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Original article

Retrospective evaluation of resuscitation medication utilization in hospitalized adult patients with cardiac arrest

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ABSTRACT

Background: Early medication administration in cardiac arrest improves outcomes. The primary objective was to evaluate the association between epinephrine administration in in-hospital cardiac arrest (IHCA) patients with non-shockable rhythm and the patient outcomes. The secondary objective was to assess the compliance of epinephrine and amiodarone administration in accordance with the advanced cardiovascular life support (ACLS) guideline.

Methods: IHCA patients aged 18 years or above were identified from the resuscitation registry of 2016 of two public hospitals and categorized according to their initial rhythms. For patients with non-shockable rhythms, the associations between IHCA outcomes, return of spontaneous circulation (ROSC), and survival to discharge, and the time of epinephrine administration were analyzed by logistic regression. The compliance rate of epinephrine and amiodarone administration during resuscitation to ACLS guideline were reported.

Results: Among 349 patients with non-shockable rhythm, the median time to epinephrine administration was 3 min (interquartile range, 1–6 min). Early epinephrine administration (<5 min), compared with late epinephrine administration (>5 min), was significantly associated with the rate of ROSC (49.2% vs 34.9%; adjusted odds ratio, 1.630; 95% confidence interval 1.008–2.635, $p = 0.046$). The time to epinephrine administration (as continuous interval) was significantly associated with the rate of ROSC ($p = 0.002$) and survival to discharge ($p = 0.029$). In addition, the compliance rate of epinephrine and amiodarone administration during resuscitation were 83.6% and 33.3%, respectively.

Conclusion: Our study found that time of epinephrine administration was significantly associated with better results in ROSC and survival to discharge in IHCA patients with non-shockable rhythm. When we divided the IHCA patients with non-shockable rhythms into early and late administration group, early epinephrine administration was associated with significantly improved ROSC, but not survival to discharge after adjusting with potential confounding factors.

Introduction

According to the American Heart Association, the survival rate to discharge of adult patients with in-hospital cardiac arrest (IHCA) ranged from 22.7% to 25.5% between 2012 and 2016 in the USA [1–5]. Based on two studies conducted in two Hong Kong public hospitals between 2002 and 2008, the survival rate to discharge of IHCA adult patients was around 5% [6,7]. Drug therapy is an essential component of advanced cardiovascular life support (ACLS). The ACLS guideline suggested that it might be reasonable to administer epinephrine as soon as feasible after the onset of cardiac arrest due to an initial non-shockable rhythm [8]. A large retrospective study in the USA has demonstrated that early

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administration of epinephrine in non-shockable rhythms was associated with increased return of spontaneous circulation (ROSC), survival to hospital discharge, and neurologically intact survival [9]. Prompt epinephrine administration (<5 min) for patients with IHCA caused by non-shockable rhythm was associated with greater survival to discharge and survival at 1 year compared with delayed administration [10]. Besides epinephrine, amiodarone is another essential resuscitation medication used in shockable rhythm to improve the rate of ROSC [11].

Non-compliance to ACLS guidelines, including errors in medication administration, has been shown to decrease ROSC and cardiac arrest survival [12,13]. Several studies have shown that the presence of a pharmacist in the resuscitation team was associated with increased ACLS compliance and documentation completeness [14–16]. Medications used during resuscitation are prepared and administered by nursing staff and often not subjected to review by pharmacists, which may increase the risk of medication error. We hypothesize that early epinephrine use within 5 min of onset of IHCA in non-shockable rhythm would improve patients' outcomes.

The objectives of this study were to evaluate the association between epinephrine administration in IHCA patients with non-shockable rhythm and the outcome after IHCA, and to assess the compliance of epinephrine and amiodarone administration during resuscitation to ACLS guideline.

Methods

This was a retrospective observational study conducted in two large public hospitals. Approvals were obtained from the Ethics Committee of the regulating bodies for both hospitals. IHCA patients were identified from the resuscitation registry of the two hospitals during the study period from 1 January 2016 to 31 December 2016.

During the study period, all patients aged 18 years or above with the onset of cardiac arrest during their inpatient hospital stay were included. In line with the ACLS guideline, IHCA patients were categorized by the initial rhythm into shockable rhythm, namely ventricular tachycardia (VT) and ventricular fibrillation (VF), and non-shockable rhythm, namely asystole and pulseless electrical activity (PEA). In order to define the scope of our study and facilitate the process of data collection and analysis, patients with no cardiopulmonary resuscitation (CPR) attempt and/or "Do Not Resuscitate" agreement prior to resuscitation, and those who had ROSC prior to epinephrine administration were excluded. Resuscitation records with missing and/or incomplete key process information (e.g. time to epinephrine administration) were also excluded.

Data were collected by reviewing the resuscitation records and medical records of all identified IHCA patients. Data were collected by an unblinded multidisciplinary team including physicians and pharmacists utilizing a structured data abstraction form. A third reviewer was consulted anytime there was a discrepancy with the first reviewers. Demographic data including age, gender, pre-existing conditions, as well as location and specialty of the ward where the cardiac arrest occurred were retrieved. Clinical data including initial electrocardiogram rhythm (VT, VF, asystole, PEA), the time of cardiac arrest, time to CPR after identification of cardiac arrest, time and dose of epinephrine and amiodarone administration, any ROSC, and survival to discharge were recorded. Pre-existing conditions of patients were quantified using Charlson Comorbidity Index (CCI) [17].

The primary outcome was the rate of ROSC, and the secondary outcomes were survival to discharge and medication administration compliance rates according to ACLS guideline. The time to epinephrine administration was calculated in whole minutes from the time of cardiac arrest identified to the time of first dose of epinephrine administered. Early administration of epinephrine was defined as the time to epinephrine administration less than or equal to 5 min. This time threshold was chosen based on previous studies of similar nature [10]. If a patient had more than one arrest event during the index admission, only the first arrest episode would be included for ROSC and survival to discharge analysis.

The rate of compliance of drug administration to ACLS guideline was measured. Indication of epinephrine use was not assessed because it was indicated for all rhythms. Standard-dose epinephrine 1 mg IV/IO every 3–5 min (except patients with documented pulse/blood pressure between doses) was considered compliant. For patients with shockable rhythm, epinephrine should be given after defibrillation and a 2-minute CPR period in addition to the above requirements. Amiodarone should only be used for shockable rhythm unresponsive to CPR, defibrillation, and epinephrine administration. The correct first dose was 300 mg IV/IO and the second dose should be 150 mg IV/IO. All cardiac arrest episodes, including multiple episodes of the same patient in the same index admission, were included for compliance assessment.

Statistical analysis

Statistical analysis was performed using Microsoft Excel and Statistical Package for the Social Sciences (SPSS) for Windows version 23.0 (SPSS Inc, Chicago, IL, USA). Descriptive statistics were used to demonstrate the basic demographics of the study population. Multivariate logistic regression was used to evaluate the association between outcomes of IHCA patients with non-shockable rhythms and the time of epinephrine administration. Possible confounding factors with data available in the resuscitation registry were considered for adjustment. Only confounding factors that were associated with outcomes were added to the multivariate regression model.

The level of significance was set at 0.05 (two-tail). A p-value less than 0.05 was considered statistically significant.

Results

A total of 456 patient cases, 287 from one hospital and 169 from a second hospital, were reviewed for the study. After excluding cardiac arrest episodes with no CPR (n = 2), no drug administration

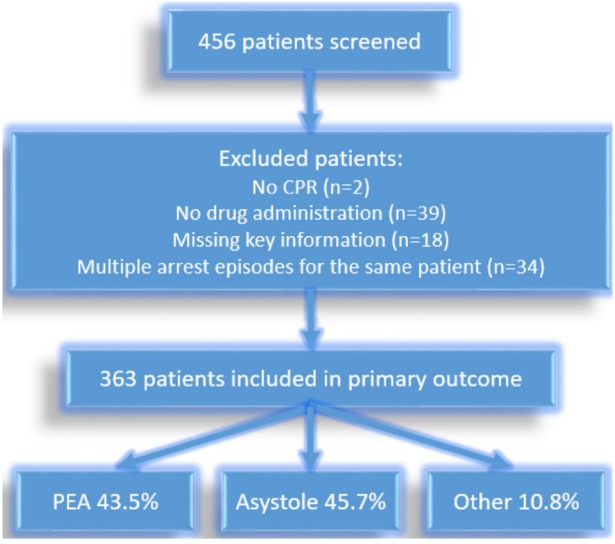

Fig. 1. Patient enrollment process and presentation flowchart.
CPR, cardiopulmonary resuscitation; PEA, pulseless electrical activity.

Table 1
Demographic background comparison of patients with different ROSC and survival outcomes. Demographics.

	All patients (n = 363)	Patients with no ROSC (n = 198)	Patients with ROSC but without survival to discharge (n = 151)	Patients with ROSC and survival to discharge (n = 14)
Mean age ± SD	75.0 ± 13.2	75.7 ± 13.6	74.8 ± 12.8	68.7 ± 12.2
Gender				
Male	226 (62.3%)	114 (57.6%)	100 (66.2%)	12 (85.7%)
Female	137 (37.7%)	84 (42.4%)	51 (33.8%)	2 (14.3%)
Specialty				
ICU/CCU/HDU	62 (17.1%)	25 (12.6%)	32 (21.2%)	5 (35.7%)
Medical	214 (59.0%)	127 (64.1%)	81 (53.6%)	6 (42.9%)
Surgical	48 (13.2%)	26 (13.1%)	20 (13.2%)	2 (14.3%)
Oncology	12 (3.3%)	6 (3.0%)	6 (4.0%)	0 (0%)
Others	27 (7.4%)	14 (7.1%)	12 (7.9%)	1 (7.1%)
Initial rhythm				
Pulseless electrical activity	158 (43.5%)	71 (35.9%)	78 (51.7%)	9 (64.3%)
Asystole	166 (45.7%)	107 (54.0%)	57 (37.7%)	2 (14.3%)
Other non-shockable rhythms^	25 (6.9%)	15 (7.6%)	9 (6.0%)	1 (7.1%)
Ventricular tachycardia/ventricular fibrillation	14 (3.9%)	5 (2.5%)	7 (4.6%)	2 (14.3

Table 2
Demographic and outcome comparison of subjects with early and late administration of epinephrine.

Demographics & outcomes	Early administration of epinephrine (<5 min) (n = 240)	Late administration of epinephrine (>5 min) (n = 109)	p-Value
Mean age ± SD	75.0 ± 13.2	75.7 ± 13.3	0.618
Gender			0.005
Male	161 (67.1%)	56 (51.4%)	
Female	79 (32.9%)	53 (48.6%)	
ICU/CCU/HDU care	51 (21.3%)	4 (3.7%)	<0.001
Mean time to CPR ± SD (min)	0.15 ± 0.55	1.10 ± 5.13	0.005
Mean Charlson Comorbidity index ± SD	3.55 ± 2.33	3.28 ± 2.37	0.327
ROSC	118 (49.2%)	38 (34.9%)	0.013
Survival to discharge	10 (4.2%)	2 (1.8%)	0.281

Note: SD = standard deviation, ICU/CCU/HDU = intensive care unit, coronary care unit, high-dependency unit, CPR = cardiopulmonary resuscitation, ROSC = return of spontaneous circulation.

Table 3
Effect of confounding factors on association between early administration of epinephrine and in-hospital cardiac arrest outcomes.

Confounding factors	Confounding effect on ROSC	OR (CI)	Confounding effect on survival to discharge	OR (CI)
Age	p = 0.4015	0.993 (0.978–1.010)	p = 0.0667	0.968 (0.934–1.004)
Gender	p = 0.0975	0.983 (0.757–1.276)	p = 0.1787	0.361 (0.055–1.395)
ICU/CCU/HDU care	p = 0.0499	1.139 (0.799–1.738)	p = 0.1753	1.328 (0.688–2.119)
Time to CPR	p = 0.6240	1.0822 (0.808–1.464)	p = 0.5383	0.615 (0.04421–0.977)
Charlson comorbidity index	p = 0.1293	0.935 (0.854–1.023)	p = 0.7117	1.06 (0.834–1.333)

ROSC, return of spontaneous circulation; ICU/CCU/HDU, intensive care unit, coronary care unit, high-dependency unit; CPR, cardiopulmonary resuscitation.

(n = 39), missing other key information (n = 18), and multiple arrest episodes of the same patient (n = 34), 363 patients were included in the primary outcome of the study as shown in Fig. 1. The mean age of participants enrolled in our study was 75.0 ± 13.2 years with 62.3% of the enrollees being male. The most common initial rhythms of participants in our study were PEA (43.5%) and asystole (45.7%). The demographics of enrolled subjects are shown in Table 1. There was no statistically significant difference in demographics between patients with ROSC and patients with ROSC and survival to discharge as there were only 14 patients with survival to discharge.

Epinephrine administration records were found in 349 patients with non-shockable rhythms. The median time to epinephrine administration from arrest was 3 min (interquartile range, 1–6 min). Those that received early administration of epinephrine were more likely male and located in the intensive care, cardiac care, or high-dependency units. Those that received early epinephrine administration were more likely to have ROSC, but not survival to discharge. The demographics and outcomes of patients with early and late administration are shown in Table 2.

Logistic regression was used to analyze the association between time of epinephrine and ROSC. Among all confounding factors entered into the regression model, only proportion of intensive care unit, coronary care unit, or high-dependency unit (ICU/CCU/HDU) care was found to be a significant confounding factor to ROSC (Table 3), so it was adjusted in the analysis. After resuscitation, 156 out of 349 patients (44.7%) with non-shockable rhythms were able to achieve ROSC. When patients were divided into early and

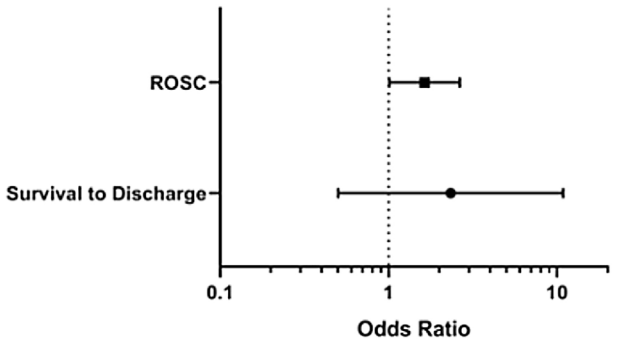

Fig. 2. Association between early administration of epinephrine and study outcomes in patients with non-shockable rhythms after adjusting for care unit location of patient.
ROSC, return of spontaneous circulation.

late administration of epinephrine, the early administration group had ROSC in 49.2% of patients, which was significantly higher than the rate (34.9%) in late administration group [$p = 0.013$, odds ratio (OR) = 1.807, 95% confidence interval (CI) = 1.131–2.886]. After adjusting the effect of ICU/CCU/HDU care, the difference remained significant ($p = 0.046$, OR = 1.630, 95% CI = 1.008–2.635) as shown in Fig. 2. When the association between time to epinephrine administration (as continuous interval) and ROSC was analyzed, time to epinephrine was found to be significantly associated with the rate of ROSC even after adjusting the effect of ICU/CCU/HDU care ($p = 0.002$).

Logistic regression was used to analyze the association between time of epinephrine and survival to discharge. None of the possible confounding factors was statistically significant when entered into the regression model (Table 3), although the quality of the CPR was not assessed. Only 12 out of 349 patients (3.4%) with non-shockable rhythms survived to discharge after resuscitation. When the association between time to epinephrine administration (as continuous interval) and survival to discharge was analyzed, time to epinephrine administration was significantly associated with the rate of survival to discharge ($p = 0.029$).

A total of 398 cardiac arrest episodes with the use of epinephrine and/or amiodarone were identified. No patients in the study received lidocaine instead of amiodarone. One episode was excluded from the compliance assessment due to illegible handwriting. The overall compliance rate was 81.1%. The results of the compliance assessment are summarized in Table 4.

Table 4
Compliance of epinephrine and amiodarone administration to advanced cardiac life support (ACLS) guideline.

Drug administration	No. of compliant case
Overall compliance (N = 397)	322 (81.1%)
Epinephrine (N = 396)	331 (83.6%)
Dose	382 (96.5%)
Time	341 (86.1%)
Amiodarone (N = 18)	6 (33.3%)
Indication	15 (83.3%)
Dose	8 (44.4%)
Time	13 (72.2%)

Note: Compliance assessment criteria.
Epinephrine.
-Dose: standard-dose 1 mg IV/IO (standard-dose was assumed to be used unless other doses were specified on the resuscitation form based on common practice during resuscitation.).
-Time: every 3–5 min (except patients had documented pulse/blood pressure between doses); after defibrillation and a 2-min CPR period (for shockable rhythm).
Amiodarone.
- Indication: for shockable rhythm.
- Dose: first dose 300 mg IV/IO, second dose 150 mg IV/IO.
- Time: after CPR, defibrillation and epinephrine administration.

Non-standard dosages of epinephrine were administered in 14 of the cardiac arrest episodes. Lower doses of epinephrine (e.g. 0.1 mg and 0.5 mg) were involved in 12 of the episodes. Higher doses of epinephrine (e.g. 10 mg) were recorded in 2 of the episodes. In terms of time of administration, epinephrine was not administered every 3–5 min in majority (47 out of 55) of the non-compliant cases. For episodes with shockable rhythm, there were 9 cases when epinephrine was administered prior to or within 2 min of defibrillation.

Amiodarone was only used in 18 cases with only one-third (6 out of 18) of these cases achieving overall compliance to ACLS guideline regarding appropriate amiodarone use, in terms of indication, dose, and time. Inappropriate dosage of amiodarone was found in 10 episodes in which 90% of the cases involved the omission of the 300 mg amiodarone dose prior to the 150 mg dose. Some non-standard dosages (e.g. 100 mg or 200 mg IV amiodarone) were also found in the resuscitation forms. Amiodarone was found to be given prior to or at the same with first defibrillation or first epinephrine administration in 5 of the episodes.

Discussion

In this study, the median administration time of epinephrine in patients with non-shockable rhythms was 3 min, which was slower than the median of 2 min reported in a similar study in the USA [10], but was faster than the median time (5 min) reported by another study performed in Hong Kong in 2007 [6]. Of the patients in our study, 68.7% were able to receive epinephrine administration within 5 min of arrest, which was lower than that (86.3%) reported in another study conducted in the USA [10].

This study demonstrated that patients with early administration of epinephrine were more likely to have ROSC after resuscitation which was in agreement with previous studies [9,10]. In some large-scale studies [7,9,10,18], patients who received early administration of epinephrine also had a better rate of survival, which was different from this study. This could be due to the fact that the number of IHCA patients who survived to hospital discharge was low. An additional hypothesis for this finding is that while epinephrine achieves ROSC it can also cause harm by reducing microvascular blood flow resulting in neuronal injury or arrhythmias. The effects on microvascular blood flow could affect patient outcomes such as neurologic status at hospital discharge and survival to discharge [19]. A larger sample size might be needed to show a significant difference. When time interval to epinephrine administration was used as an independent variable, a shorter time interval was significantly associated with both ROSC and survival to discharge. An Australian study has demonstrated that epinephrine in pre-filled syringes was faster to administer when compared with equivalent dose-packaged ampoules [20]. Pharmacy might investigate the possibility of introducing epinephrine pre-filled syringes in the emergency drug kits, e.g. commercially available preparations and aseptic preparation in pharmacy clean room, to improve the time of epinephrine administration during IHCA.

Several confounding factors were considered for adjustment to obtain the best fit model. Only proportion with ICU/CCU/HDU care was found to be significant for ROSC in our study. The confounding effect could be due to better monitoring and higher nurse to patient ratio in ICU/CCU/HDU, which allowed faster CPR and drug administration. Other factors such as age, gender, time to CPR, and comorbidities were not significantly associated with ROSC and survival to discharge, which was different from some other studies that also employed multivariate logistic regression models for analysis [9,10]. This could be attributed to the relatively small

sample size in this study, which might not have sufficient power to illustrate possible confounding effects.

Our study found that the compliance rate for amiodarone was lower than that of epinephrine. The 300 mg loading dose was omitted in half of the episodes with amiodarone use. This may be due to the parenteral amiodarone preparation available in the hospitals. The injection is available as 150 mg/3 ml ampoule, so two ampoules are required for loading. In most of the non-compliance cases, only one ampoule was given instead. Amiodarone was given to patients with non-shockable rhythm in 3 episodes. There might be a rhythm switch from non-shockable to shockable during the resuscitation process which was not properly documented. There was no association seen between compliance to the ACLS guidelines and ROSC or survival to discharge.

Early administration of amiodarone (prior to defibrillation and epinephrine administration) and epinephrine (prior to defibrillation) were observed in some patients with shockable rhythm. This might be due to unfamiliarity with the ACLS guideline and resuscitation process for shockable rhythm. ACLS guidelines recommended the use of defibrillators in patients with shockable rhythms prior to pharmacotherapy [8]. Early administration of epinephrine (within 2 min after the first defibrillation) in shockable rhythm has been shown to be associated with decreased odds of ROSC and survival in a large multicenter study in the USA [21]. For higher dose of epinephrine (10 mg), the documentor might intend to record 10 ml instead as that was the standard volume of 1 mg at both study sites. Despite potential error in documentation, these cases were treated as non-compliance.

Literature reports that the integration of a pharmacist in the resuscitation team was associated with improved compliance with treatment guideline [14–16]. However, there was no clinical pharmacist specialized in critical care at both study sites. Modification of the current resuscitation form may help to remind front-line staff of proper medication use during resuscitation. Cardiac arrest algorithm and practice key points regarding medications use can be pre-printed on the form. In view of the low compliance rate to initial dose of amiodarone, inserting a warning label about the initial dose could be considered during preparation of emergency drug kits by the pharmacy.

Limitations

There were several limitations in our study. This study was retrospective and observational by nature. Only association relationship could be established instead of a causal relationship for independent variable (early administration of epinephrine) and dependent variable (ROSC and survival to discharge). Some unmeasured confounding factors, e.g. CPR quality, might have potential influences on patients' outcomes. The effects of other drugs used during resuscitation on patients' outcomes were also not measured.

Moreover, limitations also included the accuracy of data documented in resuscitation forms. Two different resuscitation forms were adopted by the two hospitals and there was a lack of standardization for documentation of resuscitation details between observers. Lastly, the compliance result for epinephrine and amiodarone use was generated from the two study hospitals only. Generalizability of our study results to other hospitals was limited.

Conclusions

Our study found that time of epinephrine administration was significantly associated with better results in ROSC and survival to discharge in IHCA patients with non-shockable rhythm. When we divided the IHCA patients with non-shockable rhythms into early and late administration groups, early epinephrine administration was associated with significantly improved ROSC, but not survival to discharge after adjusting with potential confounding factors. Compliance rate to ACLS guideline was over 80% regarding epinephrine and much less for amiodarone. Future research directions include identifying solutions to improve compliance with the guidelines and to identify the detrimental effects of epinephrine.

Conflict of interest

The authors declare that they have no conflict of interest.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Hong Kong East Cluster Research Ethics Committee – Reference Number: HKECREC-2018-032) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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