Journal of Arrhythmia 32 (2016) 186–190

Contents lists available at ScienceDirect

Journal of Arrhythmia

journal homepage: www.elsevier.com/locate/joa

Original Article

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

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ARTICLE INFO

Article history:
Received 28 November 2015
Received in revised form
26 December 2015
Accepted 7 January 2016
Available online 10 February 2016

Keywords:
Ventricular tachycardia
Amiodarone
Nifekalant
Lidocaine
Propensity score

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.

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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http://dx.doi.org/10.1016/j.joa.2016.01.004
1880-4276/

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,

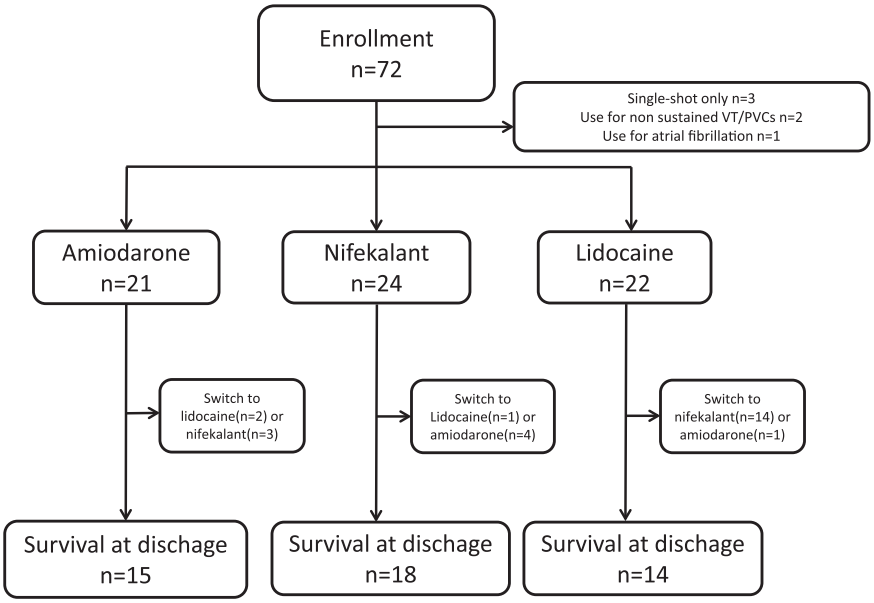

Fig. 1. Flow chart of enrolled patients and their outcomes.

$p=0.109$) as well as survival at hospital discharge (OR 1.107, 95% CI 0.236–5.20, $p=0.898$) (Table 4).

3.2. Adverse effects

When conducting adverse events surveys, three patients had hypotension, bradycardia, and significant liver dysfunction (liver enzyme values > 3 times normal values). Additionally, interstitial pneumonia occurred in one of the patients in the amiodarone group. Moreover, of the 23 patients treated with nifekalant, three experienced prolonged QT interval or torsades de pointes. In the lidocaine group, three patients complained of nausea or vomiting, presumably due to drug intoxication. In all of these cases, the drugs were discontinued. Data on the plasma concentration of each drug were not available.

4. Discussion

In management of ventricular arrhythmias, amiodarone plays a pivotal role in clinical practice, and current guidelines have recommended it as the first choice for intravenous infusion in cases of ventricular arrhythmias refractory to defibrillation. For a decade, nifekalant has been the only approved class III agent in Japan. It was demonstrated to suppress ventricular re-entry by prolonging the action's potential duration and effective refractory period without evidencing a negative inotropic effect [12–16]. Furthermore, this agent causes dose-dependent QT prolongation and torsade de pointes. In other countries, intravenous amiodarone has already been used for a few decades and has been established as a mainstay drug for various types of arrhythmias. After the clinical introduction of intravenous amiodarone in Japan, we could not determine which agent was superior for fetal ventricular arrhythmias treatment because there were a small number of clinical studies directly comparing these agents. One study reported that nifekalant was not inferior to amiodarone for the treatment of out-of-hospital cardiac arrest due to shock-resistant ventricular fibrillation [17]. Since most VTs are life threatening, one cannot afford to spare time to obtain appropriate informed consent or to randomly choose antiarrhythmic drugs. A cluster randomization method may be a practical and promising solution to meet this need.

According to our registry, three antiarrhythmic agents were used. These are amiodarone, lidocaine, and nifekalant. Lidocaine was conventionally used as first-line therapy, but several observational studies and a meta-analysis showed that lidocaine administration resulted in poor prognosis or no benefit in patients with acute myocardial infarction, therefore its routine use is not generally recommended by the current guidelines [18–20]. In contrast, another study demonstrated that prophylactic administration of lidocaine was associated with a decreased number of recurrent ventricular arrhythmias in post resuscitation periods [21]. There is insufficient data evaluating the prophylactic uses of other antiarrhythmic drugs, and 2015 AHA guidelines stated that there was insufficient evidence on the routine administration of antiarrhythmic drugs after resuscitation; however, lidocaine might be considered [1,2].

When compared with lidocaine, both amiodarone and nifekalant were proved similarly effective for ventricular arrhythmias suppression. These drugs, however, have characteristic adverse effects, such as negative inotropic and chronotropic outcomes (amiodarone), and QT prolongation resulting in torsade de pointes (nifekalant). One should be aware of frequent QT-interval prolongation after nifekalant administration. Nevertheless, the QT interval measurement is often difficult because of abnormal ST- or T-wave morphology due to ischemia or electrolyte disturbances after cardiopulmonary resuscitation. However, this agent has several advantages over amiodarone, such as an early onset and offset of an antiarrhythmic effect, and a minimal effect on hemodynamics and cardiac contractility. Sotalol has a similar effect but causes beta-adrenergic blockade, which is contraindicated in bradycardic patients. Although several studies on nifekalant have been reported thus far, in most of them, including our study, a comparison among antiarrhythmic drugs was difficult because of an insufficient numbers of patients and heterogeneous study designs [22].

Most of the previous studies consistently showed that antiarrhythmic administration had little or no benefit on the in-hospital mortality, and AHA guideline stated that no drug has yet been shown to increase the survival or neurological outcome after a cardiac arrest that is due to ventricular arrhythmias [2]. As with the previous studies, no significant differences in mortality were observed among the three antiarrhythmic drugs used in our study. These findings suggest that the choice of

Table 1
Baseline demographic and clinical characteristics of the study population by administered antiarrhythmic agent ($N=67$).

	Amiodarone	Lidocaine	Nifekalant	*p* Value
Number	21	22	24	
Age	67.3 (13.5)	65.7 (11.0)	68.5 (12.9)	0.754
Sex (female) (%)	6 (28.6)	7 (31.8)	3 (12.5)	0.256
Body weight (kg)	51.3 (10.7)	62.2 (13.7)	61.2 (12.3)	0.082
NYHA	2.0 [1.0, 4.0]	3.0 [1.0, 4.0]	2.0 [1.3, 4.0]	0.943
Left ventricular ejection fraction (%)	40.0 (12.4)	39.3 (10.6)	36.8 (15.9)	0.735
Underlying heart disease (%)				
ACS	11 (52.4)	7 (31.8)	8 (33.3)	0.458
IHD other than ACS	4 (19.0)	10 (45.5)	6 (25.0)	
Valvular disease	0 (0.0)	1 (4.5)	1 (4.2)	
Cardiomyopathy	4 (19.0)	2 (9.1)	6 (25.0)	
Idiopathic/LQT/Brugada syndrome	1 (4.8)	2 (9.1)	3 (12.5)	
Myocarditis	1 (4.8)	0 (0.0)	0 (0.0)	
Cardiopulmonary arrest (%)	1 (4.8)	10 (45.5)	4 (16.7)	0.004
IABP/ECMO use (%)	9 (42.9)	5 (27.8)	7 (30.4)	0.555
Revascularization (%)	11 (52.4)	11 (50.0)	8 (33.3)	0.367
B-type natriuretic peptide (pg/ml)	128 (143)	384 (281)	775 (489)	0.125
Systolic blood pressure (mmHg)	112 (16.9)	95 (8.5)	105 (25.2)	0.269
Serum creatinine (mg/dl)	1.66 (0.98)	1.23 (0.38)	1.93 (2.05)	0.438
Corrected QT interval (ms)	483 (55.1)	504 (58.6)	476 (46.3)	0.561
Heart rate before administration (beats per min)	77.7 (9.6)	77.6 (18.9)	94.3 (17.7)	0.076
Use of an inotropic agent (%)	12 (57.1)	6 (27.3)	14 (60.9)	0.050
Beta blocker use (%)	5(23.8)	4(18.2)	10(41.7)	0.180
Prior cardiac surgery (%)	2 (9.5)	1 (4.5)	2 (8.3)	0.808
Single-shot use of antiarrhythmic (%)				
Amiodarone	4 (19.0)	0 (0.0)	0 (0.0)	< 0.001
Lidocaine	3 (14.3)	8 (36.4)	8 (33.3)	
Nifekalant	4 (19.0)	0 (0.0)	12 (50.0)	
Oral antiarrhythmic (%)	1(4.8)	1 (4.5)	3 (12.5)	0.503
Electrical cardioversion (%)	19 (90.5)	17 (77.3)	15 (62.5)	0.089
Type of ventricular arrhythmia (%)				
Monomorphic VT	8 (38.1)	12 (54.5)	16 (66.7)	0.050
Polymorphic VT/VF	9 (42.9)	10 (45.5)	8 (33.3)	
Unknown	4 (19.0)	0 (0.0)	0 (0.0)	

Data are expressed as mean (standard deviation, SD), median [interquartile, IQR] and number (%).
NYHA, New York Heart Association functional classification; ACS, acute coronary syndrome; IHD, ischemic heart disease; LQT, long QT syndrome; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; VT, ventricular tachycardia; VF, ventricular fibrillation.

antiarrhythmic agents has little impact on the survival of the ventricular arrhythmias patients. However, we consider that these drugs exhibit short-term effects when used for the stabilization of patients` status in clinical practice. It is hoped that long-term benefit will be evaluated in a well-designed clinical trial.

There are still several questions to be answered: if the first drug fails to prevent ventricular arrhythmia, which antiarrhythmic drug should be used next; in which patients should antiarrhythmic agents be used as initial therapy; and can antiarrhythmic drugs improve outcomes. To answer these important questions, it is desirable that additional studies be performed with these agents in emergent or intensive care settings.

Table 2
Clinical outcomes by administered antiarrhythmic agents.

	Amiodarone	Lidocaine	Nifekalant	P value
Number	21	22	24	
Drug switching (%)	3 (14.3)	15 (68.2)	6 (25.0)	< 0.001
Defibrillation after 1-h administration (%)	2 (9.5)	3 (13.6)	6 (25.0)	0.421
Survival at discharge (%)	15 (71.4)	14 (63.6)	18 (75.0)	0.694
Ablation targeted for VT (%)	1 (4.8)	2 (9.1)	3 (12.5)	0.634
Taking oral antiarrhythmic agents at discharge (%)	10 (47.6)	10 (45.5)	11 (47.8)	0.985
Duration of intravenous administration (hour)	56.1 (40.7)	105.4 (123.4)	83.6 (115.5)	0.503
Cumulative dose (g)	1.52 (1.05)	8.38 (11.7)	1.23 (1.77) [a]	
Defibrillator implantation (%)	6 (28.6)	3 (13.6)	8 (34.8)	0.252

Data are expressed as mean (standard deviation, SD) or number (percentage).
[a] The standard dosage varies among agents and no statistical analysis was conducted.

Table 3
Outcomes by individual antiarrhythmic agents in adjusted analyses.

	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Primary outcome (Drug switching)				
Amiodarone	Reference			
Lidocaine	12.9 (2.82–58.6)	< 0.001	37.6 (5.1–279)	< 0.001
Nifekalant	2.0 (0.43–9.26)	0.38	4.1 (0.72–23.2)	0.11
Secondary outcome (Survival at discharge)				
Amiodarone	Reference			
Lidocaine	1.43 (0.40–5.16)	0.59	1.67 (0.40–6.95)	0.48
Nifekalant	0.83 (0.22–3.13)	0.79	1.11 (0.15–4.85)	0.89

Models were adjusted for age, sex, defibrillation therapy, cardiopulmonary arrest, use of inotropic agents, and ischemic or nonischemic heart disease. *C*-statistics for amiodarone, lidocaine, and nifekalant were 0.764, 0.810, and 0.777, respectively.
OR, odds ratio; CI, confidence interval.

Table 4
Comparison between amiodarone and nifekalant therapies adjusted by inverse propensity score weighting method.

	Crude OR (95% CI)	*p* Value	Adjusted OR (95% CI)	*p* Value
Primary outcome (Drug switching)				
Amiodarone	0.472 (0.102–2.19)	0.338	0.245 (0.045–1.318)	0.109
Nifekalant	Reference			
Secondary outcome (Survival at discharge)				
Amiodarone	1.440(0.366–5.67)	0.602	1.107(0.236–5.20)	0.898
Nifekalant	Reference			

OR, odds ratio; CI, confidence interval.

This study has several limitations. First, it was a non-randomized study with a small sample size; thus, there is the possibility of several biases in patient selection. In the lidocaine

group, the prevalence of cardiopulmonary arrest was relatively high. However, we adjusted for this effect on outcome in our univariate logistic regression model, and the results were similar to those adjusted by propensity scores. Another issue was an overfitting in estimating the propensity score in our logistic regression model. This was due to a small number of events. In this direction, some previous reports addressed this issue by using propensity scores as a method of data reduction. Therefore, we handled this problem in the same fashion [23,24]. In addition, there is no established method to estimate propensity scores and to compare effects between more than two treatment arms. We used multinomial logistic regression analysis to generate these scores and used them in logistic regression as covariates with treatment categories [25]. The tests of goodness of fit in this model showed that this hypothesis was acceptable in this study; however, residual differences may be explained by confounding effects of variables, such as physician's preference that could not be measured.

5. Conclusions

In our observational study, continuous infusions of both amiodarone and nifekalant were similarly superior to lidocaine for suppression of recurrent ventricular arrhythmias.

Disclosures

M Suzuki received lecture fees from Otsuka Pharmaceutical, Bayer Yakuhin, Medtronic Japan, Biotronik Japan, and Fukuda Denshi. W Nagahori received lecture fees from Medtronic Japan, Bayer Yakuhin, Boehringer Ingelheim, and Takeda Pharmaceutical. The remaining authors have no conflict of interest related to this study.

Acknowledgments

We are deeply grateful to the following collaborators of this study (in alphabetical order): Hirotaka Yoshiwara (Department of Cardiology, Chiba-Nishi General Hospital), Hisatoshi Sato (Department of Cardiology, Asahi Hospital), Kenji Yodokawa (Department of Cardiology, Nippon Medical School Chiba Hokusoh Hospital), Masayuki Inagaki (Department of Cardiology, Funabashi Municipal Medical Center), Satoru Kobayashi (Department of Cardiology, Saiseikai Narashino Hospital), Takayasu Ishikawa (Department of Cardiology, Chiba Cardiovascular Center), Yoshiaki Sakai (Department of Cardiology, Chiba Emergency Medical Center), and Yuji Matsudo (Department of Cardiology, Kimitsu Chuo Hospital).

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