Donnino MW, Salciccioli JD, Howell MD, Cocchi MN, Giberson B, Berg K, Gautam S, Gallaway C. *BMJ* 2014;348:g3028

Time to administration of epinephrine and outcome after in-hospital cardiac arrest with non-shockable rhythms: retrospective analysis of large in-hospital data registry

Post hoc analysis of prospectively collected multicenter registry data

Objective

- To determine if earlier administration of epinephrine in patients with non-shockable cardiac arrest rhythms is associated with increased return of spontaneous circulation, survival, and neurologically intact survival

The authors state that with cardiac arrest, initial cardiac rhythms not amenable to defibrillation are more common than shockable rhythms and that epinephrine is recommended by the American Heart Association (AHA) as the preferred medical intervention. With no well controlled trials of epinephrine to assess endpoints such as improved survival and neurologically intact survival, the authors hypothesized that in patients with cardiac arrest with non-shockable rhythm, earlier administration of epinephrine would improve in-hospital survival and neurologic outcome.

The large observational prospective "Get With The Guidelines-Resuscitation" AHA registry was used to identify index pulseless events for which the initial cardiac rhythm was asystole or pulseless electrical activity, in 570 hospitals between January 1, 2000 to November 19, 2009. The primary exposure of interest in the study was the time to epinephrine administration. The primary outcome was survival to hospital discharge and secondary outcomes included sustained return of spontaneous circulation, survival to 24 hours, and survival to hospital discharge with favorable neurologic status. Multivariable logistic regression models were constructed to assess the independent relation between time to epinephrine administration and survival to hospital discharge.

In addition, three types of sensitivity analysis were performed. The first, was an assessment of the primary exposure of delay in administering epinephrine after the initiation of chest compressions for patients where cardiopulmonary resuscitation was initiated within the first minute of recognition of cardiac arrest. Second, patients were categorized into quarters of the time distribution of delivery of the first epinephrine dose in order to assess residual treatment bias in timing of delivery of epinephrine, as the three-minute categorization scheme was developed from expert opinion and current ACLS guidelines. Third, the crude survival rates in patients who were excluded from the primary analysis because of missing covariate data were compared to those patients included in the primary analysis.

Data from 570 hospitals identified 25,095 adult patients who had an in-hospital cardiac arrest with asystole (55%) or pulseless electrical activity (45%). The median time to epinephrine administration was three minutes (interquartile range [IQR]: 1-5 minutes) and the median number of doses administered was three (IQR: 2-4). Sustained return of spontaneous circulation occurred in 12,215 patients (49%), with 6,820 (27%) surviving to 24 hours, 2,603 (10%) surviving to hospital discharge, and 1,601 (7%) surviving with favorable neurologic outcome. There was a stepwise decrease in survival in-hospital with increasing time from the first epinephrine dose. When looking at the time to administration in three-minute intervals, a significant stepwise decrease in-hospital survival with increasing time interval was observed.

The first sensitivity analysis demonstrated that increasing time between initiation of cardiopulmonary resuscitation and epinephrine administration was associated with a lower probability of in-hospital survival. The second analysis revealed a stepwise decrease in survival in hospital with increasing quarter of the first epinephrine dose. Lastly, the post hoc sensitivity analysis found no significant difference in survival rates between those with and without complete covariate data.

The study concluded that for patients who experience a cardiac arrest in hospital with a non-shockable rhythm,

earlier administration of epinephrine was strongly associated with increased probability of return of spontaneous circulation, 24-hour survival, in-hospital survival, and overall neurologically intact survival, and that delayed administration was associated with lower probability of survival. These associations remained in the aforementioned sensitivity analyses. Some of the limitations of the current study were its retrospective nature with the possibility of unmeasured confounding, as well as the potential variability in data quality with the registry drawing from different healthcare systems across the country. In addition, data on neurologic outcomes were unavailable for a small number of patients and the authors were unable to assess the quality of cardiopulmonary resuscitation in each case and whether interruptions in chest compressions were related to the outcomes.

The authors suggest the physiologic rationale for early administration of epinephrine in patients with cardiac arrest is that epinephrine is a potent peripheral vasoconstrictor as well as a coronary artery vasodilator, which increases coronary perfusion pressure, associated with return of spontaneous circulation. Current standard of care focuses on cardiopulmonary resuscitation only, even with the majority of cardiac arrests being non-shockable rhythms. With defibrillation not being useful for most cardiac arrests, the authors suggest that future quality metrics could instead focus on shortening the time to administration of epinephrine.

Conclusions

- The authors concluded that in patients with non-shockable cardiac arrest in hospital, earlier administration of epinephrine is associated with a higher probability of return of spontaneous circulation, rates of survival in hospital, and neurologically intact survival
- The timing of epinephrine is important in resuscitation efforts, as more favorable outcomes were observed with early delivery, even after adjustment for delays in the initiation of cardiopulmonary resuscitation

Table 2. Survival in Patients With In-hospital Cardiac Arrest According to Timing of Administration of Epinephrine within 3 Minute Time Intervals After Arrest

		ODDS RATIO (95% CI)		
TIMING (MINUTES)	NO (%) WHO SURVIVED TO HOSPITAL DISCHARGE	UNADJUSTED	ADJUSTED*	P-VALUE
1–3	1626 (12)	Reference	Reference	—
4–6	667 (10)	1.23 (1.12 to 1.35)	0.91 (0.82 to 1.00)	0.055
7-9	180 (8)	1.54 (1.32 to 1.81)	0.74 (0.63 to 0.88)	<0.001
>9	130 (7)	1.77 (1.47 to 2.13)	0.63 (0.52 to 0.76)	<0.001

*Adjusted for variables as listed in appendix 1, table A.

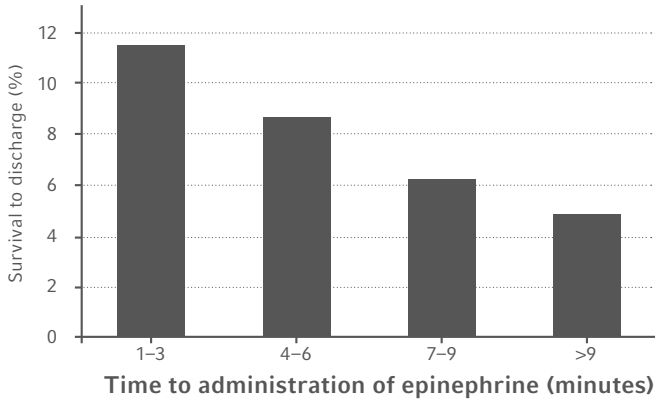

Figure 2. Probability of survival to hospital discharge with delays in time to administration of epinephrine after cardiac arrest, with unadjusted and adjusted odds ratios and 95% confidence intervals. Table A in appendix 1 lists variables used for multivariable adjustments.

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