Resuscitation 103 (2016) 125–130

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

The influences of adrenaline dosing frequency and dosage on outcomes of adult in-hospital cardiac arrest: A retrospective cohort study☆

Chih-Hung Wang[a,b], Chien-Hua Huang[a], Wei-Tien Chang[a], Min-Shan Tsai[a], Ping-Hsun Yu[c], Yen-Wen Wu[d,e,f], Kuan-Yu Hung[g], Wen-Jone Chen[a,h,*]

[a] Department of Emergency Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan
[b] Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan
[c] Department of Emergency Medicine, Taipei Hospital, Ministry of Health and Welfare, New Taipei City, Taiwan
[d] Departments of Internal Medicine and Nuclear Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan
[e] Department of Nuclear Medicine and Cardiology Division of Cardiovascular Medical Center, Far Eastern Memorial Hospital, New Taipei City, Taiwan
[f] National Yang-Ming University School of Medicine, Taipei, Taiwan
[g] Division of Nephrology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
[h] Department of Emergency Medicine, Lotung Poh-Ai Hospital, Yilan, Taiwan

ARTICLE INFO

Article history:
Received 22 August 2015
Received in revised form
16 November 2015
Accepted 16 December 2015

Keywords:
Heart arrest
Cardiopulmonary resuscitation
Emergency medicine
Critical care
Adrenaline

ABSTRACT

Aim: To investigate the influence of dosing frequency and dosage of adrenaline on outcomes of cardiopulmonary resuscitation (CPR).
Methods: We conducted a retrospective observational study in a single medical centre and included adult patients who had suffered an in-hospital cardiac arrest between 2006 and 2012. We used multivariable logistic regression analysis to evaluate the associations between independent variables and outcomes. Adrenaline average dosing frequency was calculated as the total dosage of adrenaline administered during CPR divided by the duration of CPR. Body weight (BW) was analysed as an interaction term to investigate the effect of adrenaline dosage on outcomes. Favourable neurological outcome was defined as a score of 1 or 2 on the Cerebral Performance Category scale at hospital discharge.
Results: We included 896 patients in the analysis. After adjusting for multiple confounding factors, including CPR duration, the results indicated that higher adrenaline dosing frequency was associated with lower rates of survival (odds ratio (OR): 0.05, 95% confidence interval (CI): 0.01–0.23) and favourable neurological outcome at hospital discharge (OR: 0.02, 95% CI: 0.002–0.16). A significant interaction was noted between total adrenaline dosage and BW, which indicated that, with the same adrenaline dosage, the outcomes for patients with BW ≥ 82.5 kg would be worse than those for patients with lower BW.
Conclusion: Higher adrenaline average dosing frequency may be associated with worse outcomes after CPR. Besides, according to current recommendations, patients with BW above 82.5 kg may not receive adequate dose of adrenaline.

Introduction

Advanced life support during cardiac arrest management comprises cardiopulmonary resuscitation (CPR), defibrillation, airway management, and administration of vasoactive drugs.[1–3] As a potent vasopressor, adrenaline (epinephrine) has been an integral component of advanced life support since the inception of modern CPR in the early 1960s.[4]

The alpha-adrenergic effects of adrenaline produce systemic vasoconstriction, increasing coronary and cerebral perfusion pressures, which are believed to be beneficial in achieving return of spontaneous circulation (ROSC). However, some adverse effects of adrenaline administration have also been observed in animal studies, including increased myocardial oxygen consumption[5] and reduced cerebral microcirculatory blood flow,[6]

☆ A Spanish translated version of the summary of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2015.12.008.

* Corresponding author at: National Taiwan University Hospital, Department of Emergency Medicine, No. 7 Chung-Shan S. Rd, Taipei, Taiwan.
Fax: +886 2 2322 3150.
E-mail address: wjchen1955@ntu.edu.tw (W.-J. Chen).

http://dx.doi.org/10.1016/j.resuscitation.2015.12.008
0300-9572/

which might lead to long-term mortality associated with cardiac arrest.[7,8]

For out-of-hospital cardiac arrest (OHCA), several studies have reported that the results associated with adrenaline administered by emergency medical staff in the prehospital setting were either worse or, at best, equivalent to CPR without the administration of adrenaline.[9–12] No similar studies have been conducted for patients who suffer in-hospital cardiac arrest (IHCA).

Current guidelines recommend 1 mg of adrenaline administered every 3 to 5 min during CPR. While the effects of adrenaline dosing frequency could be directly analysed, it might be difficult to investigate the effect of adrenaline dosage directly since during CPR, most physicians would administer a fixed dose of adrenaline for each injection.[1–3] In most animal studies,[13–17] weight-based doses, rather than a fixed dose, of adrenaline were used for CPR. Therefore, we included body weight (BW) in the analysis to observe the effect of adrenaline dosage on CPR outcome in an indirect manner.

Materials and methods

Setting

We conducted a retrospective cohort study at the National Taiwan University Hospital (NTUH), which is a tertiary care centre. The study was performed in accordance with the amended Declaration of Helsinki. Prior to data collection, the Institutional Review Board of the NTUH approved this study (reference number: 201508038RIN) and for this type of study, formal consent is not required. The NTUH has 2600 beds, including 220 beds in intensive care units (ICUs). According to hospital policy, a code team is activated when a cardiac arrest event occurs in the general wards. A code team consists of a senior resident, several junior residents, a respiratory therapist, a head nurse, and several registered nurses from the ICUs. Each code team member has been certified to provide advanced life support according to AHA/ILCOR resuscitation guidelines. When a cardiac arrest event occurs in the ICUs, resuscitation is performed by the staff of the ICU where the cardiac arrest event occurred and by staff from neighbouring ICUs.

Participants

We included patients who had suffered an IHCA at the NTUH between 2006 and 2012. We included patients who met the following criteria: (1) age $\geq$18 years; (2) documented absence of pulse with performance of chest compression for $\geq$2 min; and (3) no documentation of a do-not-resuscitate order. If multiple cardiac arrest events occurred in a single patient, we only recorded the first event of the same hospitalization. We excluded patients who had suffered a cardiac arrest related to major trauma. We also excluded patients without measurements of BW.

Data collection and outcome measures

We abstracted the following information for each patient from the routine medical records: demographics, actual BW measured on admission, comorbidities (see definitions in Supplemental Table 1), variables derived from the Utstein template,[18] and any critical intervention that was implemented at the time of cardiac arrest or after ROSC. The timing of the CPR process was recorded by the nursing member of the code team according to hospital-regulated protocols. The times were recorded according to hospital-wide clocks which were checked every day to ensure the times were unified across the hospital. CPR duration was defined as the time from the first chest compression provided by the code team or ICU members to the termination of resuscitation efforts, either due to sustained ROSC or declaration of death. Adrenaline average dosing frequency was calculated as total adrenaline dosage administered during CPR divided by CPR duration.[19]

The primary outcome was survival to hospital discharge. Secondary outcomes included sustained ROSC, survival for 24 h, and favourable neurological status at hospital discharge, which was defined as a score of 1 or 2 on the Cerebral Performance Category (CPC) scale.[20] We retrospectively determined the CPC score by reviewing medical records for each patient.

Statistical analysis

We used R 2.15.3 software (R Foundation for Statistical Computing, Vienna, Austria) for data analysis. Categorical data were expressed as counts and proportions; continuous data were expressed as means and standard deviations. Categorical variables were compared by the Fisher's exact test, and continuous variables were examined by the Wilcoxon rank-sum test. A two-tailed p-value of $\leq$0.05 was considered statistically significant.

We selected the odds ratio (OR) as the outcome measure. We conducted a multivariable logistic regression analysis to examine the association between variables and outcomes. CPR duration was analysed as an independent variable to decrease the possibility of confounding by indication. BW was analysed as an interaction term with adrenaline average dosing frequency to observe the effect of adrenaline dosage on outcomes.

All available independent variables, including interaction terms, were considered in the regression model, regardless of whether they were significant by univariate analysis. The stepwise variable selection procedure (with iterations between the forward and backward steps) was applied to obtain the final regression model. Significance levels for entry and to stay were set at 0.15 to avoid exclusion of potential candidate variables. The final regression model was identified by excluding individual variables with a p-value >0.05, until all regression coefficients were statistically significant.

We used generalized additive models (GAMs)[21] to examine the nonlinear effects of continuous variables on outcomes and, if necessary, to identify the appropriate cut-off point(s) for dichotomizing a continuous variable during the variable selection procedure. We also used conditional effect plots[22] to visualize the predicted probability of outcomes against variables of interest while the other independent variables in the final model remained constant. We assessed the goodness-of-fit of the fitted regression model using c statistics, adjusted generalized R^2, and the Hosmer–Lemeshow goodness-of-fit test.

Results

We identified a total of 1114 patients met the inclusion criteria for our study. Of these, 9 patients were excluded because of trauma-related cardiac arrest, and 209 patients were excluded because of lack of measurement of BW. The remaining 896 patients were included for further analysis.

The characteristics of the included patients, stratified by primary outcome, are presented in Tables 1 and 2. The mean BW was 60.1 kg. Shockable rhythms represented 14.5% of initial arrest rhythms. The mean total dosage of adrenaline administered during CPR was 8.1 mg and the mean duration of CPR was 33.3 min. The mean adrenaline average dosing frequency was 0.28 mg/min. Only 140 patients (15.6%) survived to hospital discharge and 74 of these patients (8.3%) displayed a favourable neurological status.

All independent variables listed in Tables 1 and 2 were included in the variable selection procedure for the primary outcome. The GAM plot that is shown in Supplemental Fig. 1 revealed that logit (p), where p represented the probability for survival to hospital