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Clinical paper

Amiodarone or nifekalant upon hospital arrival for refractory ventricular fibrillation after out-of-hospital cardiac arrest☆

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ABSTRACT

Background: We evaluated the association between nifekalant or amiodarone and hospital admission and in-hospital mortality for cardiac arrest patients with persistent ventricular fibrillation on hospital arrival.
Methods: This was a retrospective cohort study using the Japanese Diagnosis Procedure Combination inpatient database. We identified 2961 patients who suffered cardiogenic out-of-hospital cardiac arrest and who had ventricular fibrillation on hospital arrival between July 2007 and March 2013. Patients were categorized into amiodarone ($n = 2353$) and nifekalant ($n = 608$) groups, from which 525 propensity score-matched pairs were generated.
Results: We found a significant difference in the admission rate between the nifekalant and amiodarone groups in propensity score-matched groups (75.6% vs. 69.3%, respectively; difference, 6.3%; 95% confidence interval (CI), 0.9–11.7). An analysis using the hospital nifekalant/amiodarone rate as an instrumental variable found that receiving nifekalant was associated with an improved admission rate (22.2%, 95% CI, 11.9–32.4). We found no significant difference in in-hospital mortality between the nifekalant and amiodarone groups (81.5% vs. 82.1%, respectively; difference, −0.6%; 95% CI, −5.2 to 4.1). Instrumental variable analysis showed that receiving nifekalant was not associated with reduced in-hospital mortality (6.2%, 95% CI, −2.4 to 14.8).
Conclusions: This nationwide study suggested no significant in-hospital mortality association between nifekalant and amiodarone for cardiogenic out-of-hospital cardiac arrest patients with ventricular fibrillation/persistent ventricular tachycardia on hospital arrival. Although nifekalant may potentially improve hospital admission rates compared with amiodarone for these patients, further studies are required to confirm our results.

Introduction

Out-of-hospital cardiac arrest (OHCA) affects approximately 300,000 people in the United States, 280,000 people in Europe, and 100,000 people in Japan annually.[1–4] Among all presentations of cardiac arrest, ventricular fibrillation (VF) and pulseless ventricular tachycardia (pVT) are considered the most treatment-responsive, and have the highest rates of survival.[5] The International Liaison Committee on Resuscitation (ILCOR) guidelines 2015 suggest that immediate defibrillation with cardiopulmonary resuscitation is the essential treatment of choice for VF/pVT among OHCA patients, and that antiarrhythmic drugs can be used during cardiac arrest for refractory ventricular dysrhythmias.[6,7] The guidelines suggest the use of amiodarone in adult patients with refractory VF/pVT to improve return of spontaneous circulation (ROSC) rates.[6,7] The guidelines also suggest the use of nifekalant as an alternative to amiodarone in adult patients with refractory VF/pVT.[7] However, no robust data have shown that amiodarone is superior to nifekalant to date.[8,9]

Nifekalant and amiodarone are both classified as class III antiarrhythmic agents in the Vaughan Williams classification. Nifekalant was developed and approved for use in Japan in 1999. Several animal model studies suggested that nifekalant has potential advantages over amiodarone for treating OHCA with

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VF/pVT—namely that it has no negative inotropic effects,[10,11] lowers the defibrillation threshold,[12–14] and has a short half-life.[9] However, only two small-sized single-centre non-randomized studies ($n = 30$ and $n = 25$) have attempted to evaluate the effectiveness of nifekalant in comparison with amiodarone for OHCA with refractory VF/pVT.[15,16] A recent large randomized double-blind trial compared amiodarone, lidocaine, and saline placebo in the prehospital setting but did not evaluate the effectiveness of nifekalant compared with amiodarone.[17] Therefore, very limited clinical data suggest the effectiveness of nifekalant for OHCA.[6,7]

We hypothesized that nifekalant is superior to amiodarone with regard to hospital admission and survival rate for OHCA with VF/pVT. The purpose of the present study was to evaluate our hypothesis using a large nationwide in-hospital database in Japan, the only country in which both amiodarone and nifekalant are used clinically.

Methods

This study was approved by the Institutional Review Board of The University of Tokyo. Requirement for informed patient consent was waived because of the anonymous nature of the data.

Emergency Medical System in Japan

An Emergency Medical System (EMS) team in Japan consists of three EMS personnel, usually including at least one emergency lifesaving technician trained to provide advanced life support (advanced airway management, intravenous line placement, and defibrillation).[18] The EMS resuscitation procedures follow the Japanese guidelines for cardiopulmonary resuscitation, based on current ILCOR guidelines.[19–21] EMS providers are not permitted to terminate resuscitation in the field in Japan, unless obvious signs of death (e.g., rigor mortis, lividity) are present.[18] Therefore, all patients are transported to the nearest hospital by the EMS providers regardless of the initial cardiac rhythm, cause of cardiac arrest, or the existence of bystander witnesses. The EMS team provides defibrillation for OHCA with VF/pVT via an automated external defibrillator (AED), as soon as possible. AED use by citizens was approved in Japan in July 2004. Trained EMS providers were permitted to perform endotracheal intubation in 2004, and to administer adrenaline with remote instruction from a doctor in April 2006. There were no specific changes to the law regarding pre-hospital OHCA resuscitation after 2007 in Japan (i.e., during the study period).[19,20]

However, the EMS team was not allowed to provide antiarrhythmic drugs in prehospital settings. The Japanese Ministry of Health, Labour and Welfare approved the use of intravenous amiodarone in June 2007. Bolus administration of both amiodarone (300 mg) and nifekalant (0.3 mg/kg) is permitted for use in patients with refractory ventricular fibrillation in Japan. The first Japanese guidelines were released throughout the country by the Japan Resuscitation Council in 2010,[21] which recommended the use of amiodalone more than nikekalant, echoing the ILCOR guidelines.

Data source and variables

We retrospectively evaluated a nationwide in-hospital patient administrative database, the Japanese Diagnosis Procedure Combination (DPC) database.[22–24] The DPC database includes administrative claims and discharge abstract data for all patients discharged (including OHCA patients die at emergency room) from more than 1000 participating hospitals, covering all 82 academic hospitals and more than 90% of all tertiary-care emergency hospitals in Japan.[22–24] The database includes the following information for each patient recorded using a uniform data submission form: age; sex; medical procedures; daily records of all drugs administered and devices used; length of stay; and discharge status. We could not follow up with patients after discharge from hospital because the information was not available in the database. The primary diagnosis, comorbidities at admission, and post-admission complications classified according to International Classification of Diseases 10th Revision (ICD-10) codes are determined by the physicians in charge. Although the database does not include prehospital information, complications that occur after admission are clearly differentiated from comorbidities already present on admission (day 0). The data collection period for the database was July–December in 2007–2010, and throughout the year from 2011 onward. In accordance with the ILCOR consensus statement,[25,26] we presumed that cardiac arrest had a cardiac aetiology unless there was an obvious non-cardiac aetiology (cerebrovascular disease, respiratory disease, severe trauma, drowning, asphyxiation, or drug overdose).[23] We designated hospital volume as the number of eligible patients treated for the present study, with categorization into tertiles (low, medium, and high). Hospital type was categorized as academic or non-academic.

Patient selection and endpoint

Adult cardiogenic OHCA patients with VF/pVT on hospital arrival were identified in the DPC database from July 2007 to March 2013. We did not include in-hospital cardiac arrest cases for the present study. The inclusion criteria were as follows: (1) age ≥18 years; (2) diagnosis of OHCA (ICD-10 codes at primary diagnosis and comorbidities on admission, I46.0 [cardiac arrest with successful resuscitation], I46.1 [sudden cardiac death] and I46.9 [cardiac arrest, unspecified]); (3) VF/pVT (requiring provision of defibrillation even after hospital arrival); and (4) intravenous administration of either amiodarone or nifekalant on admission. The exclusion criteria were as follows: (1) patients with non-cardiogenic cardiopulmonary arrest (i.e., J60 to J61.9 [subarachnoid and cerebral hemorrhage], I71.0 to I71.9 [aorta dissection and aneurysm], I26.0 to I26.9 [pulmonary embolism], J45.9 and J46 [severe asthma], S00 to T98 [trauma, burns, hanging, accidental hypothermia, drowning, electrocution, anaphylaxis, drug overdose], J69 and T71 [asphyxiation], or K25.0, K25.2, K26.0, K26.2, K27.0, K27.2, K28.0, K28.2, K92.0 to 92.2, I85.0 to I85.9 [acute gastrointestinal bleeding or oesophageal/gastric varices]); (2) patients with C00 to C97 (malignancy); (3) patients with R54 (caducity); (4) patients who received open-chest cardiac massage on admission; (5) patients administered both amiodarone and nifekalant on admission; and (6) patients whose outcome data were missing. Thus, we evaluated patients administered either amiodarone or nifekalant among the eligible patients.

The endpoints used in this study were hospital admission rate (patients who achieved ROSC and were admitted to hospital) and all-cause in-hospital mortality.

Statistical analysis

We used propensity score and instrumental variables analyses to address the issue of measured and unmeasured confounding factors.[27,28] All statistical analyses were performed using IBM SPSS version 22 (IBM Corp., Armonk, NY) and Stata/SE 13.0 (StataCorp, College Station, TX), and $p < 0.05$ was considered statistically significant.

We performed one-to-one matched analyses using nearest-neighbor matching based on patients' estimated propensity scores.[28] We estimated the propensity scores by fitting a logistic regression model for amiodarone/nifekalant administration as a function of the background patient characteristics and

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