Delayed administration of epinephrine is associated with worse neurological outcomes in patients with out-of-hospital cardiac arrest and initial pulseless electrical activity: insight from the nationwide multicentre observational JAAM-OHCA (Japan Association for Acute Medicine) registry

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Aims
The delayed administration of epinephrine has been proven to worsen the neurological outcomes of patients with out-of-hospital cardiac arrest (OHCA) and shockable rhythm or asystole. We aimed to investigate whether the delayed administration of epinephrine might also worsen the neurological outcomes of patients with witnessed OHCA and initial pulseless electrical activity (PEA).

Methods and results
The JAAM-OHCA Registry is a multicentre registry including OHCA patients between 2014 and 2017. Patients with emergency medical services (EMS)-treated OHCA and initial PEA rhythm were included. The primary exposure was the time from the EMS call to the administration of epinephrine. The secondary exposure was the time to epinephrine dichotomized as early (<15 min) or delayed (>15 min). The primary outcome was the achievement of a favourable neurological outcome, defined as Cerebral Performance Categories Scale 1–2 at 30 days after OHCA. Out of 34,754 patients with OHCA, 3,050 patients were included in the present study. After adjusting for potential confounders, the delayed administration of epinephrine was associated with a lower likelihood of achieving a favourable neurological outcome [adjusted odds ratio (OR) 0.96; 95% confidence interval (CI) 0.93–0.99; P = 0.016]. The percentage of patients who achieved a favourable neurological outcome in the delayed epinephrine group was lower than that in the early epinephrine group (1.3% vs. 4.7%; adjusted OR 0.33; 95% CI 0.15–0.72; P = 0.005). A restricted cubic spline analysis demonstrated that delayed epinephrine administration could decrease the likelihood of achieving a favourable neurological outcome; this was significant within the first 10 min.
Conclusions

The delayed administration of epinephrine was associated with worse neurological outcomes in patients with witnessed OHCA patients with initial PEA.

Graphical Abstract

Keywords

Resuscitation • Out-of-hospital cardiac arrest • Epinephrine • Pulseless electrical activity

Introduction

According to the Heart Disease and Stroke Statistics 2020 Update from the American Heart Association, the weighted national estimate of emergency department visits with a principal diagnosis of cardiac arrest was 56.8 per 100,000 population or 183,629 people out of the total population of the USA. Although the outcomes of witnessed out-of-hospital cardiac arrest (OHCA) have improved with the revision of The International Liaison Committee on Resuscitation (ILCOR) guidelines, in the Cardiac Arrest Registry to Enhance Survival (CARES), in 2018, the rate of survival to hospital discharge was only 10.4% and the rate of survival with a good functional status was 8.2%. As for patients who initially presented a shockable rhythm, the number of survivors with a favourable neurological outcome increased as the use of public access defibrillators increased. However, there has been no significant improvement in the neurological outcomes of OHCA in patients who initially presented a non-shockable rhythm.

Pulseless electrical activity (PEA) has been increasing over the past decades with a corresponding decrease in the shockable rhythm. The analysis of the Swedish Registry of Cardiopulmonary Resuscitation demonstrated that the survival of patients with PEA increased from 1% to 5%, while the survival rate of patients in asystole increased modestly from 0.6% to 1.3%. These studies indicate that PEA and asystole should be considered separate entities, and it would be worthwhile investigating treatment strategies to improve not only survival but also the neurological outcomes of patients who initially present PEA.

Epinephrine has been reported to increase 30-day survival in comparison to placebo, and it is recommended as first-line drug for the resuscitation of patients with PEA. A subgroup analysis of a randomized trial of epinephrine administration during OHCA showed that the return of spontaneous circulation (ROSC) rate was three-fold higher in the epinephrine group in the subgroup of patients who initially presented a non-shockable rhythm, while there was no differences in the ROSC rate in the subgroup of patients who initially presented a shockable rhythm. These findings might indicate the usefulness of epinephrine in OHCA who initially presented a non-shockable rhythm.

Several observational studies have shown that the early administration of epinephrine is associated with better neurological outcomes in patients with OHCA; however, these studies included patients with both shockable and non-shockable rhythms. Hansen et al. showed that the delay in the administration of epinephrine was associated with reduced odds of achieving a favourable neurological outcome in patients who initially presented a non-shockable rhythm; however, the benefit of epinephrine was limited to patients with asystole. It has not been determined whether the early administration of epinephrine could improve the neurological outcomes in OHCA of non-traumatic origin with initial PEA.

The aim of the present study was to determine whether the time to the administration of epinephrine could affect the neurological outcomes in patients with witnessed OHCA patients with initial PEA.

Methods

JAAM-OHCA registry

The Japanese Association for Acute Medicine–Out-of-Hospital Cardiac Arrest (JAAM-OHCA) Registry is a prospective, multicentre registry of
patients with OHCA who are transported to critical care medical centres or hospitals with an emergency care department. Prehospital data were obtained from the All Japan Utstein Registry of the Fire and Disaster Management Agency as previously reported. In-hospital data were collected via an Internet-based system by physicians or medical staff at each institution. The JAAM-OHCA Registry committee integrated the prehospital and in-hospital data.

**Patient selection**
The present study employed this registry from 2014 to 2017. Patients with witnessed non-traumatic OHCA with initial PEA who received epinephrine were included in this analysis.

**Primary and secondary exposures**
A previous study showed an association between the prognosis of OHCA patients and the time from emergency medical services (EMS) agency arrival on the scene to the administration of epinephrine; however, the time from EMS call to EMS arrival on the scene might differ according to the distance between the nearest EMS station and the place patients collapsed. Considering this fact, the primary exposure in this study was the time (in minutes) from the EMS call to the first administration of epinephrine. A previously mentioned study dichotomized time from EMS arrival on the scene to the administration of epinephrine into the early (<10 min) and delayed (≥10 min) and showed that the delayed group had worse outcomes in comparison to the early group. Given that mean time from EMS call to EMS arrival on the scene was 4–5 min, we divided eligible patients into early (<29 min, median) and delayed (≥29 min) administration groups, and applied the same analysis as described above. Second, we evaluated the timing of epinephrine administration as a categorical variable, and applied the multivariable logistic regression analysis described above and a multiple imputation analysis.

The potential non-linear associations between the OR for a favourable neurological outcome and the timing of epinephrine administration were examined using restricted cubic splines adjusted for age, sex, and aetiology of OHCA. All tests were two-tailed, and P-values of <0.05 were considered to indicate statistical significance. Analyses were performed using the SAS statistical package (version 9.4, SAS Institute, Cary, NC, USA). The analysis code and the data derived in this research will be shared by the corresponding author upon reasonable request.

**Consent to participate/consent for publication**
To give patients or their family members the opportunity to refuse to be included in this registry, the special committee and each participating institution showed a document regarding opt-out consent on the website and/or the board of the emergency department, and the requirement for informed consent was waived.

**Results**

**Patient characteristics**
From January 2014 to December 2016, 34,754 consecutive patients with OHCA were screened and 4,168 patients with witnessed non-traumatic PEA were identified (Figure 1). Out of these, 393 patients without epinephrine administration, 11 patients whose records were shared by the corresponding author upon reasonable request. Consent to participate/consent for publication

**Statistical analysis**
Patient characteristics were compared using the Pearson’s χ² test for categorical variables, and Student’s t-test or the Wilcoxon rank sum test for continuous variables where applicable, and are presented as the mean ± standard deviation or median with interquartile range.

We conducted several statistical analyses to examine the relationship between the timing of the administration of epinephrine and the achievement of a favourable neurological outcomes. First, we evaluated the timing of the administration of epinephrine as a continuous variable by a multivariable logistic regression model that included the same baseline covariates as above. Estimates from 10 iterations were combined with the use of Rubin’s rule. Odds ratios were presented with 95% confidence intervals (CIs) and P-values. As a sensitivity analysis, we divided eligible patients into early (<29 min, median) and delayed (≥29 min) administration groups, and applied the same analysis as described above. Second, we evaluated the timing of epinephrine administration as a categorical variable, and applied the multivariable logistic regression analysis described above and a multiple imputation analysis.

The potential non-linear associations between the OR for a favourable neurological outcome and the timing of epinephrine administration were examined using restricted cubic splines adjusted for age, sex, and aetiology of OHCA. All tests were two-tailed, and P-values of <0.05 were considered to indicate statistical significance. Analyses were performed using the SAS statistical package (version 9.4, SAS Institute, Cary, NC, USA). The analysis code and the data derived in this research will be shared by the corresponding author upon reasonable request.

**Ethics approval**
This study protocol was organized to ensure compliance with the Declaration of Helsinki and the Guidelines for the Epidemiological Research published by the Japanese Ministry of Health, Labour and Welfare. The original study protocol was approved by the Institutional Review Board (IRB) at Kyoto University as the corresponding institution, as well as each participating hospital.

**Consent to participate/consent for publication**
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**Results**

**Patient characteristics**
From January 2014 to December 2016, 34,754 consecutive patients with OHCA were screened and 4,168 patients with witnessed non-traumatic PEA were identified (Figure 1). Out of these, 393 patients without epinephrine administration, 11 patients whose records were missing information about epinephrine administration, 104 patients who received epinephrine after an ROSC, and 610 patients with
missing information about the timing of epinephrine administration were excluded. The remaining 3050 patients were included in the present analysis.

The patient characteristics are shown in Table 1. The mean age was 73.7 years, 1836 (60.2%) patients were male. The time from the EMS call to CPR [8 (2–11) min vs. 4 (1–7) min; \( P < 0.001 \)], time from the EMS call to arrival on the scene [8 (7–10) min vs. 7 (6–8) min; \( P < 0.001 \), and the time from the EMS call to epinephrine administration [30 (23–37) min vs. 14 (13–15) min; \( P < 0.001 \)] were longer in the delayed group in comparison to the early group. The frequency of cardiac arrest due to cardiac causes was lower in the early group; however, the difference did not reach statistical significance (58.0% vs. 63.9%; \( P = 0.092 \)). The frequency of bystander CPR (36.1% vs. 50.7%; \( P < 0.001 \)) and the use of doctor car or doctor helicopter (10.9% vs. 25.4%; \( P < 0.001 \)) was lower in the delayed group.

**Clinical outcomes**

Each additional minute of time from witnessed OHCA to the administration of epinephrine was associated with a 5% decrease in the odds of a favourable neurological outcome in the univariate analysis (unadjusted OR 0.95; 95% CI 0.92–0.98; \( P = 0.002 \)), a 4% decrease in the multivariate analysis (adjusted OR 0.96; 95% CI 0.93–0.99; \( P = 0.016 \)), and a 4% decrease in the combination of multiple imputation and a multivariate analysis (adjusted OR 0.96; 95% CI 0.93–0.99; \( P = 0.010 \)) (Table 2). A shorter time from witness to the administration of epinephrine was associated with better 30-day survival in univariate analysis (unadjusted OR 0.96; 95% CI 0.95–0.98; \( P < 0.001 \)), multivariate analysis (adjusted OR 0.96; 95% CI 0.95–0.98; \( P < 0.001 \)), and multiple imputation analysis (adjusted OR 0.96; 95% CI 0.95–0.98; \( P < 0.001 \)) (Table 2). Missing patterns of patient characteristics were shown in Supplementary material online, Table S1.

When the time to epinephrine was analysed as a categorical variable, the delayed epinephrine group had worse neurological outcomes in comparison to the early group in the univariate analysis (1.3% vs. 4.7%; OR 0.28; 95% CI 0.14–0.56; \( P < 0.001 \)) (Figure 2), the multivariate analysis (adjusted OR 0.33; 95% CI 0.15–0.72; \( P = 0.005 \)), and the multiple imputation analysis (adjusted OR 0.58; 95% CI 0.40–0.85; \( P = 0.006 \)) (Table 2). It was still significantly associated with a worse neurological outcome (adjusted OR 0.28; 95% CI 0.13–0.61; \( P = 0.001 \)), even in the multivariable analysis, which included TTM, ECMO, and IABP (Supplementary material online, Table S2). When the time to epinephrine was dichotomized based on the median value (29 min), the delayed epinephrine group consistently had worse neurological outcomes in the univariate analysis (OR 0.41; 95% CI 0.22–0.77; \( P = 0.006 \)) and multivariate analysis (OR 0.46; 95% CI 0.24–0.88; \( P = 0.020 \)) (Supplementary material online, Table S3).

A non-linear relationship was observed between the odds of a favourable neurological outcome and the time to the administration of epinephrine, with the odds of a favourable neurological outcome rapidly decreasing within 10 min (Figure 3).

**Table 1** Patient characteristics

| Variables                      | \( \leq 15 \text{ min} (n = 213) \) | \( >15 \text{ min} (n = 2837) \) | P-value |
|--------------------------------|-----------------------------------|---------------------------------|---------|
| Demographics                   |                                   |                                 |         |
| Age, years                     | 75.0 ± 13.0                       | 73.6 ± 14.8                     | 0.14    |
| Male                           | 123 (57.8)                        | 1713 (60.4)                     | 0.45    |
| Cause of cardiac arrest        |                                   |                                 |         |
| Cardiac cause                  | 136 (63.9)                        | 1644 (58.0)                     | 0.092   |
| Non-cardiac cause              | 77 (36.2)                         | 1193 (42.1)                     | 0.092   |
| Cerebral vascular disease      | 9 (4.2)                           | 151 (5.3)                       | 0.49    |
| Lung disease                   | 9 (4.2)                           | 232 (8.2)                       | 0.039   |
| Malignancy                     | 6 (2.8)                           | 85 (3.0)                        | 0.88    |
| Other                          | 53 (24.9)                         | 725 (25.6)                      | 0.83    |
| Intervention                   |                                   |                                 |         |
| Bystander CPR                  | 108 (50.7)                        | 1025 (36.1)                     | <0.001  |
| Intubation                     | 211 (99.1)                        | 2808 (99.0)                     | 0.10    |
| Doctor car or doctor helicopter| 54 (25.4)                         | 308 (10.9)                      | <0.001  |
| Time course                    |                                   |                                 |         |
| Time from call to CPR, min     | 4 (1–7)                           | 8 (2–11)                        | <0.001  |
| Time from call to EMS arrival on the scene, min | 7 (6–8) | 8 (7–10) | <0.001 |
| Time from call to epinephrine, min | 14 (13–15) | 30 (23–37) | <0.001 |

Data are shown as n (%) or the means ± standard deviation otherwise specified.

CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; GCS, Glasgow coma scale; ROSC, return of spontaneous circulation; SMD, standardized mean difference.
Discussion

The major finding of the present study was that each minute of delay to the administration of epinephrine was associated with a 6% reduction in the likelihood of achieving favourable neurological outcome in patients with witnessed OHCA with initial PEA. This association remained significant even after adjustment for other important factors, including aetiology of OHCA (cardiac/non-cardiac), doctor car or helicopter transportation, presence of an eyewitness, intubation, time from EMS call to CPR, time from EMS call to the arrival of EMS on the scene, TTM, ECMO, and IABP. The restricted cubic spline analysis demonstrated that the odds of a favourable neurological outcome rapidly decreased within 10 min.

The use of epinephrine is recommended in the ILCOR International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations (CoSTR)\(^\text{17}\); however, its effectiveness for patients with OHCA has long been discussed. A randomized controlled trial showed that epinephrine use was associated with higher rates of short-term survival but not with survival to hospital discharge.\(^\text{9}\) Another randomized controlled trial demonstrated that the survival rate at hospital discharge of patients who received epinephrine showed no significant improvement.\(^\text{18}\) However, the statistical analyses of these trials were underpowered, which limited their ability to detect significant differences. A recent randomized controlled trial and two meta-analyses showed that—in comparison to placebo—the use of epinephrine improved the rate of survival to hospital discharge in OHCA patients.\(^\text{19,20}\) However, epinephrine did not improve the neurological outcomes and the time to epinephrine administration was not taken into account in these trials.

Table 2  The univariate, multivariate, and multiple imputation analyses when the time to epinephrine was analysed as a continuous variable

| Variable | Time to epinephrine as continuous | Time to epinephrine as categorical |
|----------|-----------------------------------|-----------------------------------|
|          | Adjusted OR (95% CI) | P-value | ≤15 min (n = 213) | >15 min (n = 2837) | P-value |
| Univariate analysis | | | | | |
| CPC 1–2 | 0.95 (0.92–0.98) | 0.002 | 1 (reference) | 0.28 (0.14–0.56) | <0.001 |
| Alive | 0.96 (0.95–0.98) | <0.001 | 1 (reference) | 0.56 (0.33–0.95) | 0.032 |
| Multivariate analysis | | | | | |
| CPC 1–2 | 0.96 (0.93–0.99) | 0.016 | 1 (reference) | 0.33 (0.15–0.72) | 0.005 |
| Alive | 0.96 (0.95–0.98) | <0.001 | 1 (reference) | 0.60 (0.35–1.05) | 0.073 |
| Multiple imputation | | | | | |
| CPC 1–2 | 0.96 (0.93–0.99) | 0.010 | 1 (reference) | 0.58 (0.40–0.85) | 0.006 |
| Alive | 0.96 (0.95–0.98) | <0.001 | 1 (reference) | 0.78 (0.59–1.03) | 0.083 |

CI, confidence interval; OR, odds ratio.

Figure 2  Favourable neurological outcome and 30-day survival Cerebral Performance Categories 1–2 at 30 days (A) and 30-day survival (B) in the early and delayed epinephrine groups. CI, confidence interval; OR, odds ratio; PS, propensity score.
Second, and had adverse effects on the cerebral microvascular blood flow, such as increasing the severity of cerebral ischaemia during CPR. The delayed administration of epinephrine prolonged CPR, which might result in the accumulation of a higher dose of epinephrine, possibly hindering cerebral microvascular blood flow. This may be one of the reasons why the delayed administration of epinephrine was harmful.

Our study showed that the delayed administration of epinephrine decreased the percentage of patients who achieved a favourable neurological outcome by 4%. However, given that the incidence of OHCA was 183,629 out of the total population of the USA or 127,018 out of the total population of Japan, and 20% of the OHCA patients were in PEA (approximately 70,000 people out of the total population of the USA), even small increases in the percentage of patients who achieve a favourable neurological outcome could have a significant clinical impact.

Study limitations
The present study was associated with several limitations. First, the quality of CPR was not assessed in this study. A retrospective study demonstrated that the adherence to the advanced cardiovascular life support protocol throughout an event was correlated with an increased rate of ROSC in the setting of cardiac arrest. Second, there may have been difficulties in obtaining vascular access in the delayed epinephrine administration group, which might have affected the results because repeated attempts could lead to the interruption of CPR. Third, comorbidities were not recorded in our database, which might have influenced the outcomes. However, we performed several analyses and obtained the same results. Despite these limitations, we analysed a large national database that included more than 30,000 OHCA patients, which supports the generalizability and conclusion drawn in the present study.

Conclusions
The delayed administration of epinephrine was associated with worse neurological outcomes in patients with witnessed non-traumatic OHCA with initial PEA.
Delay in epinephrine in OHCA with PEA

Supplementary material

Supplementary material is available at European Heart Journal: Acute Cardiovascular Care online.

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