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ORIGINAL RESEARCH

Comparison of epinephrine administration intervals in out-of-hospital cardiac arrest: a retrospective study

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Abstract

Epinephrine plays an important role in cardiopulmonary resuscitation (CPR) and is recommended to be administered at 1 mg every 3 to 5 minutes. However, there have been few studies comparing the outcomes between 3 and 4 minutes. In this study, we compared the prognosis between administration of epinephrine at intervals of 3 and 4 minutes in out-of-hospital cardiac arrest (OHCA). If there is no difference in prognosis between the two groups, we can suggest it is efficient to administer epinephrine at intervals of 4 minutes, which is two cycles of advanced cardiac life support (ACLS), considering the ACLS cycle is 2 minutes. We conducted a retrospective study on patients aged 18 years and above admitted for non-traumatic OHCA at Ulsan University Hospital's Emergency Department between May 2021 and October 2023. Patients were categorized based on epinephrine administration intervals of every 3 or 4 minutes during in-hospital CPR. Primary outcomes assessed were return of spontaneous circulation (ROSC) rate, survival until intensive care unit (ICU) admission, and cerebral performance categories (CPC) at hospital discharge. Additional analyses included total CPR time and epinephrine dose used. Propensity score matching was employed to mitigate baseline characteristic differences between the two groups. Results revealed no significant differences in ROSC rates, survival until ICU admission, or CPC scale scores at discharge between the 3- and 4-minute interval groups. The study suggests that extending the interval of epinephrine administration to 4 minutes does not compromise patient outcomes compared to the conventional 3-minute interval. This study underscores the potential for optimizing CPR protocols to improve patient care and resource utilization.

Keywords

Cardiopulmonary arrest; Resuscitation; Epinephrine; Cardiopulmonary resuscitation

1. Introduction

While patients die from various causes, all patients experience cardiopulmonary arrest (CPA) at the end of their life. In cases of cardiac arrest, medical personnel administer cardiopulmonary resuscitation (CPR) [1]. Performing CPR involves several components, including chest compressions, airway management, defibrillation, drugs, postcardiac arrest care and other treatments [2, 3]. Among these, epinephrine administration is important for CPR because it contracts the arteries and arterioles through the alpha-adrenergic receptor, which can be helpful in achieving return of spontaneous circulation (ROSC) [4, 5]. However, the frequent use of epinephrine can increase oxygen demand, which is harmful [5]. Currently, according to the latest American Heart Association CPR guideline algorithm, epinephrine is recommended to be administered at 1 mg every 3–5 minutes [1, 6].

In several CPR training programs, such as advanced cardiovascular life support (ACLS) and Korean advanced life support, instructors encourage the use of epinephrine every 4 minutes during CPR, which is the same as every two cycles of rhythm checks. Administering epinephrine every two cycles of rhythm check can simplify the process of CPR. Studies on the prognosis of patients who were administered epinephrine for less than 3 minutes, more than 5 minutes, or every 3–5 minutes are relatively common [7–10]. However, studies investigating the prognosis of patients who are administered epinephrine every 3 and 4 minutes have not yet been reported. Thus, we investigated whether the rate of ROSC in initial CPR and neurological outcome depended on the epinephrine interval. If the outcomes differ, it may be helpful to establish an accurate interval for epinephrine administration. If the outcomes do not differ, administering epinephrine every 4 minutes can be helpful for beginner medical personnel.

2. Materials and methods

2.1 Study design and setting

This retrospective, case-controlled study was performed in patients aged 18 years or older who were admitted to the Ulsan University Hospital's Emergency Department (ED) between May 2021 and October 2023 for non-traumatic out of hospital cardiac arrest (OHCA). Ulsan University hospital is the sole tertiary hospital in Ulsan city. Paramedics of public ambulances can perform CPR at the prehospital state. They can administer defibrillation when a shockable rhythm is detected and use advanced airway management techniques such as endotracheal intubation and inserting supraglottic airway devices. Paramedics who have completed advanced regional education with an emergency medicine specialist can administer epinephrine for patients with CPA up to 2 times every 4 minutes. Medical records were retrospectively reviewed, and general variables and clinical characteristics were collected. Patients were classified according to the interval for administering 1:1000 epinephrine as a 1 mg bolus via intravenous injection or intraosseous infusion during in-hospital CPR, which was performed every 3 or 4 minutes. The epinephrine interval was ordered by a CPR leader, who was a resident or professor in the ED, at the beginning of in-hospital CPR. Every time epinephrine was administered, it was recorded by a nurse, and we categorized the cases based on this record. Patients transported from other hospitals were excluded due to insufficient medical records. Patients transported by helicopters were excluded because of prolonged rescue times.

2.2 Study outcomes

The primary outcome was the ROSC rate at initial CPR in each group. Both sustained and non-sustained ROSC were counted as achieving ROSC. We also analyzed the survival rate until admission to the intensive care unit (ICU) and patients' cerebral performance categories (CPC) at hospital discharge. The total CPR time and total epinephrine dose used during CPR were also analyzed.

2.3 Variables and measurement

General patient characteristics, including sex, age and underlying diseases, were examined. Underlying diseases included diabetes mellitus, hypertension, coronary artery disease, stroke and heart failure. The clinical characteristics of the patients, including initial rhythm, application of shock before hospital admission, cause of arrest, witnessed status, bystander CPR performed, administration of epinephrine before hospital admission and prehospital CPR time, were examined. Initial rhythms were classified as shockable or non-shockable. A shockable rhythm was defined as ventricular fibrillation or pulseless ventricular tachycardia. A non-shockable rhythm was defined as asystole and pulseless electrical activity. The causes of arrest were classified into cardiac and non-cardiac. Examples of cardiac origins were myocardial infarction, heart failure, and arrhythmia. Examples of non-cardiac origins include hyperkalemia, acidosis, cancer and gastrointestinal bleeding. The cause of arrest was based on death certificates. The presence of underlying diseases, CPC score at discharge, total CPR time, and total epinephrine dose used during CPR were analyzed based on medical records.

2.4 Statistical analysis

The chi-squared test or Fisher's exact test was used for categorical variables, and the Student's *t*-test was used for numerical variables to compare the general and clinical characteristics of the 3- and 4-minute interval groups. All variables were normally distributed according to the Kolmogorov-Smirnov test. Adjustment for different distributions of baseline characteristics (sex, age, initial rhythm, shock before hospital arrival, cause of arrest, witnessed status, bystander CPR performed, administration of epinephrine before ED arrival, and CPR time before ED arrival) was performed to reduce bias and potential confounding factors between the two groups using a 3:1 propensity score matching analysis with the nearest neighbor method based on a greedy matching algorithm that could sort data by estimated propensity scores. The balance test of covariates in the matched group was performed by measuring the standardized mean differences. Before propensity score matching, patients with an unknown cause of cardiac arrest were omitted because of statistical inappropriateness. All standardized mean differences in the baseline variables were $<$0.2. After propensity score matching, the results of both groups were compared using the chi-squared test. In this study, we compared the rate of ROSC in the ED, survival rate until ICU admission, CPC scale score at discharge, total CPR time, and total dose of epinephrine used during CPR between the two groups. Data manipulation and statistical analyses were performed using SPSS software, version 24 (SPSS Inc., IBM, Armonk, NY, USA) and R software, version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). The R "Matchit" package was used for propensity score matching. All reported *p*-values were two-sided, and $p < 0.05$ was considered significant.

3. Results

In total, 240 patients were enrolled in this study. A total of 190 (79.2%) patients received epinephrine every 3 minutes, and 50 (20.8%) patients received epinephrine every 4 minutes (Fig. 1).

There were no significant differences in sex and age between the groups. There were no significant differences in the factors closely related to the possibility of ROSC, such as initial rhythm, shock before hospital arrival, cause of arrest, witnessed status, bystander CPR performed, administration of epinephrine before ED arrival, and prehospital CPR time. There were more patients with diabetes mellitus or stroke in the 3-minute group than in the 4-minute group; there were no differences in other medical history (Table 1).

After propensity score matching, there were no differences in ROSC in the ED, survival rate until admission to the ICU, or CPC scale scores at hospital discharge between the two groups. The total CPR time and epinephrine dose used during CPR did not differ significantly between the two groups (Table 2).

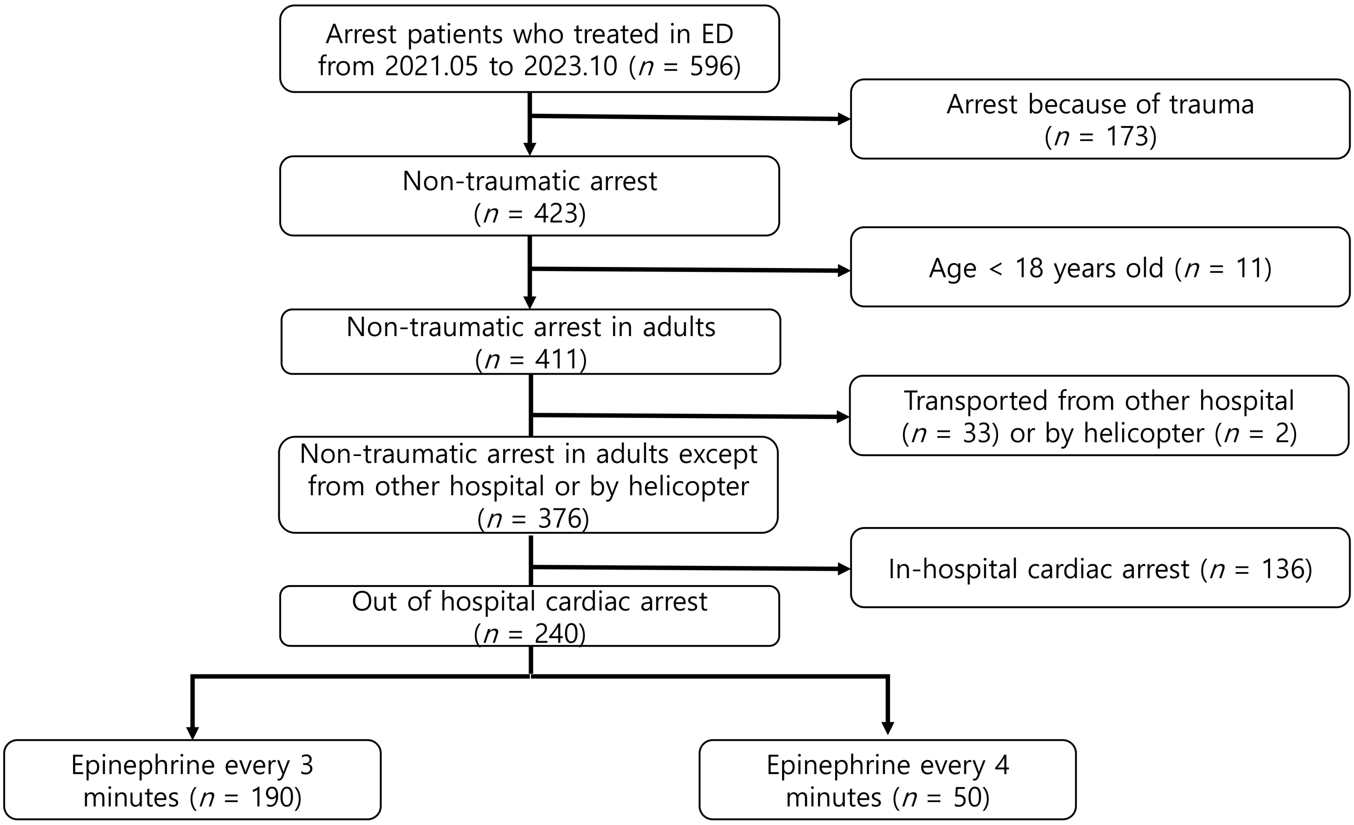

FIGURE 1. Flowchart of enrollment in this study. ED, Emergency Department.

TABLE 1. Baseline characteristics of two groups.

	3 minutes (N = 190)	4 minutes (N = 50)	Total (N = 240)	*p*-value
Sex (%)				
Male	115 (60.5)	31 (62.0)	146 (60.8)	0.849
Female	75 (39.5)	19 (38.0)	94 (39.2)	
Age, years old	67.53 ± 14.16	71.48 ± 15.44	68.35 ± 14.50	0.087
Initial rhythm (%)				
Shockable	22 (11.6)	7 (14.0)	29 (12.1)	0.640
Non-shockable	168 (88.4)	43 (86.0)	211 (87.9)	
Shock before hospital (%)				
No	165 (86.8)	44 (88.0)	209 (87.1)	0.828
Yes	25 (13.2)	6 (12.0)	31 (12.9)	
Cause of arrest (%)				
Cardiac	45 (23.7)	9 (18.0)	54 (22.5)	0.392
Non-cardiac	145 (76.3)	41 (82.0)	186 (77.5)	
Witnessed status (%)				
Unwitnessed	46 (24.2)	8 (16.0)	54 (22.5)	0.216
Witnessed	144 (75.8)	42 (84.0)	186 (77.5)	
Bystander CPR performed (%)				
No	42 (22.1)	14 (28.0)	56 (23.3)	0.381
Yes	148 (77.9)	36 (72.0)	184 (76.7)	
DM (%)				
No or unknown	139 (73.2)	26 (52.0)	165 (68.8)	0.004
Yes	51 (26.8)	24 (48.0)	75 (31.3)	

TABLE 1. Continued.

	3 minutes (N = 190)	4 minutes (N = 50)	Total (N = 240)	*p*-value
HTN (%)				
No or unknown	112 (58.9)	26 (52.0)	138 (57.5)	0.377
Yes	78 (41.1)	24 (48.0)	102 (42.5)	
CAD (%)				
No or unknown	164 (86.3)	39 (78.0)	203 (84.6)	0.147
Yes	26 (13.7)	11 (22.0)	37 (15.4)	
Stroke (%)				
No or unknown	171 (90.0)	39 (78.0)	210 (87.5)	0.022
Yes	19 (10.0)	11 (22.0)	30 (12.5)	
HF (%)				
No or unknown	175 (92.1)	44 (88.0)	219 (91.3)	0.361
Yes	15 (7.9)	6 (12.0)	21 (8.8)	
Administration of epinephrine before hospital (%)				
No	166 (87.4)	39 (78.0)	205 (85.4)	0.095
Yes	24 (12.6)	11 (22.0)	35 (14.6)	
Prehospital CPR time, minutes	21.40 ± 11.63	23.28 ± 10.41	21.79 ± 11.39	0.300

DM, diabetes mellitus; CPR, cardiopulmonary resuscitation; HTN, hypertension; HF, heart failure; CAD, coronary artery disease.

TABLE 2. Propensity score matched results of two groups.

	Propensity score matched data			
	Overall (n = 174)	3 minutes (n = 127)	4 minutes (n = 47)	*p*-value
ROSC in ED (%)				
Yes	78 (44.8)	52 (40.9)	26 (55.3)	0.106
Survival rate until ICU admission (%)				
Yes	39 (22.4)	30 (23.6)	9 (19.1)	0.516
CPC scale at hospital discharge (%)				
CPC 1–2	3 (1.7)	2 (1.6)	1 (2.1)	0.804
CPC 3–5	171 (98.3)	125 (98.4)	46 (97.9)	
Total CPR time, minutes	44.1 ± 17.4	42.9 ± 17.6	47.4 ± 16.7	0.120
Total epinephrine dose used during CPR	6.2 ± 4.0	6.1 ± 4.2	6.4 ± 3.2	0.562

ROSC, return of spontaneous circulation; ED, emergency department; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; CPC, cerebral performance categories.

4. Discussion

The current CPR guidelines suggest that epinephrine should be administered during CPR every 3–5 minutes [1], but to our knowledge, no studies have analyzed the interval for epinephrine administration in detail. To establish simpler and more efficient CPR protocols, we investigated resuscitation outcomes following intervals for epinephrine administration of 3 and 4 minutes. There was no significant difference in the ROSC rate, survival rate until admission to the ICU, and CPC scale score at discharge from the hospital between the two groups (Table 2).

In previous studies, the survival rate of CPA improved when there was good teamwork between nurses and ED doctors [11–13]. In other studies, job training for nurses was found to improve the ROSC rate of CPR [14, 15]. In the current ACLS guidelines, pulse and rhythm checks are performed every 2 minutes, and epinephrine administration is performed every 3–5 minutes [1]. If the CPR leader orders the administration of epinephrine every 3 minutes, then the timing of epinephrine administration and rhythm checks can be confused. This increases workload during ACLS and harms teamwork between nurses and doctors [11]. If there is no significant difference in prognosis between the administration of epinephrine every 3 minutes and every 4 minutes, then a 4-minute interval is consistent with two cycles of ACLS, which can be helpful for simplifying the process of CPR. Epinephrine administration during CPR has both advantages and disadvantages, which can explain our study outcomes. There was no significant difference in resuscitation outcome. Considering the above findings, we suggest that epinephrine administration every 4 minutes should be considered in ACLS. The strategy of administering epinephrine every two cycles of CPR can be expected to improve the efficiency of the ED, where ACLS needs to be performed with limited human resources and time. For example, simplifying the CPR protocol can enhance other CPR processes, such as accurate chest compression and detailed monitoring, which can help to achieve ROSC. Considering other studies that have suggested the nurse-to-bed ratio as the only factor controlling the incidence of CPA, it is predicted that more efficient bed management will be possible in the ED if fewer nursing personnel are deployed through efficient ACLS [16]. This can be particularly helpful for novice medical personnel [12].

One limitation of this study was that its data quality was lower than that of prospective studies due to the retrospective nature of the study design, despite performing propensity score matching to increase statistical power [17]. Given the limitations of retrospective studies, there were many patients whose medical records for underlying diseases were not accurately recorded, and there is a possibility that the evaluation of underlying diseases was not accurately performed, considering that they were tied to the presence or absence of underlying diseases. As this was a single-center study that did not include data from several other emergency centers, it could lead to biased research results, considering that the environment varies from hospital to hospital [18]. In addition, local prehospital CPR rescue protocols might vary, so the results in other cities may differ. The CPC scale could only be evaluated at the time of discharge and subsequent outpatient follow-up at this hospital, and there were limitations to this because it was difficult to clearly evaluate the CPC scale for patients who did not or rarely visit the hospital after long-term hospitalization [19]. If the CPC scale is used for follow-up after the same period, the prognostic evaluation will be more accurate. To proceed with more advanced research, two groups with consistent baseline characteristics should be selected through prospective research so that the prognosis between the two groups can be accurately compared. Such a prospective study will help to confirm whether the 4-minute interval for epinephrine administration has positive effects on outcomes following CPR. Securing a larger number of cases by performing a multicenter study between hospitals could lead to more accurate research results when compared with a single-center study. Considering the nature of the ED, even if a patient visited the hospital because of cardiac arrest, there were some cases in which the family wanted to stop CPR immediately after the visit [20, 21]. In this case, there was a limitation that could have led to bias in determining the patient's prognosis.

5. Conclusions

In this study, there were no significant differences in the ROSC rate and other resuscitation outcomes between patients who received epinephrine at 3-minute and 4-minute intervals during CPR. We suggest the "epinephrine for every 2 cycles of CPR" strategy as a simple protocol for medical personnel performing CPR.

ABBREVIATIONS

CPA, cardiopulmonary Arrest; CPR, Cardiopulmonary Resuscitation; ROSC, Return of Spontaneous Circulation; ACLS, Advanced Cardiovascular Life Support; ED, Emergency Department; OHCA, Out of Hospital Cardiac Arrest; ICU, Intensive Care Unit; CPC, Cerebral Performance Categories; DM, Diabetes Mellitus; HTN, Hypertension; CAD, Coronary Artery Disease; HF, Heart Failure.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

MGJ, JSH and SHK—designed the research study. MGJ—performed the research. JSH and SHK—provided help and advice on this study. MGJ and JSH—analyzed the data and wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was reviewed and approved by the Institutional Review Board of the Ulsan University Hospital (UUH-IRB-2024-02-019). The data used in this study were anonymized before use. All the methods used in this study were performed in accordance with the Declaration of Helsinki guidelines. The requirement for informed consent was waived by the Institutional Review Board because of the retrospective nature of this study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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