Immediate Intravenous Epinephrine (Within 1-minute) Versus Early Intravenous Epinephrine (After 1-minute) for In-Hospital Cardiopulmonary Arrest: A Multicenter Retrospective Review

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Abstract

Background: intravenous epinephrine has been a key treatment for cardiopulmonary arrest since the early 1960s. Although, many studies have questioned neurological outcome benefit, it remains to be recommended in international guidelines for its benefit on return of spontaneous circulation (ROSC). The ideal timing for the first epinephrine dose is uncertain. We aimed to look at the association of immediate epinephrine administration (within 1-minute of cardiac arrest recognition) with return of spontaneous circulation (ROSC) up to 24-hours and beyond 24-hours.

Methods: this was a multicenter retrospective chart review of patients undergoing cardiopulmonary resuscitation.

Results: immediate epinephrine administration (within 1-minute) is associated with higher rates of ROSC up to 24-hours (OR=2.36, 95% CI; [1.46-3.81]) and beyond 24-hours (OR=2.26, 95% CI; [1.06-4.83]).

Conclusions: we encourage immediate administration of epinephrine in conjunction with high-quality CPR, as this is associated with higher rates of ROSC.

1. Introduction

Epinephrine has been a key treatment of advanced cardiac life support (ACLS) since cardiopulmonary resuscitation (CPR) guidelines were first published in early 1960s. [1] Epinephrine's alpha-agonist effect causes increased aortic diastolic pressure, thereby augmenting coronary blood flow and cerebral blood flow. [1] Various studies have shown that Epinephrine is associated with increased return of spontaneous circulation (ROSC) rates, owing to the alpha-agonistic effects. [2, 3] However, there is uncertainty about its effect on survival to hospital discharge and neurologic recovery. [4, 5, 6] On the other hand, Epinephrine may produce a mismatch between oxygen demand and delivery which results in lactic acidosis. Moreover, the vasoconstrictor effects may prolong ischemia in some tissues. This has been seen particularly in Swine brain. [7, 8] In fact, direct visualization of brain capillaries reveal constricted microvessels, with little or no perfusion to brain tissue. This effect was attributable to the alpha-1 agonist effects of Epinephrine. [1, 7, 8]

Goto et al, looked at the pre-hospital use of intravenous Epinephrine and its effect on return of spontaneous circulation and neurological outcomes. When given within 9-minutes of cardiac arrest, Epinephrine is associated with higher rates of return of spontaneous circulation (ROSC), when compared with patients not receiving Epinephrine. Neurologic outcomes, however were poorer in patients receiving Epinephrine at any given time during cardiac arrest. [5]

The American Heart Association (AHA) recommends administering Epinephrine as early as feasibly possible and thereafter, every 3–5 minutes. [9] Various trials suggest a time-dependent effect of Epinephrine on outcomes of CPR; earlier administration of intravenous Epinephrine may improve outcomes. [10, 11] However, previous studies have shown delays in the administration of epinephrine are

common in clinical practice, and thus found to be associated with worse outcomes in both adults and children. [12, 13]

A study in 2014 showed that earlier administration of epinephrine in patients with non-shockable cardiac arrest rhythms are associated with increased ROSC and survival. Moreover, a stepwise decrease in survival with every increase in interval of time to epinephrine. [12] Another study in 2016 found that there were improvements in ROSC and survival with functional recovery with timely administration of Epinephrine. [14] Recently, in 2019 a study revealed that delays in intravenous epinephrine administration was associated with lower survival. [15]

The lack of rigorous experimental studies on the clinical outcomes associated with epinephrine has led the resuscitation community to continue to recommend its use in cardiac arrest. However, the PARAMEDIC-2 trial might change the way clinicians think about Epinephrine. The study, conducted by Perkins et al. in the United Kingdom, included 8,014 patients with out-of-hospital cardiac arrest. Patients were randomized to receive either epinephrine (n = 4,015) or placebo (n = 3,999). Primary outcome was 30-day survival, and secondary outcomes included survival to hospital discharge and neurologically intact status. The authors found that administration of epinephrine increased 30-day survival rates (3.2% in the epinephrine group, compared to 2.4% in the placebo group). However, a larger proportion of patients in the epinephrine group were neurologically devastated, with modified Rankin scores of 4–5 (31% in the epinephrine group, compared to 17.8% in the placebo group). This result explains the lack of overall improvement in neurologically intact survival in the epinephrine group, despite the higher rate of overall survival. [16, 17] The authors postulate that, despite improving macrovascular cerebral perfusion pressures, epinephrine may cause microvascular ischemia in the brain, thereby worsening anoxic brain injury. A key finding of the PARAMEDIC-2 trial is that the mean time to Epinephrine administration was 21.5 minutes. This dramatic different time frame precludes generalizability to the in-hospital setting.

Although Epinephrine can increase the likelihood of achieving ROSC, the optimal time of Epinephrine is still uncertain. [17] It seems intuitive that immediate administration of epinephrine in combination with cardiopulmonary resuscitation will maintain perfusion and therefore, reduce bad outcomes. Our primary objective is to compare the association of immediate administration of epinephrine (within 1-minute) with early administration of epinephrine (≥ 2-minutes) with sustained ROSC (≥ 20-minutes – 24-hours) and ROSC for more than 24-hours in non-shockable in-hospital cardiopulmonary arrest.

2. Materials And Methods

2.1 Study design: This is a multicenter retrospective chart review at ***. After obtaining IRB approval (registration no. H-02-J-002, approval no. A00440), researchers retrospectively collected data from cardiac arrest flowsheets from each site between January 2016 and January 2017. We included patients 1) ≥ 18 years-old, 2) non-shockable rhythms, 2) received intravenous Epinephrine during cardiopulmonary resuscitation, 3) witnessed in-hospital arrest and 4) only the first resuscitation attempt (for patients requiring more than one attempt at resuscitation). We excluded patients suffering traumatic arrest, were

pregnant, had shockable rhythms, in the operating room, had a Do-Not-Resuscitate (DNR) order, and aged 17 years-old or less.

2.2 Study setting: It is standard procedure in the *** to activate a code blue announcement throughout the hospital to summon the resuscitation team. The agreed upon definition for cardiopulmonary arrest at each site is cessation of cardiac function manifested as a non-palpable carotid pulse. Upon recognition, personnel are required to call for assistance and immediately start chest compressions. Each site requires medical staff to be certified in basic life support at the minimum. Code blue team members are typically composed of a critical care physician, an anesthesiologist, an intensive care unit nurse, in addition to the primary team and staff nurse from the location of arrest. Team members responding to code blue activations are certified in advanced cardiac life support to ensure standardized treatment. The composition of the resuscitation team may differ from institution to another, based on staff expertise and patient needs. Cardiopulmonary arrest flow sheets may differ in format between institutions; however, all contain key information based on Utstein guideline for documentation. Data included on the flow sheet include: patient information and demographics, time and date of arrest, location of arrest, available team members and time of response, initial and subsequent rhythms, medications and doses administered, type of airway device placed, presence or absence of return of spontaneous circulation, and post-arrest vital signs. Data is entered in real time during the resuscitation by a nurse designated and trained in documentation.

2.3 Definitions: Time to epinephrine was defined as the interval in minutes from recognition of loss of pulse to the first bolus dose of 1 milligram intravenous epinephrine. A registered nurse is dedicated for documenting time intervals during resuscitation in all resuscitations. Each center provide special training for documenting events during resuscitations to ensure standardization.

2.4 Statistical analysis: We used descriptive statistics to characterize the study population. We used t-test to compare the means of age and CPR duration between the 2 groups. We used chi square test to compare number of patients intubated between the 2 groups. Outcomes between the groups were compared using the chi square test. A p-value of less than 0.05 was considered significant. We conducted all analyses using Microsoft Excel 2016 data analysis ToolPak (Redmond, WA, USA).

3. Results

We screened a total of 589 charts from 3 different sites. After excluding patients less than 18-years-old, pregnant women, traumatic cardiopulmonary arrests, cardiopulmonary arrests occurring in the operating room, shockable rhythms, and patients who did not receive intravenous Epinephrine, we were left with 345 patients for analysis. Table 1 shows the baseline characteristics of patients. The mean time to Epinephrine administration was 2.38 minutes (± 5.08 minutes). Sustained return of spontaneous circulation (ROSC) (20-minutes – 24-hours) occurred in 105 patients (30.35%); 47 (13.58%) survived to hospital admission and 13 (3.76%) survived to hospital discharge.

Immediate (within 1-minute) Epinephrine administration was more frequently observed in 211 patients (60.98%), whereas early (≥ 2-minutes) Epinephrine administration was seen in 135 patients (39.02%), as shown in Table 2.

Our results reveal that the immediate administration of intravenous Epinephrine is associated with higher rates of ROSC (20-minutes – 24-hours); 36.67% vs. 19.87% (OR = 2.36, 95% CI; [1.46–3.81]), and higher rates of ROSC (> 24-hours); 14.44% vs. 6.92% (OR = 2.26, 95% CI; [1.06–4.83]) (Table 3). Moreover, age, CPR duration and endotracheal intubation were similar between the 2 groups.

A graphical illustration (Fig. 1) shows a stepwise decrease in sustained ROSC (20-minutes – 24-hours) with every 1-minute delay in Epinephrine administration: 36.67% showed sustained ROSC when receiving their first dose of Epinephrine between 0–1 minute. This is decreased to 21.21% when the first dose of Epinephrine was received between 2–3 minutes, 21.21% when Epinephrine received between 4 – 3 minutes and down to 13.79% when the first dose was administered at 6-minutes or later. Figure 2 also demonstrates a decrease in ROSC for than 24-hours when epinephrine was administered at 2-minutes or later.

Table 1
Baseline characteristics of patients

Characteristic	N (%)
Gender (n = 346)	
Male	208 (60.12%)
Female	138 (39.88%)
Race (n = 347)	
Saudi	181 (52.16%)
Non-Saudi	166 (47.84%)
Mean age in years±(SD)	61.42 ± 18.94
Initial rhythm (n = 346)	
Asystole	215 (62.14%)
Pulseless Electrical Activity (PEA)	131 (37.86%)
Outcome (n = 346)	
ROSC (> 20-min – 24-hrs)	105 (30.35%)
Survival to Admission (> 24-hrs)	47 (13.58%)
Survival to Discharge	13 (3.76%)
Mean Times (n = 346)	
Time to Epinephrine [mean in minutes±(SD)]	2.38±(5.08)
Duration of CPR [mean in minutes±(SD)]	19:06±(10:12)

Table 2
Rate of Immediate Epinephrine (within 1-minute) Administration versus Early Epinephrine (≥ 2-minutes) Administration

	N (346)	%
Immediate (within 1-minute)	211	60.98%
Early (≥ 2-minutes)	135	39.02%

Table 3
Association Between Immediate Administration of Epinephrine (within 1-minute) versus Early Administration of Epinephrine (≥ 2-minutes) With Variable and Outcomes (Mean age, CPR duration, Endotracheal intubation during CPR, ROSC (> 20 minutes but less than 24-hours), Survival to Admission (ROSC > 24-hours))

Variable/Outcome	Immediate (within 1-minute)	Early (≥ 2-minutes)	P-value	Odds ratio [95% CI]
Mean age (in years)	62.75	58.74	1.96	–
CPR Duration (in minutes)	19:06	19:04	1.96	–
Endotracheal intubation during CPR	89 (63.57%)	84 (65.12%)	0.06	–
ROSC (> 20-minutes but less than 24-hours)	77 (36.67%)	32 (19.87%)	< 0.01	2.36 [1.46–3.81]
Survival to Admission (> 24-hours)	40 (14.44%)	9 (6.92%)	0.02	2.26 [1.06–4.83]

4. Discussion

Our findings reveal that immediate administration of intravenous Epinephrine is associated with increased sustained return of spontaneous circulation (ROSC) (20-minutes – 24-hours) and survival to admission. Little controversy exists over the ability of Epinephrine to increase ROSC rates. In aggregate, there is strong agreement across large number of clinical studies, that Epinephrine use improves the chances of ROSC but does not benefit survival. [18, 19, 20] Notably, some studies suggest that Epinephrine might actually worsen neurologic outcome with increasing cumulative dose of Epinephrine. [21] Early Epinephrine administration is practically achievable in-hospital as opposed to out-of-hospital settings. Our study reveals that majority of patients received epinephrine within 1-minute of recognition (60.98%). A study by Hansen at al. [22] conducted a secondary analysis on 26,755 patients in the out-of-hospital setting. A 10-minute cutoff for time to emergency medical services (EMS) arrival to Epinephrine administration was used. The majority received Epinephrine > 10 minutes from EMS arrival (54.2%). The highest survival to discharge was noted when Epinephrine was given before 4 minutes, which occurred in 7% of patients. Moreover, each additional minute of time to from EMS arrival to Epinephrine was associated with 4% decrease in odds of survival to hospital dishcarge (odds ratio [OR], 0.96; 95% confidence interval [CI], 0.95–0.98). However, there are profound differences between patients with in and out of hospital, in terms of patients' characteristics, underlying etiology, treatment and timing of treatment, and outcomes.

Donnino et al. [12] conducted a post hoc analysis of prospectively collected data in a large multicenter registry of in-hospital cardiac arrests (Get With The Guidelines-Resuscitation). They included 25,095 patients from 570 hospitals with asystole (55%) or pulseless electrical activity (45%). The median time to Epinephrine administration was three (interquartile range 2–4). Survival to 24-hours occurred in 6,280 (27%) patients, whereas only 2,603 (10%) survived to dishcarge. A stepwise decrease in survival to

discharge with additional minute of first administration of Epinephrine: 929 (12%) survived when epinephrine was given in the first minute, 392 (12%) in the second minute, 305 (11%) in the third minute, 208 (9%) in the fourth minute, 335 (10%) in the fifth minute, 124 (10%) in the sixth minute, and 310 (7%) in the seventh minute or later ($P < 0.001$). Results of our study reveal slightly higher rates of asystole (62.14%) but less pulseless electrical activity (37.86%). Survival to 24-hours in our study was 30.35% of patients, which is close to results observed by Donnino et al. In our study the mean time to first Epinephrine administration was 2.86 ± 5.06 minutes and most patients received Epinephrine within 1-minute (60.27%) of recognition of cardiopulmonary arrest. We used a cutoff of 1-minute for first Epinephrine administration. This was used due to the time-sensitive interventions required during the low-flow state, in order to maintain coronary and cerebral perfusion without interruption. Results of this study show that immediate Epinephrine administration is associated with higher rates of ROSC (20-minutes – 24-hours) (odds ratio [OR], 2.36; 95% confidence interval [CI], 1.46–3.81) and survival to admission (odds ratio [OR], 2.26; 95% confidence interval [CI], 1.06–4.83) when compared with early Epinephrine. Additionally, Figs. 1 and 2 demonstrate a sharp decrease in ROSC from 36.67% when Epinephrine was administered between 0–1 minutes to 21.21% when Epinephrine was administered between 2–3 minutes and in survival to admission from 14.44% in the 0–1 minute group to 6.92% in the ≥ 2 minute group. Therefore, the number of patients who need to be treated with epinephrine to achieve one patient with ROSC (20 min-24 hrs) is 6 and to achieve one patient with ROSC (> 24-hours) is 13.

While the American Heart Association (AHA) recommend immediate and uninterrupted chest compressions to maintain coronary and cerebral perfusion, no strong recommendations exist in terms of timing of first Epinephrine administration nor do they recommend a maximum dose. In fact, the latest AHA guidelines recommend that Epinephrine be administered as early as feasibly possible and thereafter every 3–5 minute intervals. The physiologic rationale for early Epinephrine administration is strong. The combination of immediate high-quality chest compression and immediate Epinephrine administration could potentially result in better outcomes. Although, the results of our study encourage immediate Epinephrine administration, they question the benefit of Epinephrine after a certain amount of time.

4.1 Limitations

This was a retrospective analysis and therefore are only able to comment on association rather than causation. Data represents experiences from three different sites and therefore, may cause variations in results. Moreover, we did not attempt to adjust for other confounding factors such as; age, underlying diagnosis, initial rhythm, cumulative epinephrine dose, CPR metrics, time and location of arrest, etc. This may preclude the generalizability of our results.

5. Conclusion

Immediate epinephrine administration is associated with better rates of ROSC for up to 24-hours and beyond 24-hours for in-hospital cardiopulmonary arrests with non-shockable rhythms. This is achievable in the in-hospital setting. Therefore, we encourage initiating immediate CPR in conjunction with

immediate epinephrine administration. Larger studies are required to find the true benefit of immediate epinephrine administration.

Declarations

Ethics approval and consent to participate

This study was approved by the *** (registration no. H-02-J-002, approval no. A00440)

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests

Availability of data and material

Data are available upon request from the corresponding author

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Authors contributions

AB conceived, designed the study and drafted the manuscript. MS, AA and AAl collected data and perform statistical analysis. BA, RA, and MA analyzed the results. All authors reviewed, revised and approved the final version.

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Figures

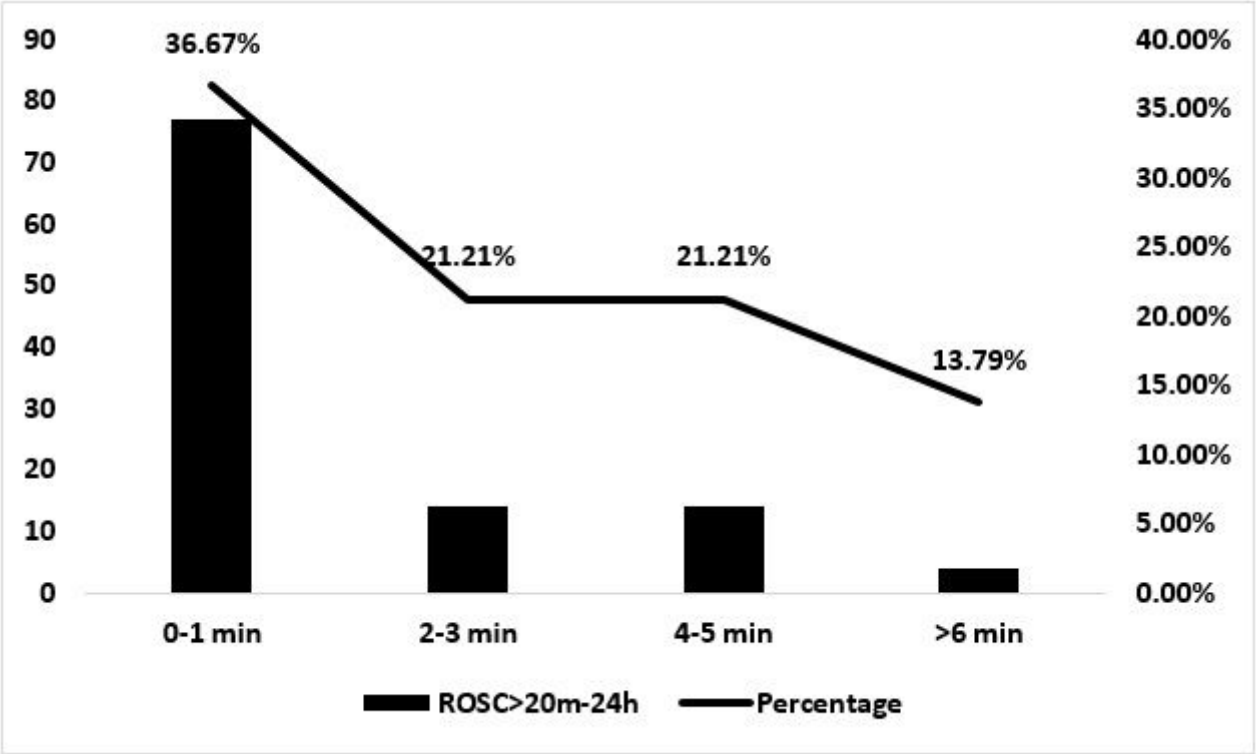

Figure 1

Association Between Timing of First Dose of Epinephrine With Sustained Return of Spontaneous Circulation (≥20-minutes but <24-hours)

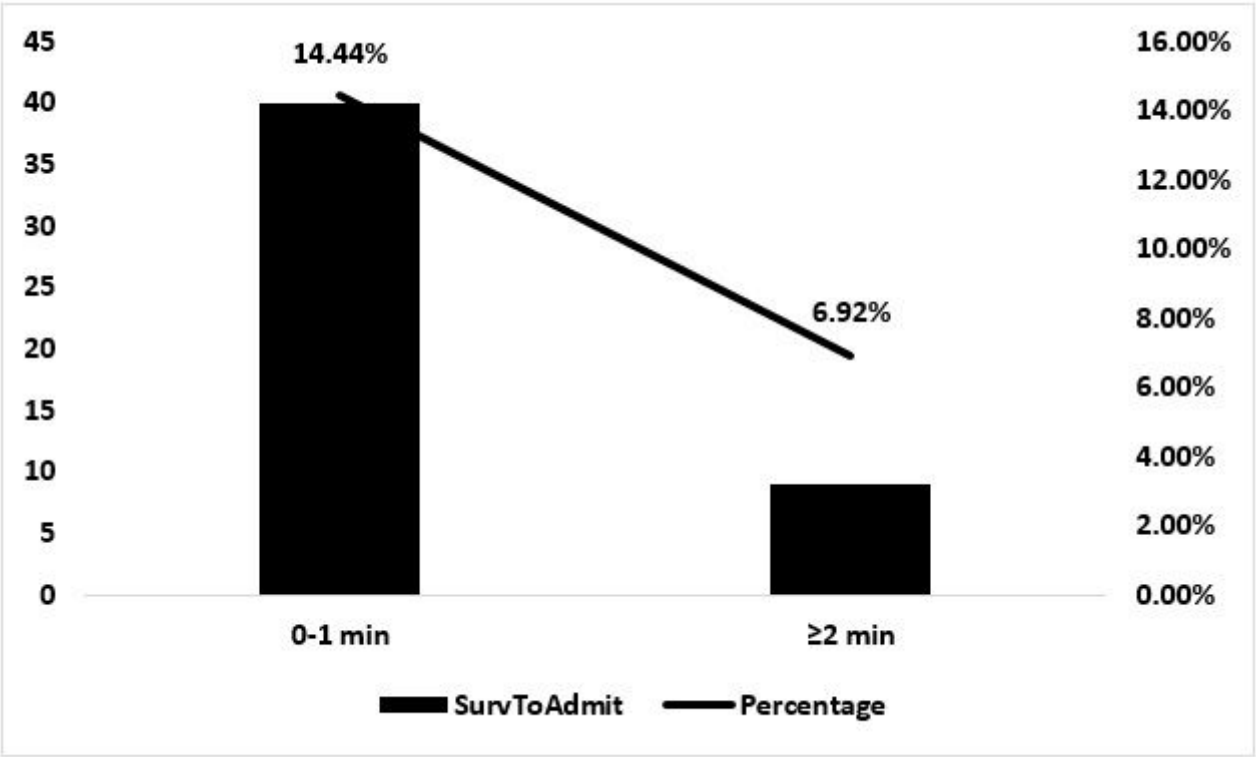

Figure 2

Association Between Timing of First Dose of Epinephrine With Survival to Admission