PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and safety of 1c class antiarrhythmic agent (propafenone) for supraventricular arrhythmias in septic shock compared to amiodarone: protocol of a prospective randomized double-blind study
AUTHORS	Balik, Martin; Waldauf, Petr; Maly, Michal; Matousek, Vojtech; Brozek, Tomas; Rulisek, Jan; Porizka, Michal; Sachl, Robert; Otahal, Michal; Brestovansky, Petr; Svobodova, Eva; Flaksa, Marek; Stach, Zdenek; Pazout, Jaroslav; Duska, Frantisek; Smid, Ondrej; Stritesky, Martin

VERSION 1 - REVIEW

REVIEWER	Dr. Guido Tavazzi University of Pavia, Department of Diagnostic and Paediatric Science. Fondazione Policlinico San Matteo, IRCCS, Pavia, Italy.
REVIEW RETURNED	27-May-2019

GENERAL COMMENTS	The study protocol has a strong pathophysiological background and it is supported by a well conducted retrospective study. The methodology is appropriate and well declared.

REVIEWER	Michihito Kyo Department of Emergency and Critical Care Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan
REVIEW RETURNED	03-Jun-2019

GENERAL COMMENTS	bmjopen-2019-031678 In the manuscript entitled “Prospective randomized double-blind study of efficacy and safety of 1c class antiarrhythmic agent (propafenone) for supraventricular arrhythmias in septic shock compared to amiodarone”, the authors presented the protocol of prospective randomized double-blind study. This study was planned to include 220 patients for four years, and assess the efficacy of propafenone compared to amiodarone for patients with supraventricular arrhythmias in septic shock. The protocol of this study was well designed, however, it would be needed to addition some important points to interpret this protocol.

	Major comments Exclusion criteria Amiodarone has severe side effects, such as interstitial pneumonia and liver dysfunction. What is the reason of the such diseases not excluded? Interventions and research protocol Paroxysmal AF rhythm sometimes restores to sinus rhythm spontaneously. What is the timing of randomization? If AF rhythm restores to sinus rhythm before administration of intervention drug, how do you treat such patients. After 24 hours of continuous administration of intervention drug, how do you treat the patients, if AF rhythm persists. Minor comments Inclusion criteria What is the age of the included patients? Interventions and research protocol How do you use anticoagulant drug?

REVIEWER	SILVIO A. ÑAMENDYS-SILVA, MD, MSc, FCCP, FCCM Medica Sur Clinic & Foundation, Instituto Nacional de Cancerología & Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico,
REVIEW RETURNED	20-Jul-2019

GENERAL COMMENTS	Abstract: The authors should reduce the text to 250-word. -Ethics and Dissemination: add (No. 1691/16 S-IV) The introduction is much longer and contains too much general knowledge. The introduction has too many references. The author should use the most recent, most direct, most succinct, and the most relevant references. The statistics should be carefully and clearly described.

VERSION 1 – AUTHOR RESPONSE

1.) The title now clearly shows that this is a protocol “Efficacy and safety of 1c class antiarrhythmic agent (propafenone) for supraventricular arrhythmias in septic shock compared to amiodarone: protocol of a prospective randomized double-blind study”

2.) The quality of the English was checked once more by the native speaker. Please suggest a BMJ linked language editing if you still find the English level insufficient for the BMJ.

3.) The “Strengths and Limitations Section” after the abstract now focuses more on the methodology and design: “- Randomized controlled trial comparing propafenone versus amiodarone in septic shock patients with normal to moderately reduced EF_LV should eliminate the bias of previous trials where patients with all levels of LV systolic function and various illness severities were compared.

- The trial should answer the issue of safety of the 1C class agent propafenone given within the summary of product characteristics in the critically ill – in contrast to the older trials on less severely ill patients.

- The outcomes of cardioverted patients with improved diastolic function will be compared to matched patients who remain in persisting arrhythmias.

- The analysis of applied complex echocardiography protocol may propose simple echo parameters which may help in the decision on rhythm versus rate control approach.

- Due to the scarcity of data in the current literature the hypotheses are based on a single large retrospective study on septic shock patients with SV arrhythmias"

4.) The interstitial pneumonia and liver dysfunction are known side effects of long-term amiodarone administration which are very rare in a short-term medication for an acute onset supraventricular arrhythmia. Moreover, chronic atrial fibrillation patients with possible history of a long-term amiodarone use are excluded from the trial. The following text was added to the Exclusion Criteria section: "An interstitial pneumonia is not considered a contraindication to randomization with regards to delayed effects of amiodarone upon the lung parenchyma28 and expected short period of its administration. Similarly, liver dysfunction is not a contraindication for amiodarone assuming a titrated short duration of the medication."

5.) We are very grateful for the comment on spontaneous cardioversion before the randomized patient receives the study drug. This has been already recorded in couple of patients. We proceed as it is now added to the Interventions and Research Protocol Section: "If a patient spontaneously cardioverts before the drug is administered, i.e. between randomization and drip initiation, the patient is monitored accordingly and included in the intention-to-treat analysis."

6.) If the patient does not cardiovert within the expected 24h then we continue the therapy and monitor the left atrial function with echocardiography and ECG as it is already specified in the current version of the manuscript in the interventions and Research Protocol section: "If cardioverted later than until 24h then echocardiography is performed at 1h and 4h after cardioversion, the times of cardioversion and arrhythmia relapses are always recorded."

7.) The age of the adult critically ill is now specified in the Inclusion Criteria section: (16-85 years)

8.) The anticoagulation management is not a part of the study protocol and we do not change the individually set anticoagulation medication with the onset of arrhythmia. The study focuses on the critically ill with multiple primary sources of septic shock including also surgical and wound related sepsis. Moreover, included patients with a new onset supraventricular arrhythmia have normal-to-moderately reduced left ventricular systolic function which significantly reduces a risk of intracardiac thrombus formation (Stroke Prevention in Atrial Fibrillation Study Group Investigators. Ann Intern Med 1992, JASE 2011) – in contrast to patients with severe LV dysfunction and/or chronic arrhythmia who are excluded. Within the study protocol we aim for cardioversion within the first 24h which also reduces the risk of thrombogenicity.

9.) The abstract has now 297 words which is within the limits for the BMJ Open given in the instruction to authors. I would like to ask the Editorial Office if this part of the manuscript should be abridged to 250 words.

10.) The code of the approved protocol has been added to the Ethics and Dissemination of the abstract.

11.) The Introduction has been now shortened to 697 words, 3 references have been deleted.

12.) The paragraph on statistics underwent changes in methodology depiction and wording: “All analysis will be conducted in R Core Team (2019) and will be available as an appendix together with the raw data. Exploratory data analysis will be performed for both baseline and outcome parameters. Continuous parameters will be described as means and standard deviations and as medians and the interquartile ranges if not normally distributed. Log-normally distributed parameters will be logarithmically transformed if needed. Binary data will be described as counts and frequencies. Statistical significances of differences between groups will be described as odds ratio, hazard ratio or mean difference according to the type of analysis with 95% confidence interval. Both intention-to-treat and per protocol analysis will be performed.

The primary outcome (proportion of patients that have achieved rhythm control at 24 hours after the start of the infusion) will be analysed using logistic regression and time to event analysis (Cox regression).The secondary outcomes (proportion of patients that needed rescue treatments), recurrence of arrhythmias, ICU mortality, 28-day and 1-year mortality will be analysed using logistic regression. If significant differences in baseline characteristics are found between analysed groups then multivariate regression for adjustments to these variables will be performed.

The required number of patients is based on the power analysis and data from the pilot retrospective study 4 5. The entry parameters for sample size analysis were estimated by the probabilities of cardioversion of 75% for the amiodarone group and 90% for the propafenone group within 24h from the onset of arrhythmia, randomisation ratio 1:1, p=0.05 and power 0.8. To achieve a statistically significant difference under these conditions 100 patients need to be included into each group, altogether 200 patients into the trial. Assuming 10% drop out the authors plan to randomize 220 patients.”

VERSION 2 – REVIEW

REVIEWER	Michihito Kyo Department of Emergency and Critical Care Medicine, Hiroshima university, Japan
REVIEW RETURNED	12-Aug-2019

GENERAL COMMENTS	bmjopen-2019-031678.R1 In the manuscript entitled “Efficacy and safety of 1c class antiarrhythmic agent (propafenone) for supraventricular arrhythmias in septic shock compared to amiodarone: protocol of a prospective randomized double-blind study”, the authors resubmitted this manuscript which is modified correctly according to the reviewer’s comment. It would be needed to modify one point. Minor comments Interventions and research protocol Page 8 line 13: I think this sentence is not correct in grammatically.