The Influence of Age and Epinephrine Administration Timing on Favorable Neurological Outcomes among Witnessed Cardiogenic Cardiac Arrest

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Received: 22 March 2017; Accepted: 05 May 2017; Published: 12 May 2017

Abstract

Aim: The aim of this study is to evaluate the influence of patient’s age and the time-limited effect of epinephrine administration on neurological outcomes at one month in patients with witnessed cardiogenic cardiac arrest.

Materials and methods: A total of 31,518 witnessed cardiac cause with epinephrine (Epi) administration with presuming cardiac arrest patients (aged 15-89 years) between 2008 and 2012 were enrolled in this Japanese nationwide, prospective, population-based observational study. Patients excluded cases with missing, outlier and unknown data, achieved the return of spontaneous circulation (ROSC) within 2 minute after public access defibrillation or Emergency Medical Technician (EMT) defibrillation due to their confounding effects. Remaining 18441 patients who receive pre-hospital epinephrine administration were eligible for analysis. Patients were divided into the four age-layered groups as follows: the adult group (15 to 64 year, n = 4861), the young elderly group (65 to 74 year, n = 4390), the advance elderly group (75 to 84 year, n = 6318) and the very elderly group (85 to 89 year, n = 2872). The primary endpoint was Cerebral Performance Category (CPC) 1-2 at one month after the collapse, and the secondary outcome was ROSC. Multivariable logistic regression model and Adjusted Odds Ratios (AOR) are presented as 95% confidence intervals (CIs) between the age groups and epinephrine administration time (5-18min, 19-23min, 24-29min, 30-62min).

Results: The characteristics of the adult group had a higher proportion of male (84%), Public Access Defibrillations (4.3%), EMT defibrillation (56.1%) and Ventricular Fibrillation/Ventricular Tachycardia (VF/VT) rate (45.9%) than the older age elder groups. But, lower proportion of ROSC% (16.4%), Dispatcher assist CPR instruction rate (45.9%) among the groups. However, in the adult group had a higher CPC 1-2 rate at 1 month (6.7%), than that of the young elderly group (3.2%), the advance elderly group (1.0%) and the very elderly group (0.5%), respectively. After adjusted known confounding factor, AOR of CPC 1-2 was greatest in the adult group (5 to 18min; AOR 2.78, 95% CI 4.13-1.90), and CPC 1-2 was gradually decreased with increased time (19 to 23 min, AOR 1.61, 95% CI 2.43-1.08).

Conclusion: This study indicated that patient’s age strongly influences factor onto favorable Neurological Outcomes due to Epinephrine administration for witness OHCA.

Keywords: Age influence; Adverse Effect of Epinephrine; Time limited effect of Epinephrine; ROSC; Neurological Outcome; Elderly Resuscitation

Background

Increasing number of out-of-hospital cardiac arrest (OHCA) become a global health concern [1,2]. Several components contributed to improved OHCA outcomes, such as early recognition of cardiac arrest by laypersons, dispatcher-assisted cardiopulmonary resuscitation (CPR), public access AEDs and improved Emergency Medical Services (EMS). The effectiveness of Public Access Defibrillation (PAD) and ambulance crew defibrillation is well known to be time-dependent [3]. While advanced life support interventions are commonly believed to increase OHCA survival, the effectiveness of epinephrine administration is controversial.

The effectiveness of epinephrine has been discussed for over two decades [4-9], but a definitive conclusion has not been determined yet. Animal studies show that while epinephrine administration significantly increases return of spontaneous circulation (ROSC), it may also increase mortality [10,11]. To date, epinephrine is still recommended latest international resuscitation guidelines [12] both for pre-hospital and in-hospital resuscitation. However, there is no definitive evidence that it improves neurological outcomes in the pre-hospital settings [6,13]. Moreover, recent studies have shown that early administration of epinephrine improves ROSC even not survival to discharge [14-19].

Due to increasing the number of elderly in Japan, the average life expectancy in Japan is 80.8 years old in male, 87.1 years old in female in 2015 [20]. In this study, we investigated that the influence of patient’s age and effectiveness of time limited epinephrine administration.

Material and Methods

Study design

A nationwide, prospective, population-based observational study. The study design was approved by institutional review board of Kokushikan University.

Setting

Japan has 127.5 million population in 378,000 km² inhabitants’ area of in 2012.

EMS systems

The EMS systems of Japan reported elsewhere [15,16,21]. In brief, 770 fire departments operate EMS services in Japan, with 60683 Basic Emergency Medical Technicians (EMT-B) and 22,870 Emergency Life-Saving Technician (ELSTs) on board 5,004 ambulances in 2012 [21]. Each ambulance has three EMT crew, including at least one ELST and two EMT-B.

EMS call

A single EMS number “119” is used nation widely. All incoming call times and all dispatch time were electronically recorded by synchronized radio-controlled watches. EMS dispatch, which is operated by local fire departments, which also gives CPR instructions via phone with hands-only CPR before EMS arrival (T-CPR)[21].

EMT Field protocol

All EMT-B provide field basic life support (BLS) and ELST provide Advanced Life Support (ALS) [22] followed by Japan Resuscitation Council (JRC) Resuscitation Guidelines 2010. Specially trained
Advanced ELSTs called “endotracheal certified ELSTs” have been permitted to insert endotracheal tubes (ET) since July 2004 and to administer intravenous (IV) epinephrine since 2006 [21].

After the initial assessment and ECG rhythm by EMS provide are obtained, EMS defibrillation is applied as quickly as possible. Advanced airways, laryngeal mask airway (LMA), Combi-tube, King Airway (LT), esophageal gastric tube airway (EGTA) and Intra Tracheal Intubation (ITT), are applied if patients manifest difficulty with ventilation. Continuous bag valve mask (BVM) is selected when the initial ventilation is successful. If patients do not have ROSC after the initial EMS defibrillation, an ELST can choose to provide intravenous (IV) access and administer Epinephrine for patients aged over 8 years old with pulseless electrical activity, witnessed asystole, and/or refractory VF/VT rhythms after defibrillation. Prefilled syringes are used for a single administration of Epinephrine (1 mg of Epinephrine to 1 mL of distilled water; 0.1% adrenaline injection; Terumo, Tokyo, Japan), and Epinephrine given every 2 min until ROSC achieved and/or hospital arrival [21].

Medical control system

The medical control (MC) system is composed of fire agencies, local medical associations, the local government, and emergency hospital. Nationwide field BLS and ALS protocols published by the Ministry of Health and Labor were adopted by regional MC councils [21]. Online direct verbal permission from an MC physician is required when ELSTs use LMA, EGTA, LT, Combi-tube and ITT, IV access, and Epi administration. ELSTs are not allowed to administer Epi without a physician’s direct order.

Data collection and measured variables

Nationwide Japan Utstein data collected by the Ministry of Internal Affairs and Communications and Fire and Disaster Management Agency (FDMA). Each cardiac arrest’s data was recorded by an ELST based on EMS run sheets through electronic data capture system prospectively in local fire departments. Data collection and verification are done by data quality managers in fire departments. The data collection method has been reported on the Utstein guidelines for OHCA since 2005 [15-17]. This data cannot be concatenated anonymously and it has been socially approved that it will be used for the purpose of scientific analysis and improvement of prehospital care.

All variables including gender, age, type of bystander (family member, colleague, and others), witness status, initial ECG rhythm (VF/VT, PEA, asystole, and others), elapsed time intervals during resuscitation, type of bystander-initiated CPR, type of advanced airway management (BVM, LM, LT, EGTA, and ITT), intravenous fluids, and Epi administration, as well as pre-hospital ROSC, one-month survival, and neurological status at one month after the event (using the Glasgow- Pittsburg CPC 1 to 5 grading scale) [16]. This Utstein data was approved and permitted for this study from the FDMA.

Study population

Data from 925,288 patients with OHCA registered between January 2006 and December 2012 in Japan’s nationwide database. From this database, 31,518 patients aged 15 to 89 years with witnessed OHCA with cardiac or presumed cardiac origin were eligible for this analysis. We excluded 13,006 cases with a missing initial rhythm, unknown Bystander CPR (BCPR), unknown CPC, unknown airway management device, outlying response time data (more than the ninety-ninth percentile), and ROSC before EMS arrival, unknown drug administration, and drug administration post-ROSC. Also, cases with ROSC achieved within 2 min after PAD by a layperson or EMS defibrillation were excluded, because these patients would not have required resuscitation with Epi (Figure 1). We also excluded two patients with a less than 5 min duration between 119-call and Epi administration, which were likely erroneous entries.

Exposure variables

Since our primary interest was to analyze the time-dependent effects of Epi, our analysis was made four group equally partitioned into quarter the total number of patients of the 18,411 EPI administered as follows (Table 1). The early Epi administration group (5 to 18 min), the intermediate Epi group (19 to 23 min), the late Epi group (24 to 29 min), and the very late Epi group (30 to 62 min), respectively (Figure 2).

Also, Patients were divided into the 4 aged layered groups as follows: the adult group (15 to 64 years, n=4861), the young elderly group (65 to 74 years, n=4390), the advance elderly group (75 to 84 years, n=6318) and the very elderly group (85 to 89 years, n=2872) to verify age influence to effect of Epi administration.

Outcome measurement

The primary outcome was CPC 1-2 at one month after collapse, and the secondary outcome was field return of spontaneous circulation (ROSC) among the groups.

Statistical analysis

Analysis of variance and multiple logistic regression analyses were used to analysis among the groups.

Firstly, we simply compared the characteristics of patients’ background among the age groups, such as age, gender, type of bystander CPR, nature of bystander, T-CPR, PAD by lay person, defibrillation by EMT, initial ECG rhythm, response time, scene to hospital time, and 119 call to epinephrine administration, ROSC, good CPC 1-2 at one month at time of discharge and CPC 3-4.

Secondly, since our primary interest was to analyze the influence of age difference and time-dependent effects on neurological outcomes at one month, Descriptive statistics were used to describe the study population among the four layer of age groups, which was Epi administered (15-54 years, 65-74 years, 75-84 years, and 85-89 years).

Additionally, AOR and 95% CI between the Epi administration groups for outcomes among the age groups were calculated adjusting for confounders such as the year (2006-2009/2010-2012), age, gender (female/male), nature of BCPR (with BCPR/without BCPR), BCPR (compression only CPR/conventional CPR), use of T-CPR, type of airway device selected (SGA, ET/BVM), initial ECG rhythm, PAD (yes/no), EMT defibrillation (yes/no), response time, scene-to-hospital time, and EPI administration time.

Multiple logistic regression analysis was used for ROSC and CPC1/2 between age and 119 to epinephrine administered time. Each EPI groups were compared to the influence on the outcomes with the late EPI group among the following groups; early (5 to 18 min), intermediate (19 to 23 min), late (24 to 29 min), and very late (30 to 62 min). All statistical analyses were performed using the JMP statistical package (version 11.2.1; SAS Institute Inc., Cary, NC).

Ethical Issue

The Author had full access and take full responsibility for the integrity of the data. All authors have read and agree to manuscript as written.

Results

Clinical characteristics of eligible patients among four age groups

Clinical characteristics of four layer of age groups were shown on Table 1. In the adult groups (15 to 64year) tend to higher proportional of PAD (4.2%), defibrillation by EMT (45.9%) and VF/VT (45.9%) in the initial ECG rhythm rather than the young elderly group (age: 65 to 74 years, n=4218), the advance elderly group (age: 75 to 84 years,
Figure 1: Definition of study cohort and excluded criteria.

Table 1: Clinical Characteristics of Eligible Patients with and Without Epinephrine Administration.
n=6099) and the very elderly group (age: 85 to 89 year, n=2756).
However, proportional of ROSC (16.4%), T-CPR instruction (46.4%), compression only CPR (37.1 %) were equivalent among groups. Other variables were almost identical among groups.

CPC 1-2 rate at one month after collapse were 6.3% in the adult group, 3.0% in the young elderly group, 0.93% in the advance elderly group and 0.56% in the very elderly group, respectively. In accordance with increased age, the results of CPC1-2 become poor (Table 1).

Comparison of adjusted confounding variables among the age groups

Table 2 is shown the adjusted known cofounding variable among the groups (Table 2). The greater odds ratios were seen in the adult age groups on the variables of epinephrine administered year, gender, nature of bystander, type of bystander CPR, T-CPR given, PAD by lay person, defibrillation by EMT, initial ECG rhythm, response time, scene to hospital time.

After adjusting for knowing confounders, the odds ratio of CPC1-2 significant decrease while every minute epi administration time delay in all age groups.

Interaction with good neurological outcome and time interval of 119 call to Epi administration among the age group

Figure 3 shows the multiple logistic regression analyses on CPC1/2 at 1 month and 119 to epinephrine administered time which categorized into 5 to 18 min., 19 to 23 min., 24 to 29 min. and 27 to 62 min among the groups (Figure 3). Total 4902 (27.6%) patients received epinephrine 5 to 18min after 119call, 4719(26.6%) in 19-23min, 4172(23.5%) in 24-29min and 3952(22.3%) in 30-62min.

After adjusting those of all of known confounding factor (epinephrine administered year, gender, nature of bystander, type of bystander CPR, T-CPR given, PAD by lay person, defibrillation by EMT, initial ECG rhythm, response time, scene to hospital time), The greater odds ratios of CPC 1/2 were seen in the early epinephrine administration (5 to 18min; AOR 2.8, 95% CI 1.9-3.9). But this tend to gradually decreased with increased time (middle epinephrine administration; 19 to 23 min, AOR

1.6, 95% CI 2.4-1.1) compared with late epinephrine administration (24 to 29 min as a reference) in all age groups. In accordance with time interval of 119 call to epinephrine administration becomes longer, the odds ratio of CPC1/2 become low value (Figure 3).

**Discussion**

Major findings of this study are epinephrine administration improves when given early stage (5 to 18 min) onto CPC 1-2 compared than late administration (24 to 29 min) among the all age group. Also, we found the strong correlation with age group and time interaction of epinephrine administration on neurological outcome among the group.

The reason why we could confirm this efficacy of epinephrine administration is that we have removed many known confounding factors as much as we can. Particularly, patients who achieved ROSC within 2 min after receiving PAD and/or EMT defibrillation were excluded because they would not have been eligible to receive epinephrine [3]. These patients are usually included in the previous studies on epinephrine efficacy, and would likely confound the results due to the strong association of early ROSC with survival.

Because elderly population (over 65 years) grow up to 25-30% exceeded in Japan, a different reaction of epinephrine administration after cardiac arrest in the elderly, the difference, we found in ROSC rate, CPC1-2 due to time from cardiac arrest, as well as the treatment, was almost the same.

Our study clearly indicates that age is strongly confounding factor onto favorable neurological outcomes due to epinephrine administration for witness OHCA. Our results helped to resolve the question of the clinical efficacy of epinephrine, which has been discussed for several decades [4-9].

Our speculation of low success rate on shockable rhythm because usual oxygen demand of the heart muscle is very low in the elderly. Therefore, by higher age and long over a period of from cardiac arrest, the oxygen content of the heart muscle is reduced.

Therefore, those biological ages categorized four group shows the different reaction to administered epinephrine to neurological outcome. A significant neurological benefit was seen in the adult group which CPC 1-2 rate at 1 month were 6.7% in the adult group, 3.2% in the young elderly group, 1.0% in the advance elderly group and 0.5% in the very elderly group, after adjusted known confounding factor, AOR of CPC 1-2 was greatest in the adult group administration (AOR 2.78, 95% CI 4.13-1.90), and gradually decreased with increased time (AOR 1.61, 95% CI 2.43-1.08) compared with late Epi administration.

This trend was identical in all age groups but elderly group gradually epinephrine has become ineffective. It is a good exploration with elderly may weak with hypoxia as compared to the myocardium younger generation. Or it might have did not reach sufficient chest compression depth deteriorate with a rib cage fracture due to the chest compressions of for the elderly.

Recently, several other studies have analyzed the time limits to effects of epinephrine in pre-hospital settings. Hayashi first mentioned time limits of epinephrine’s effect in 2012 [15] when he reported that with epinephrine administration within 10 minutes of an EMS call, patients with VF/VT had superior neurological outcomes after one month in Osaka prefecture. However, average response times in Japan were 8.3 minutes in 2012 and are gradually increasing year by year [19]. Thus, the goal of early epinephrine administration which Hayashi mentions is increasingly difficult to achieve.

Gordon et al reported that epinephrine administered very early stage improved 1 month survival discharge but not in good neurological outcome [19]. They found 119 call to epinephrine administer time is significant association with OHCA patients’ outcome.

In our study, the age subgroup analysis indicates that early Epi administration 5-18 minutes after 119 call had a greater odds ratio of ROSC, CPC1-2 (after one month) than that of middle (19-23min) and Late (24-30 min) Epi administrations among the all age groups, respectively.

**Figure 3:** Interaction with good neurological outcome and time interval of 119 call to Epi administration among the age group.
Quick epinephrine administration within 18 minutes after emergency call is not easy, since average response times are becoming longer in Japan. Based on the results of this study, if local EMS OHCA protocols mandate the use of epinephrine, it should be ideally delivered within 18 minutes of an EMS call [23]. The results, herein study, a total 4902 (27.6%) patients received epinephrine 5 to18min and 4719 (26.6%) patients received epinephrine 19-23min after 119 call [7]. Probably it is possible to give early epinephrine administration in prehospital field in Japan. More importantly, prior to EMS arrival, it is important to maintain the quality of basic life support, promote early, continuous, high quality chest compressions, early defibrillation, and ensure good post resuscitation care in order to provide the best chance of neurologically intact survival. This study does not address the question of the relative efficacy of early CPR, early defibrillation compared to early epinephrine administration. We believe our results should not distract EMS systems from the importance of proven fundamentals like high quality CPR and early defibrillation.

Limitations
This study includes several limitations. The major limitation of this study was non-randomized controlled study. Also, we cannot exclude the possibility for another uncontrolled confounding factor. The Japan Utstein database does not include information regarding treatment in the Emergency Department (ED) and Intensive Care Unit (ICU), which may impact survival outcomes. Also, the database does not record the actual quality of EMS-CPR and downloadable data from AEDs is also not available.

Another important limitation is selection bias by ELSTs may be occurring, with epinephrine administration being selected under the local epinephrine protocols. Local protocols determined by medical control committees, as these vary throughout Japan, rather than due to selection bias by ambulance crews. It was also not possible to evaluate or account for variation in skills amongst ELSTs between groups. However, despite these limitations, the large sample size of this study and strengths of a nationwide, population-based registry make a compelling argument for the validity of our conclusions.

Conclusions
Our study suggests early epinephrine administration within 5-18 min from 119 call improves favorable neurological outcomes in adult age group, young elderly group, and advanced elderly group. Our results suggest that EMS protocols should promote epinephrine in the early stages of OHCA. Further randomized controlled investigations of effectiveness of early epinephrine administration are warranted.

Acknowledgments
We express our extraordinary respect for all EMT and ELSTs in Japan to their efforts

Authors' Contribution
HT carried out the all the studies, statistical analysis, participated in the sequence alignment and drafted the manuscript. HT participated in the design of the study and performed the statistical analysis. RS and HT performed the statistical analysis and drawing figure and table. HU and TN conceived of the study, and participated in its design and coordination. MO advice and assistance in the planning of this paper and ST helped to revise the manuscript. All authors read and approved the final manuscript.

References