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Original Article

A multicenter observational study of the effectiveness of antiarrhythmic agents in ventricular arrhythmias: A propensity-score adjusted analysis

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ABSTRACT

Background: Ventricular tachyarrhythmias (VTs) are life-threatening events that result in hemodynamic compromise. Recurrence is common and may worsen a patient's clinical course despite appropriate treatment. This study aimed to examine the effectiveness of antiarrhythmic drugs for suppression of VTs.
Methods: In this cohort study, eligible patients were those who were admitted to one of the nine cardiovascular care centers and treated with continuous infusion of an antiarrhythmic drug for at least 1 h to prevent recurrence of VTs after return of spontaneous circulation. To adjust for differences in baseline characteristics among treatment groups, propensity scores for administered agents were generated and used as covariates in regression analyses.
Results: Seventy-two patients were enrolled and 67 patients were included in the final analysis. Amiodarone ($n=21$, 31.3%), nifekalant ($n=24$, 35.8%), and lidocaine ($n=22$, 32.8%) were administered as first-line therapy for suppression of VTs. In the adjusted analyses, the odds ratio (OR) of switching to a different drug was significantly higher in the lidocaine group (OR 37.6, 95% CI 5.1–279, $p<0.001$) than in the amiodarone group, but not in the nifekalant group (OR 4.1, 95% CI 0.72–23.2, $p=0.11$). There was no significant difference in mortality rate in the lidocaine group (OR 1.67, 95% CI 0.40–6.95, $p=0.48$) or the nifekalant group (OR 1.11, 95% CI 0.15–4.85, $p=0.89$) compared with the amiodarone group.
Conclusion: Amiodarone and nifekalant are similarly effective in preventing VT recurrence, but their impact on survival rate is minimal. These data indicate that both nifekalant and amiodarone can be used for treatment of refractory VT.
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1. Introduction

Ventricular tachyarrhythmias (VTs) are life-threatening events that result in hemodynamic compromise; therefore, patients often require immediate treatment such as electrical cardioversion. Despite appropriate management of ventricular arrhythmias, recurrence is common and may worsen the clinical course of the patients. The American Heart Association (AHA) guideline on cardiopulmonary resuscitation (CPR) and emergency cardiovascular care states that when ventricular arrhythmias are refractory to defibrillation, antiarrhythmic agents, such as amiodarone, lidocaine, and magnesium sulfate, can be used [1,2].

Lidocaine has been used empirically for the prevention of ventricular arrhythmias. However, when compared to amiodarone, it has not been demonstrated to improve the return of spontaneous circulation (ROSC) or survival to hospital discharge. Some studies suggested that amiodarone was superior to lidocaine for the management of ventricular arrhythmias [3,4]. However, its antiarrhythmic effect has a late onset, and a large dose is needed to terminate ventricular arrhythmias in emergent settings. Furthermore, bradycardia and hypotension may occur after resuscitation as a result of its β-adrenergic blocking effect and vasoactive effect of the excipients, polysorbate 80 and benzyl alcohol [5].

Nifekalant, a pure potassium channel blocker, was clinically approved and is currently used only in Japan. Although some reports suggested that nifekalant was efficient for the treatment of refractory ventricular arrhythmias, only a small number of studies have directly compared class III drugs because it is difficult to carry out a randomized study in an emergent and critical care setting [6–11].

Once an antiarrhythmic agent is effective for defibrillation or suppression of malignant arrhythmias, most physicians continue administering it for a certain period, but the optimal drug and duration of the therapy for the prevention of arrhythmia

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recurrence are not well understood. Hence, we conducted this study to investigate the role of antiarrhythmic agents for suppression of ventricular arrhythmias in clinical practice.

2. Material and methods

2.1. Study setting

This observational cohort study was conducted at nine cardiovascular centers in Chiba prefecture in Japan from 2005 to 2009.

2.2. Patient enrollment

Patients who were treated with a continuous infusion of intravenous antiarrhythmic agents for at least 1 h to prevent the recurrence of ventricular arrhythmias in a hospital setting were eligible for enrollment. When a patient was unstable due to sustained ventricular arrhythmias at presentation, electrical cardioversion was immediately delivered to stabilize hemodynamics, and then antiarrhythmic therapy was initiated to prevent arrhythmia recurrence. The choice of a specific antiarrhythmic drug depended on each physician, and was in line with the major guidelines for CPR and ventricular arrhythmias.

After obtaining the patients' informed consent, these were enrolled within 48 h after administration of preventive antiarrhythmic drugs and their clinical course was followed until discharge. Patients' baseline data were collected to adjust for their potential confounding effect on the choice of treatment and outcomes. The baseline data included age, sex, underlying heart diseases, cardiac function, administered drugs and their dose and duration, and clinical courses and outcomes. The ethical committee in each hospital approved this study design.

2.3. Exclusion criteria

Patients were not eligible if they met any of the following criteria: multiple antiarrhythmic drugs were administered intravenously from the beginning, oral antiarrhythmic agents were being taken at the time of hospital admission, treatment was with a single-shot antiarrhythmic drug only, or an intravenous antiarrhythmic agent was administered for less than 1 h. These situations were considered to hinder the evaluation of suppressive effects of the antiarrhythmic drugs.

2.4. Outcomes definition

In the evaluation of drugs effectiveness, the primary outcome was defined as any switch or addition of an antiarrhythmic drug due to their ineffectiveness or adverse effect. The purpose of prophylactic antiarrhythmic drugs after resuscitation care is to prevent recurrent ventricular arrhythmias deteriorating the hemodynamic state, but the criteria of drug effectiveness was not well established. In the case of recurrent ventricular arrhythmias immediately after initiation of an antiarrhythmic drug, it is difficult to determine whether the drug is effective due to its short course duration. Once we determine that the drug is ineffective or harmful regardless of the reason, we usually switch it to another drug or add other drugs to it; therefore, we considered this definition as an appropriate indicator in this study.

The secondary outcome was survival at discharge. The drug adverse effects were also investigated for drug safety. The distinction between interruption and completion of drug administration depended on whether the drug was switched to another intravenous drug. The end of intravenous administration was considered when drug cessation occurred without switching to an oral drug or with switching to the same drug in oral form.

2.5. Statistical analysis

Values were expressed as the mean $\pm$ standard deviation when the data were normally distributed data or the median $\pm$ interquartile range when the data did not follow a normal distribution. Continuous baseline variables were compared among groups by one-way analyses of variance. Categorical baseline variables were compared by Chi-square test or Fisher's exact test, as appropriate. Because of a relative small number of patients in logistic regression analysis that included multiple covariates, propensity scores were generated to estimate the probability of treatment assignment by using multinomial logistic regression, and the propensity scores were used as a single covariate in the logistic regression analysis. The variables for estimating propensity scores included age, sex, prehospital cardiopulmonary arrest, electrical cardioversion, ischemic or nonischemic heart disease, types of ventricular arrhythmias (monomorphic, polymorphic ventricular tachycardia or ventricular fibrillation), use of beta-blockers, and inotropes or mechanical hemodynamic support before antiarrhythmic drug administration. In order to determine the validity of the comparisons adjusted by propensity scores, the distribution and overlap of the calculated propensity scores were checked for each agent. A variance inflation factor was employed to investigate independent variables multicollinearity. In the analysis comparing the difference between two antiarrhythmic agents, the inverse propensity score weighting method was employed. A two-tailed p value < 0.05 was considered significant. All statistical analyses were performed by R version 3.2.0.

3. Results

3.1. Primary and secondary outcomes

A total of 72 patients were enrolled in this study. Five of them were excluded based on exclusion criteria, and the other 67 were analyzed using the regression model as they had presented with complete data (Fig. 1). Their baseline characteristics and clinical outcomes are shown in Tables 1 and 2, respectively. Amiodarone was administered as the first-line therapy in 21 patients, lidocaine in 22 patients, and nifekalant in 24 patients. There were significant differences in baseline characteristics among these groups, such as in the prevalence of cardiopulmonary arrest on arrival and use of inotropic agents.

In crude analysis, lidocaine use was significantly associated with a subsequent drug change or addition when compared with amiodarone use (odds ratio (OR) 12.9, 95% confidence interval (CI) 2.82–58.6, $p=0.001$) (Table 3). There was no difference among the three agents in survival at discharge ($p=0.694$).

Furthermore, in the adjusted analyses using propensity scores, a drug change to another agent occurred significantly more often in the lidocaine group (OR 34.2, 95% CI 4.62–253, $p < 0.001$) when compared with the amiodarone group, but not in the nifekalant group (OR: 4.63, 95% CI: 0.81–26.5, $p=0.086$). However, there were no significant differences in survival at discharge when the amiodarone group was compared with the lidocaine and nifekalant groups, respectively (lidocaine group: OR 1.67, 95% CI 0.40–6.95, $p=0.48$; nifekalant group: OR 1.11, 95% CI 0.15–4.85, $p=0.89$).

In post-hoc analysis, amiodarone and nifekalant groups were compared by using the inverse propensity score weighting method. This analysis showed no significant difference in the rate of drug change or addition (OR 0.245, 95% CI 0.045–1.318,

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