [8]. Electrical cardioversion (ECV) is the standard treatment for acute AF, but identification of patients with increased risk of ECV failure or early AF recurrence is of importance for rational clinical decision-making. A study by Jaakkola et al. showed that the risk of unsuccessful outcome of Electrical Cardioversion (ECV) can be predicted using 5 simple clinical variables: age, whether or not it is the first AF, cardiac failure, vascular disease and whether or not there's a short interval from the previous AF episode [9]. In obese patients for instance, high impedance can also decrease the effective energy delivered to the atria in large-bodied patients [10]. AF has been treated with DC shocks delivered trans-thoracically, but in 5-30% of patients, the procedures fail to restore sinus rhythm (SR) [11]. Higher energy external DC cardioversion (DCC) has long been used for ventricular arrhythmias [12, 13]. There have been some studies that have reported on the delivery synchronized higher energy external DCC as an alternative approach for cardioversion in patients with AF refractory to conversion with standard external cardioversion energies [14, 15].

A study by Saliba et al. in 1999 showed that external higher energy cardioversion is effective in restoring sinus rhythm in patients with AF refractory to standard energy DC cardioversion

and that this method is safe and does not result in clinical evidence of myocardial impairment [15].

Despite the benefit shown, this study was conducted 19 years ago and the practice was not implemented as a standard of care. The investigators would therefore like to revisit the evidence behind the effectiveness of double sequential defibrillation. The investigators hope to prove the benefit behind this intervention and ultimately disseminate the findings through international conferences.

The investigators hypothesize that applying high energy shock waves to the chest through double sequential external defibrillation (DSED) may overcome the inadequate penetration of electrical shock to the atrium and restore SR more effectively than DC cardioversion, after two attempts of DC cardioversion.

Specific aims

Objectives

The objective of this study is to assess the effectiveness of double sequence defibrillation in reverting patients with AF refractory to two trials of direct current cardioversion.

Hypothesis

In patients with AF refractory to 2 or more trials of DC cardioversion, the use of double sequential defibrillation has a higher success rate in terms of reverting patients to sinus rhythm as compared to an additional trial of DC cardioversion.

Research design and methods

a) Study design and setting

This study is a Phase III, randomized controlled, superiority trial, with two parallel groups, conducted in one academic medical center. The study will be conducted in a 376-bed, tertiary care academic hospital (American University of Beirut Medical Center) for a period of 5 years. It will take place in a 22-bed Coronary Care Unit (CCU), which is run as a closed unit by onsite coverage 24-hr/7 days, under the care of 16 cardiologists.

b) Inclusion/exclusion

Mainly, all AF patients admitted to the CCU for DC cardioversion, and refractory to at least two trials of DC cardioversion will be eligible for this study. Excluded from this study will be patients with AF not requiring DC cardioversion, or those with AF who reverted after a maximum of two trials of DC cardioversion.

c) Sampling

Patients presenting to the CCU with persistent AF for direct current (DC) cardioversion, who meet the inclusion criteria and fail to revert to normal sinus rhythm after two DC cardioversion attempts will be invited for enrollment in the study. No sampling will be carried out for the sake of this study.

d) Intervention

Patients meeting the eligibility criteria will receive double sequential defibrillation (DSED) or a third DC cardioversion (standard of care).

DSD is the process of using two defibrillators near simultaneously at their highest allowed energy setting and aims to treat refractory AF. The first set of pads is placed in the traditional anterolateral position and the second set can be either placed adjacent to the first set (anterolateral) or in the antero-posterior position. Shocks are then delivered simultaneously or near simultaneously [16].

e) Randomization:

Randomization will be performed as permuted block randomization. Blocks of different sizes will be used as the randomization unit for the purpose of randomization. More specifically, block sizes of 4, 6 and 8 will be used. Computer generated randomization list will be provided by the statistician.

f) Allocation concealment:

To minimize selection bias in the study due to the allocation knowledge of the recruiting personnel, allocation concealment will be adopted in this study. Accordingly, the RAs who are responsible for recruiting patients into the study will use sealed opaque envelopes where the allocation would be specified within. When a patient meets the inclusion criteria, and consents to the study, the next envelope in place will be opened to identify the allocation of this patient into the intervention or control group.

g) Outcome

The investigators' outcome measure will be the number of participants with atrial fibrillation who revert to normal sinus rhythm using DSED after two failed attempts of DC cardioversion. This will be determined by conducting an Electrocardiogram (EKG) immediately after DSED. The EKG will be read by a trained physician to determine if the patient has successfully reverted to sinus rhythm.

h) Other factors and data collection

A data collection form (Appendix 1) will be used to collect information about the subject. This information will be obtained by the research fellow during his private interview with the patient after consent is taken. Some data will also be obtained from the electronic health records by the same CITI certified research fellow. Data will be related to AF and to the risk stratification tool (AFCVS score). Variables include demographics (age, gender), metrics (BMI, waist-hip ratio), past medical history (hypertension, diabetes mellitus, etc.), past surgical history (CABG, PCI, etc.), medications, social history, vital signs, physical exam, echocardiography results, NYHA score.

i) Sample size

There are no similar studies published in the literature assessing the efficacy of DSED on refractory AF. Accordingly, for the purpose of sample size calculation, the investigators considered a conservative approach in the calculation. More specifically, the investigators considered that 50% of patients with refractory AF will revert to sinus rhythm after 3 trials of DC cardioversion. Based on clinical experience, the investigators expect 78% to achieve

positive outcome after 2 trials of DC cardioversion followed by a third trial of DSED. This will yield an expected difference of 28% in DSED between the intervention and control groups. Considering a power of 80% and an alpha of 0.05, the investigators will require 50 patients in each arm, a total of 100 patients.

j) Statistical analysis

In the univariate analysis, the distribution will be presented as means \pm standard deviations and frequencies (percentage) for the continuous and categorical variables, respectively. In the bivariate analysis, student's t-test and Pearson's chi-square test will be used to assess the significance of the statistical association between the independent variables (continuous and categorical) and the two groups (Intervention and control) of the outcome. Furthermore, results will be presented as odds ratios (OR) and their corresponding 95% confidence intervals (CI).

A multivariate analysis will be carried out for the association between the intervention and outcome, while controlling for potentially confounding variables. More specifically, multivariate logistic regression analyses will be carried out. A stepwise selection procedure will be used including all risk factors found to be statistically significant at the bivariate level in addition to those considered as being clinically meaningful. Similarly, results will be presented as OR and their corresponding 95% CI.

The primary analysis is an intention-to-treat analysis (ITT) of unadjusted results. ITT being defined as analysis of all participants as randomized, regardless of whether the participants respected the study protocol or not (effectiveness). Sensitivity analysis will be carried out as per-protocol analysis consisting of analyzing individuals according to the treatment that the participants took, independently of their randomization.

P-values will be considered statistically significant if ≤ 0.05 . SPSS version 25.0 will be used to carry out the data cleaning, management and analyses.

Ethical considerations

The RA will consent patients, right after the cardiologist consents for the standard DC cardioversion procedure, using lay language prior to cardioversion. The risks and benefits of DC cardioversion and double sequential external defibrillation, as well as alternatives to their use will be thoroughly described. A copy of the informed consent will be given to each participant.

Data collection will be carried out by CITI certified research assistants. Only the information in patient charts and records will be observed and recorded. This study will not in any way influence the decision-making process or actions of AUBMC staff treating the patient.

All data collected will be stored in a manner that restricts identifiers to the PI and on a need to know basis for other researchers, and in keeping with the ten-year safe and secure storage regulations. All data will be entered in an excel sheet located on a password-protected computer of the primary investigator. After completion of the analysis, all patient identifiers located on the excel document will be removed.

Time frame

The study is expected to start in winter 2018 and will extend over 7 years: one year for study implementation, 5 years for patient recruitment and one year for data analysis and manuscript write up. It is projected to end in winter 2025.

Consent to participate in a research study

Double sequential external defibrillation: a randomized controlled trial in patients with atrial fibrillation refractory to DC cardioversion

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You are being asked to participate in a clinical research study conducted at the American University of Beirut. Please take your time to read the following information carefully before you decide whether you want to take part in this study or not. Feel free to ask your doctor if you need more information or clarification about what is stated in this form and the study as a whole.

PURPOSE AND DESCRIPTION OF THE STUDY:

Atrial fibrillation is the most common sustained cardiac arrhythmia in clinical practice, characterized by abnormal, irregular heartbeats. Patients are at increased risk for death, heart failure and hospitalization. The restoration (cardioversion) of the normal sinus rhythm is performed in many patients with atrial fibrillation to improve symptoms. Therefore, physicians attempt to restore sinus rhythm in patients with atrial fibrillation, often using direct current (DC) shocks ('electrical cardioversion'). Electrical cardioversion, which involves delivering a shock to the heart with a defibrillator, requires admission to hospital, a short-acting anesthetic and a direct current shock. Sometimes repeated electrical cardioversions are required if a patient's heart rhythm fails to become normal. A certain patient population with specific comorbidities and characteristics often do not respond to cardioversion, thus failing to achieve the normal (sinus) rhythm. This happens in 5 to 30 % of patients.

Double sequential external defibrillation (DSED) is the process of delivering two near-simultaneous shocks instead of one shock (standard of care). It involves delivering two immediately consecutive electrical shocks to the chest, using 2 defibrillators. Instead of applying one set of patches (2 patches) to the chest, 2 sets will be attached (3 in the front part of your chest and 1 in the back). More energy will be delivered to your chest during DSED. The aim of this study is to prove that DSED has a higher success rate in terminating Atrial Fibrillation and restoring sinus rhythm in patients who have failed to revert to sinus rhythm previously, despite two attempts of DC Cardioversion (Standard of Care).

Previous data has shown that when two attempts of DC cardioversion have failed to restore normal sinus rhythm in certain patients, applying high energy shock waves to the chest through DSED, may restore normal sinus rhythm, and terminate atrial fibrillation.

This study is a Phase III, randomized controlled, superiority trial, with two parallel groups, conducted in one academic medical center. Patients presenting to the coronary care unit (CCU) with atrial fibrillation for DC cardioversion, who meet the inclusion criteria and fail to revert to normal sinus rhythm after two DC cardioversion attempts will be randomized into two arms: the first one will receive a third trial of DC cardioversion (standard of care) and the second one will receive double sequential defibrillation.

Recruitment will be done at AUBMC, involving patients with atrial fibrillation presenting to the CCU for DC cardioversion.

Your participation in the study entails the following:

-Answering questions about your medical history to the Research Assistants and allowing them to review your electronic health records. Information to be collected include: demographics, smoking status, past medical history, alcohol intake, illicit drug use, exercise status, previous DC cardioversion and medications used. You have the right to refrain from answering sensitive questions.

-Being randomized to one of the interventional arms which will be performed as stratified randomization. This means that you will have an equal chance of being allocated to the control (standard of care) or study arm (DSED).

The attending physicians will assess if the patients with scheduled DC cardioversion meet the study's inclusion criteria. The physicians will approach the patients in their respective rooms in the coronary care unit (CCU) at AUBMC, in a private setting. The physicians will describe the study and the two procedures (DC cardioversion and DSED) that might be used thoroughly and explain the risks and benefits of both. Verbal and written informed consent will then be obtained by the attending physician for standard DC cardioversion and participation in this study, in their respective rooms in the coronary care unit (CCU) at AUBMC, in a private setting.

The attending physicians performing the scheduled DC cardioversion will inform the RAs about the approval of the patient to participate in the study. The RAs will then obtain a detailed history from the patients to fill the data collection sheet.

Your participation in this study will not require additional time, as compared to the standard of care.

Usual interview time: 5 minutes

Usual procedure time: 10-15 minutes.

The investigator expects to recruit a total of 100 patients over a span of 5 years, divided between two arms: 50 patients in the control arm (standard of care) and 50 patients in the study arm (DSED).

WHAT ARE THE RISKS OF THE STUDY?

The foreseeable risks/discomfort associated with this DSED involve the same risks that are seen with direct current cardioversion. So, there are no or very few added risks when compared to the standard manner of treatment. The most common complications of direct current cardioversion and defibrillation are harmless arrhythmias. Serious complications include ventricular fibrillation, a dangerous potentially fatal arrhythmia. Below, please find

the evidence behind the specific risks of cardioversion (which is the standard of care) and defibrillation; and their incidence.

Most complications are self-limiting (ex. changes in the electrocardiogram, hypotension related to sedation and/or vasodilation) or relatively benign (ex. skin irritation). Cutaneous burns — Following cardioversion or defibrillation, skin burns occur in 20 to 25 percent of patients and are more likely with improper technique and placement of electrodes. The risk of burns is less with the use of biphasic waveforms and the use of gel-based pads. The risk of cutaneous burns may be higher in patients undergoing double sequential defibrillation compared to the standard DC cardioversion.

Please note that there may also be unforeseeable risks.

HOW WILL MY CONFIDENTIALITY BE PROTECTED?

Your name, birth date, and other personally identifying information will be removed from your data. Therefore, medical information will be de-identified. Only the original investigators will be able to trace your samples and information to you. Information collected in this study may be reviewed by authorized individuals from the IRB or Lebanese Government for the purpose of making sure that proper systems, procedures, and regulations are being followed. These measures will all be conducted ensuring there is no breach of participants' privacy.

All study results will be shared with the subjects and could be used for patient care. Unless required by law, only the study doctors and designee, the ethics committee and inspectors from governmental agencies will have direct access to your research records without violating confidentiality. The physician who has invited you to participate may elect to end your participation at her/his will.

WHAT IF I AM SUBJECTED TO HARM?

AUBMC will cover the cost of treating, on its premises, medical adverse events resulting directly from the medication and/or medical procedures of this research study. Otherwise, it will not cover for the costs of medical care for any medical condition or issue

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Your participation will help medical researchers better understand various diseases and develop better treatments, which may help you or others in the future. Participation in this study might benefit you since there's promising data showing the superiority of DSED in terminating refractory Atrial Fibrillation to multiple attempts of Direct Current Cardioversion; as compared to the standard of care. You will not receive any cash or payment for your participation in this research project. There will be no anticipated expenses.

WHAT ARE MY OTHER OPTIONS?

Taking part in research is entirely voluntary. You do not have to participate in this study if you do not want to do so. Your decision about whether or not to participate will in no way

affect your present or future medical care, your participation in other research studies, or your relationship with the research team.

If you agree to participate in this research study, the information will be kept confidential. Unless required by law, only the study doctor and designee, the ethics committee and inspectors from governmental agencies will have direct access to your medical records.

Investigator's Statement:

I have reviewed, in detail, the informed consent document for this research study with _____ (name of patient, legal representative, or parent/guardian) the purpose of the study and its risks and benefits. I have answered to all the patient's questions clearly. I will inform the participant in case of any changes to the research study.

Name of Investigator or designee

Signature

Date & Time

Patient's Participation:

I have read and understood all aspects of the research study and all my questions have been answered. I voluntarily agree to be a part of this research study and I know that I can contact Dr. Gilbert Abou Dagher and/or Dr. Marwan Refaat at 961-1350000 Ext 6617/5366 or any of his/her designee involved in the study in case of any questions. If I feel that my questions have not been answered, I can contact the Institutional Review Board for human rights at 961-1-350000 Ext 5445. I understand that I am free to withdraw this consent and discontinue participation in this project at any time, even after signing this form, and it will not affect my care or benefits. I know that I will receive a copy of this signed informed consent.

Name of Patient or Legal Representative
or Parent/Guardian

Signature

Date & Time

Witness's Name
(if patient, representative or parent do not read)

Witness's Signature

Date & Time

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