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Propafenone for supraventricular arrhythmias in septic shock—Comparison to amiodarone and metoprolol☆·☆☆

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ABSTRACT

Purpose: The occurence of supraventricular arrhythmias associate with an unfavourable prognosis in septic shock. Propafenone could be a feasible antiarrhythmic.
Materials and methods: Patients collected over a period of 24 months were divided into the three groups based on antiarrhythmic: Group1(amiodarone), Group2(propafenone), Group3(metoprolol). Type of arrhythmia, cardioversion rates, demographic, haemodynamic, laboratory parameters were recorded in the first 24 h. The outcome data were compared between the groups.
Results: 234 patients (99.1% ventilated) were included, the prevailing arrhythmia was acute onset atrial fibrillation (AF,69.7%). Except for the dosage of noradrenaline (0.35(0.14–0.78) in Group1(n = 142)vs 0.25(0.10–0.50),p < 0.01 in Group2(n = 78)vs 0.14(0.07–0.25)μg/kg·min,p < 0.05 in Group3(n = 14)) the ejection fraction of left ventricle, rates of renal replacement therapy, arterial lactate and procalcitonin levels were not different between the groups. The cardioversion rate in Group1(74%) was lower than in Group2(89%) and Group3(92%). ICU and 28-day mortalities of Group1 were not significantly higher than in Group2 and Group3. Multivariate analysis demonstrated higher 12-month mortality in Group1 than in Group2 (HR1.58(1.04;2.38),p = 0.03).
Conclusions: Propafenone demonstrated a higher cardioversion rate than amiodarone with a similar impact on the outcome. Patients remaining in acute onset arrhythmia did not demonstrate significantly higher ICU, 28-day and 12-month mortalities compared to those successfully cardioverted or to those having chronic AF.

1. Introduction

The septic shock is characterized by reduced afterload, unstable filling conditions, LV diastolic and systolic dysfunction, catecholamine surge and chronotropic dysregulation which all together may lead to rhythm disorders [1-8]. An impact of sepsis related fever on heart rate is also a contributing factor. Amongst the general ICU population, the incidence of SV arrhythmias is increased in septic shock patients, and it is associated with worse short and long term prognosis [9-11]. Besides improving oxygenation, preload and electrolyte corrections, the mainstay of treatment is represented by amiodarone preferred for its lower cardiodepressant side effect compared to other agents and electric cardioversion [10-13]. Amiodarone carries potential significant side effects including hypotension and the evidence of its efficacy in the septic shock population is lacking [9,10,14]. The use of 1C class antiarrhythmic drugs in SV arrhythmias treatment has not been properly evaluated in the critically ill. There are only a few case reports describing serious adverse effects apparently related to their dose related cardiotoxicity [15-17]. Moreover, their usage has been discouraged by reports describing cardiotoxicity and poor outcome on long term use in the cardiology population [15]. Consequently, 1C class agents, like propafenone and

Abbreviations: SV, supraventricular; AF, atrial fibrillation; SR, sinus rhythm; LV, left ventricle; RV, right ventricle; LA, left atrium; EF_LV, ejection fraction of left ventricle; CRRT, continuous renal replacement therapy; ICU, intensive care unit; LOS, length of stay; LOS-Aon, length of stay from arrhythmia onset; SOFA, sequential organ failure score; APACHE II, acute physiology and chronic health evaluation; BW, body weight; CRP, C reactive protein; PCT, procalcitonin; NAD, noradrenaline; PCr, plasma creatinine; LA_ESd, size of left atrium; RV_ED, enddiastolic size of right ventricle; TAPSE, tricuspid annular plane systolic excursion; PH, pulmonary hypertension; MR, mitral regurgitation; CVP, central venous pressure; IPPV, intermittent positive pressure ventilation; PEEP, positive enddiastolic pressure; MV, minute ventilation; FiO_2, inspiratory fraction of oxygen.

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flecainide [18], are not routinely used in critically ill - regardless of the limited application of these conclusions for fully monitored intensive care patients. Propafenon is derived from propandiolamine, which is a chemical compound of betablockers, and acts on the rapid depolarizing phase (phase 0) and also, to minimal extent, on beta-adrenergic receptors [14,19].

More than 50% of patients with heart failure in the ICU show a diastolic heart failure, often associating with a rhythm disorder [20].The reported benefits of betablockers in sepsis and septic shock [21-25] could also be related to improvement of LV diastolic function and arrhythmia management. With regards to these findings, the antiarrhyhmic efficacy of betablockers and the betablocker derivative propafenone could be higher in septic shock patients compared to the efficacy of the most frequently administered amiodarone with a less betablocking activity.

The primary aim of this retrospective study was to monitor the current management of SV arrhythmias in order to pave way for a prospective study. We hypothesized that propafenone could be a drug of choice in septic shock patients with mildly to moderately reduced EF_LV. In addition, the benefits of propafenone can be proved in patients where amiodarone is not capable of maintaining SR. As part of the safety and efficacy study the routine dosage might be feasible to restore SR without an adverse effect on haemodynamics and major impact on the outcome. The follow up parameters may not differ between the antiarrhythmic agents when compared between the groups including patients with chronic arrhythmias. This research, albeit retrospective, will fill in the gap in knowledge of 1C class antiarrhythmics administration in the critically ill and serve as a basis for further prospective and controlled studies.

2. Material and methods

The data extracted from departmental registry and patient information system (Medea, Stapro, Prague) of the 15 bed general intensive care unit in the university hospital was retrospectively analyzed for a period of 24 months from January 2013 to December 2014. Included patients were then followed for their 12-month outcome. The University Hospital Ethical Board waived a need for an informed consent due to the retrospective nature of the study (No.825/16S-IV) and anonymous data set undergoing statistical analysis.

A diagnosis of septic shock was made according to the criteria set for systemic inflammatory syndrome [26] with administration of noradrenaline due to hypotension non-responsive to correction of preload. In addition, a positivity of at least one inflammatory marker of the monitored CRP and PCT was required together with administration of antibiotics for an infectious source.

The exclusion criteria were absence of septic shock, dependence on pacemaker and status after MAZE procedure.

The patients were then divided into three groups according to the intravenous antiarrhythmic agent: amiodarone (Group1), propafenone (Group2) and metoprolol (Group3). The agents were indicated in SV arrhythmia compromising circulation in patients already on infusion of noradrenaline for septic shock. Due to severe haemodynamic instability some patients underwent concomitant electric cardioversion. Complex haemodynamic monitoring including echocardiography was also applied to correct preload and to avoid metoprolol or propafenone in severe LV systolic dysfunction. Agents other than amiodarone were preferred in known thyreopathy or in intolerance of amiodarone.

Haemodynamic parameters including the dosages of the most frequently used vasoactive agents at the onset of the arrhythmia and ventilator settings were stored. Demographic data, APACHE II, SOFA, laboratory data at the onset of arrhythmia and therapy for thyroid disorder were recorded as well as the rates of CRRT.

The statistic analysis was divided into two stages. The first 24 h stage focused antiarrhythmic efficacy and covered the type of arrhythmia, antiarrhythmic agent administered, cardioversion rates after administration including rates of additional electrical cardioversion and patient's previous antiarhythmic history. Any changes of the agents were monitored after recording the primary efficacy of the antiarrhythmic therapy. The second follow up stage compared the ICU mortality, the 28-day mortality and the 12-month mortality between the groups divided according to the final antiarrhythmic agent at 24 h. The outcome was also compared between patients with successful cardioversion and those remaining in arrhythmias. The impacts of cardioversion and various antiarrhythmic agents on the length-of-stay (LOS) and on the length-of-stay from the onset of arrhythmia (LOS-Aon) were sought.

Patients with a chronic arrhythmia were excluded from the first 24 h efficacy study to restore SR. Nevertheless, they were included in the second follow up study assessing an impact of antiarrhythmics on the outcome parameters.

Statistic methods (Stata 14.1, StataCorpLP, Texas, USA) covered the analysis of continuous and categorical data. Continuous data with normal distribution (e.g. age, SOFA, APACHE II, EF_LV) was expressed as means ± standard deviations. Data with lognormal distribution (e.g. dosage of noradrenaline, creatinine, PCT, lactate) was presented as medians and interquartile ranges. The categorical data was analyzed with logistic regression, Cox regression was applied for survival analysis. For the outcome study the linear regression analysis involved univariate and multivariate testing, the significance was set at $p < 0.05$. In multivariate analysis, the standardized continuous parameters were used for better comparability of regression coefficients (odds ratios and hazard ratios). Standardization was made by subtraction of the mean value from the unstandardized parameter and dividing by its standard deviation.

3. Results

Amongst the 1349 admitted to the ICU over 24 months, 301(22.3%) received antiarythmic treatment for SV arrhythmias. 67 patients were excluded because of the absence of criteria for sepsis [26], 27 for no concomitant antibiotic treatment and absence of elevation of at least one of the two monitored inflammatory markers (CRP < 6 mg/l,PCT < 0.5 mg/l), 6 for the absence of noradrenaline infusion (i.e. severe sepsis only), and 19 for admission to the general ICU due to complications after an elective MAZE procedure. 15 patients fully dependent on any pacing modality were also excluded.

234 remaining critically ill patients (APACHE II 24.3 ± 11.4, SOFA at first arrhythmia day 10.6 ± 4.1, age 67.2 ± 11.3 years, 139 males (59.4%)) were included, of those 232(99.1%) were mechanically ventilated.

The primary sources of septic shock were respiratory (n = 134;57.3%), abdominal (n = 59;25.2%), urosepsis (n = 17;7.3%), wound/surgical (n = 12;5.2%), catheter related (n = 10;4.2%), maxilofacial (n = 1;0.4%) and neuroinfection (n = 1;0.4%). The included (n = 234) septic shock patients had mild to moderate renal insufficiency with a plasma creatinine level of 136(92–204)μmol/l. 64(27.4%) patients had acute kidney failure requiring CRRT with regional citrate anticoagulation. CRRT is a strong predictor of mortality in IPPV patients with septic shock and circulatory failure [27]. The mean arterial lactate level was 2.4(1.4–3.8)mmol/l, the mean PCT was 2.6(0.7–8.8)ng/ml. 45(19.2%) had some form of thyreopathy. 117(50%) patients had ischaemic heart disease (79(56%) of the Group1, 34(43.6%) of the Group2 and 4(28.6%) of the Group3).

136(58%) patients took antiarrhythmic drugs prior to admission to the ICU: 18.8% received betablockers, 8.1% amiodarone, 1.3% amiodarone and betablockers, 4.7% propafenone and 2.6% digoxine of which one was in association with a betablocker.

The rates of various SV arrhythmias, primary intravenous drug of choice and final medication at 24 h are shown in the flowchart (Fig. 1). The prevailing type of SV arrhythmia was acute onset AF in 69.7% and chronic AF in 14.5%. Time to arrhythmia onset was 1.0 (0.0–3.0) days from admission to the ICU (1.0 (0.0–3.0) days in Group1, 2.0 (0.0–4.0) days in Group2($p = 0.11$ vs Group1, $p = 0.15$ vs group3) and 1.5 (0.0–2.0) days in Group3($p = 0.55$ vs Group1)). 10.3% received electric cardioversion prior to antiarrhythmic drugs followed by the