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Pulseless Electrical Activity: Patient Outcomes with Alteplase Administration in Cardiac Arrest

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Abstract

Purpose: The purpose of this study was to evaluate the timing of fibrinolytic administration post-arrest onset and its effect on patient outcomes including arrest survival.

Methods: We performed a single center, retrospective chart review of patients receiving alteplase for PEA arrest. Outcomes were evaluated in a sub-group of patients, code survivors versus non-survivors. Primary outcome was time period from arrest onset to alteplase administration and its effect on survival. Secondary outcomes included: alteplase dose administered, resuscitation duration post-alteplase administration and return of spontaneous circulation (ROSC) following fibrinolysis. Safety outcomes included the incidence of major and minor bleeding events.

Results: Twenty-seven PEA arrest patients were included. Average time from code onset to alteplase administration was 28 ± 12.5 minutes in the overall cohort. Patients who survived the code (n=5) were administered alteplase within 19.2 ± 10.1 minutes of arrest onset compared with an average post-arrest administration time of 30.1 ± 12.2 minutes in non-survivors (n=22). The mean duration of resuscitation post-alteplase administration was 9 ± 3.7 minutes in the patients who survived versus 12.5 ± 19.0 minutes in patients who expired during the code. There were three major and one minor bleeding event.

Conclusion: We found a high mortality rate in patients with PEA during cardiac arrest. Early alteplase administration was not associated with a statistically significant improvement in patient outcomes including ROSC and code survival. Future studies with larger sample sizes are needed to detect smaller clinically significant differences in code survival with earlier alteplase administration.

Keyword: Pulseless electrical activity; Cardiac arrest; Cardiopulmonary resuscitation; Fibrinolysi; Alteplase

Abbrevation: PEA: Pulseless Electrical Activity; ROSC: Return of Spontaneous Circulation; SD: Standard Deviation; PE: Pulmonary Embolism; AMI: Acute Myocardial Infarction; CPR: Cardiopulmonary Resuscitation; ISTH: International Society of Thrombosis and Haemostasis; DVT: Deep Vein Thrombosis; BMI: Body Mass Index; VTE: Venous Thromboembolism; PRBCs: Packed Red Blood Cells; CRYO: Cryoprecipitate; PLTs: Platelets; t-PA: Tissue Plasminogen Activator

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Background

Cardiac arrest is a rare event associated with significant mortality. Annually in the United States, there are 540,000 cardiac arrest cases, with the majority of episodes occurring out-of-hospital [1]. Approximately 209,000 adults are treated for in-hospital cardiac arrest each year, and it is estimated that 23.9% of those adults survive to discharge [2]. Despite recent advances in emergency response service and post-resuscitation care, survival to hospital discharge rates following out-of-hospital cardiac arrest remains low at only 5%-15% [1]. Adult cardiac arrests caused by ventricular fibrillation or pulseless ventricular tachycardia have been associated with better outcomes compared to those characterized by asystole or pulseless electrical activity (PEA)

rhythms [3]. PEA is present in approximately 20% of all cardiac arrest cases, both in- and out-of-hospital, and survival to hospital discharge occurs in only 4% of patients with this rhythm [4].

Current recommendations support the use of fibrinolytic therapy in cardiac arrest patients, including those with PEA, only when an acute thrombus (e.g. pulmonary embolism [PE] or acute myocardial infarction [AMI]) is known or highly suspected [5]. There are no randomized control trials looking at outcomes following in-hospital undifferentiated cardiac arrest and the use of fibrinolytics, leaving our evidence-based knowledge limited to case studies. Therefore, the potential role of these agents in the treatment of undifferentiated PEA arrest remains controversial. Additionally, there is lack of data describing outcomes related to alteplase administration in this patient population, and whether timing of fibrinolytic administration following arrest onset, fibrinolytic dosing and duration of resuscitation post-administration has a significant effect on rates of code survival. We hypothesized that early administration of alteplase during treatment of in-hospital PEA arrest would be associated with improved patient outcomes including arrest survival.

Methods

Study design and outcome

We conducted a single center retrospective descriptive analysis where medical chart reviews were completed for all patients receiving alteplase for cardiac arrest with PEA. Outcomes were evaluated in a sub-group of patients, code survivors vs. code non-survivors, defined a priori. The primary study outcome was time period from arrest onset to alteplase administration and its effect on code survival. Secondary outcomes included dose of alteplase administered, duration of cardiopulmonary resuscitation (CPR) post-alteplase administration, return of spontaneous circulation (ROSC) following fibrinolysis, and number of patients reaching hospital discharge in code survivors. ROSC was defined as any palpable pulse, regardless of duration. Safety outcomes included incidence of major and minor bleeding events as defined by International Society of Thrombosis and Haemostasis (ISTH) criteria [6]. The ISTH criteria for major bleed was defined as fatal bleeding or symptomatic bleeding in a critical area or organ, or a bleed causing a drop in hemoglobin of ≥ 2 g/dL or leading to transfusions of ≥ 2 units of whole blood or red blood cells. Minor bleeds were defined as all non-major bleeds. Safety outcomes were assessed only in code survivors. The study was approved by our hospital's Institutional Review Board.

Patient selection

The review timeline for patient enrollment spanned a five year time period from January 2010 to December 2014. All adult emergency department or admitted patients who received at least one bolus dose of alteplase during an episode of PEA arrest were included in the analysis. All patients with an active order for alteplase were identified based on hospital medication charging reports. Patients were excluded from the final analysis if they received a dose of alteplase for an indication other than PEA arrest, or if they had an active order for alteplase but never received a dose.

Statistics

Due to the descriptive nature of this analysis, all outcomes were expressed as a mean or median + standard deviation (SD). All continuous variables were analyzed using paired t tests and categorical variables were analyzed using Fisher's exact tests. Based on a reported 22.3% survival rate following in-hospital PEA arrest, this study was designed with an 80% power to detect an absolute increase in the rate of survival of 20% [7]. Twenty patients needed to be analyzed, and two tailed p-values were considered statistically significant at <0.05.

Results

Patient selection

A total of 276 patients were screened for study enrollment in accordance with alteplase charging records. There were 249 patients excluded from the analysis. A total of 241 patients received a dose of alteplase for a non-PEA arrest indication and eight patients had an active order for alteplase, however, the dose was never administered, leaving 27 patients in the final analysis. Indications for non-PEA arrest administration of alteplase included treatment of stroke, systemic fibrinolysis for PE or deep vein thrombosis (DVT), and catheter-directed thrombolysis via the EkoSonic Endovascular System procedure for either PE or DVT. Of the 27 patients included in the final analysis, there were five code survivors and 22 code non-survivors.

Patient baseline demographics are summarized in **Table 1**. The mean age in the overall patient cohort was 61 ± 14.3 years, and code survivors were approximately 13 years younger compared to non-survivors. The majority of patients included in the analysis had a body mass index (BMI)>30. Seventy-eight percent of patients in the overall cohort were either current smokers or had a past medical history significant for smoking. Many of the patients had several risk factors for bleeding post-alteplase administration including, but not limited to, active antiplatelet or anticoagulant therapy (74.1%), a recent bleeding event (33.3%) or surgical procedure performed within the past 6 months (25.9%). Other patients had a history of venous thromboembolism (VTE), either DVT (22.2%) or PE (18.5%). The five most prevalent comorbidities identified in this patient population in descending order of prevalence was hypertension (63%), dyslipidemia (55.6%), diabetes mellitus (37%), asthma/chronic pulmonary obstructive disorder (33.3%), and malignancy (22.2%).

Primary outcome

In the overall patient cohort, the average time from code onset to alteplase administration was 28 ± 12.5 minutes. In code survivors, the average time from code onset to alteplase administration was 19.2 ± 10.1 minutes versus 30.1 ± 12.2 minutes in non-survivors (p=0.073). Primary results are summarized in **Figure 1**, secondary and safety results summarized in **Table 2**.

Secondary outcome

The median dose of alteplase administered was 50 mg administered as a bolus over five minutes. This prescribing pattern is consistent with our institution's recommendations

Table 1: Patient baseline demographics.

	Overall cohort	Code survivors	Code non-survivors
Variable	(n=27)	(n=5)	(n=22)
Age, years*	61 ± 14.3	51 ± 9	64.4 ± 14.2
Weight, kg*	88.6 ± 27.3	87.8 ± 25.9	88.8 ± 28.5
BMI, kg/m2*	30.3 ± 9.6	30.3 ± 8.2	30.3 ± 10.2
Male, n (%)	18(66.7)	4(80)	13(59)
Ethnicity, n (%)			
Caucasian	16(59.3)	2 (40)	14(63.6)
Black	6(22.2)	2 (40)	4(18.2)
Hispanic	4(14.8)	1 (20)	3(13.6)
Other	1(3.7)	0 (0)	1(4.5)
Arrest location, n (%)			
In-hospital	24(88.9)	4(80)	20(90.9)
Emergency room	3(11.1)	1(20)	2(9.1)
Smoking status, n (%)			
Former smoker	14(51.9)	1(20)	13(59.1)
Current smoker	7(25.9)	3(60)	4(18.2)
Home medication, n(%)			
Antiplatelet agent	7(25.9)	1(20)	6(27.3)
Anticoagulant	5(18.5)	1(20)	4(18.2)
Inpatient medication, n(%)			
Antiplatelet agent	4(14.8)	1(20)	3(13.6)
Anticoagulant	16(59.3)	4(80)	12(54.5)
Recent bleeding event Δ, n (%)	9(33.3)	1(20)	8(36.4)
Recent surgery Δ, n (%)	7(25.9)	2(40)	5(22.7)
History of VTE, n (%)			
DVT	6(22.2)	3(60)	3(13.6)
PE	5(18.5)	2(40)	3(13.6)
Prior MI, n (%)	1(3.7)	0(0)	1(4.5)
Other PMH, n (%)			
Hypertension	17(63)	2(40)	15(68.2)
Dyslipidemia	15 (55.6)	2(40)	13(59)
Diabetes mellitus	10 (37)	1 (20)	9 (40.9)
Asthma/ COPD	9 (33.3)	0 (0)	9 (40.9)
Malignancy	6 (22.2)	1 (20)	5 (22.7)
Coronary artery disease	6 (22.2)	1 (20)	5 (22.7)
Congestive heart failure	5 (18.5)	1 (20)	4 (18.2)
Renal disease	4 (14.8)	0 (0)	4 (18.2)

*Data presented as mean + SD; Δ Within past 6 months
BMI: Body Mass Index; VTE: Venous Thromboembolism; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; MI: Myocardial Infarction; PMH: Past Medical History

for dosing and administration of alteplase in cardiac arrest. Mean duration of CPR post-alteplase administration was 9 ± 3.7 minutes versus 12.5 ± 19.0 minutes in code survivors and non-survivors, respectively (p=0.205). Four of the five code survivors received a 50 mg one time bolus administered over 5 minutes, and one code survivor received an initial 50 mg bolus followed by a second 50 mg bolus. Three of the five code survivors had ROSC following fibrinolysis, whereas two code survivors had ROSC prior to alteplase administration. A total of three code survivors reached hospital discharge.

a confirmed AMI per electrocardiogram and cardiac biomarker measurements. Actual arrest etiologies were derived from autopsy reports. Fifteen of the 22 code non-survivors had an autopsy performed. There was a relative even distribution of

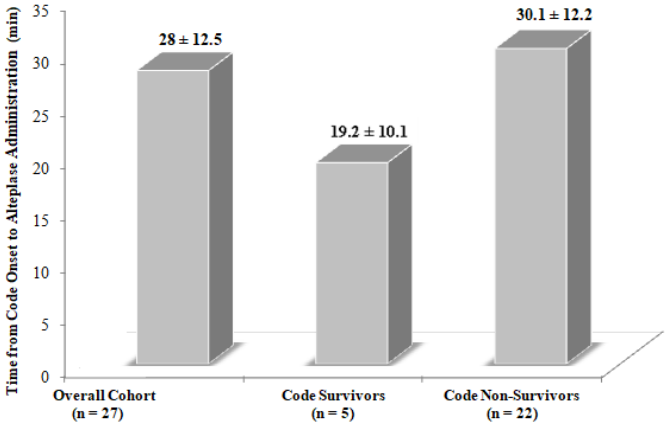

Figure 1 Primary Outcome: Time from Code Onset to Alteplase Administration in Code Survivors vs. Code Non-Survivors. In code survivors, the average time from code onset to alteplase administration was 19.2 ± 10.1 minutes versus 30.1 ± 12.2 minutes in non-survivors (p=0.073). Data presented as mean +/- SD.

Table 2: Secondary and safety outcomes.

	Overall Cohort (n= 27)	Code Survivors (n= 5)	Code Non-Survivors (n = 22)	p value
Secondary Outcomes				
Alteplase dose administered, mg Δ	50	50	50	_
Duration of resuscitation post-alteplase administration, min*	11.89 ± 17.2	9 ± 3.7	12.5 ± 19.0	0.205α
ROSC following fibrinolysis, n (%)	6(22.2)	3 (60)	3 (13.6)	0.056β
Patients discharged from hospital, n (%)	3(11.1)	3 (60)	0 (0)	0.003β
Safety Outcomes†				
Incidence of major bleeding event, n (%) ¥	3(11.1)	3 (60)	0 (0)	0.003β
Incidence of minor bleeding event, n (%) ¥	1 (3.7)	1 (20)	0 (0)	0.185β

Presumed and confirmed arrest etiologies are depicted in **Figure 2**. Fifty-two percent of PEA arrest patients were classified as undifferentiated cases and received alteplase without confirmation of arrest etiology. Forty-one percent of patients had a confirmed PE per chest computed tomography reports and other radiographic imaging sources, and 7% of patients had

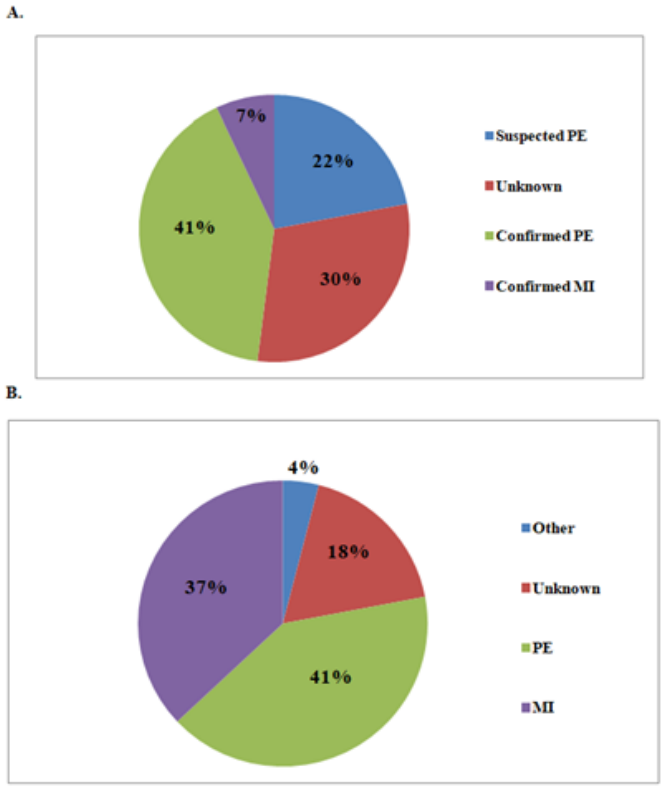

Figure 2 A. Cardiac Arrest Etiologies: Presumed Cause of Arrest Prior to Alteplase Administration. B. Actual Cause of Arrest Confirmed via Autopsy. PE: Pulmonary Embolism; MI: Myocardial Infarction.

PEA arrest cases attributed to an AMI (37%) as to a PE event (41%). Two of the three patients who reached hospital discharge suffered a massive PE leading up to the arrest, and the cause of the arrest in the other survivor remains unknown. All three discharged survivors are currently alive, two with restored baseline functionality and one with extensive anoxic brain injury.

Safety outcome

Safety outcomes were assessed only in code survivors as electronic blood bank administration records were either unavailable or not updated for patients who had expired during the code. In the code survival cohort (n=5), there were three incidents of a major bleeding event (60%) and one incident of a minor bleeding event (20%). The first major bleeding event consisted of a superficial hematoma at the CPR site requiring transfusion with five units of packed red blood cells (PRBCs), two units of cryoprecipitate (CRYO), and two units of platelets (PLTs). Following transfusion and a second PEA arrest event, the patient expired. The second major bleeding event required transfusion for post-alteplase blood loss from oozing line sites, including three units of PRBCs and one unit of CRYO. The patient received in total nine units of PRBCs, six units of CRYO, and ten units of PLTs. The patient expired soon after resuscitation efforts were complete due to bleed expansion. The final major bleeding event was attributed to an extensive gastrointestinal bleed for which the patient received nine units of PRBCs and two units of PLTs. This patient survived to hospital discharge. There was one incident of minor bleeding characterized by an episode of epistaxis and bleeding within the patient's oral cavity.

Discussion

Summary of survival finding

Early administration of alteplase was not associated with a significant improvement in patient outcomes including ROSC and code survival. With a statistically significant effect size of 20% for such a rare event with profound mortality, it is difficult to detect small differences from which clinically significant conclusions can be drawn. Five of the 27 patients included in our in-hospital arrest analysis survived the code and 11% (n=3) survived to hospital discharge. This observed survival rate is higher than the reported 4% survival to discharge rate reported by Abu-Laban and colleagues for out-of-hospital PEA arrest patients, yet lower than the 22.3% survival rate following in-hospital PEA arrest reported by Girotra et al. [7].

Literature review

The most robust clinical trial literature related to use of fibrinolytic agents in the cardiac arrest patient population is limited to studies enrolling patients with out-of-hospital arrest. Decision algorithms and dosing of fibrinolytic agents as they relate to patient outcomes in the undifferentiated cardiac arrest patient population are lacking. In our analysis, we sought to evaluate if early administration of the fibrinolytic agent alteplase during treatment of PEA arrest was associated with improved patient outcomes including code survival. Adults with cardiac arrest typically have underlying coronary artery disease with some degree of myocardial ischemia, and approximately 70% of cardiac arrest cases have been attributed to an AMI or PE [8-10]. For the treatment of both ST-segment elevation AMI and massive PE, current guidelines support the use of thrombolytic therapy as an effective treatment option [11,12]. Despite the known benefit of the use of such agents in the treatment of both AMI and PE, and the high incidence of AMI and PE as causes of sudden cardiac arrest, initiation of thrombolytic therapy during CPR in cardiac arrest patients, both in- and out-of-hospital, is not routinely recommended.

Two studies failed to show an improvement in either short- or long-term outcomes with the administration of fibrinolytics in cardiac arrest [4,9]. Furthermore, Bottiger and colleagues support concern for bleeding complications, including intracranial hemorrhage post-administration [9]. Contrary to this, several case series, retrospective and prospective studies have suggested a benefit from thrombolysis during undifferentiated cardiac arrest, including favorable contributions to hemodynamic stability, ROSC, and improvement in long-term survival and functional recovery [13-16]. Experimental data in animal models suggests that cardiac arrest is associated with disseminated intravascular activation of blood coagulation without adequate endogenous fibrinolysis, leading to the proposed mechanism of thrombolysis during CPR resulting in improvement in microcirculatory flow [5,17]. The imbalance of cascade activation and intrinsic fibrinolysis can lead to microthrombi development even after a short period of CPR [18].

Due to weaknesses attributed to conception and design in the studies just described, there has been increased interest in conducting randomized placebo-controlled trials evaluating the use of fibrinolytics in this patient population. Abu-Laben et al conducted a randomized multicenter trial that looked at the effect of tissue plasminogen activator (t-PA) administration on survival to hospital discharge in adult patients with undifferentiated out-of-hospital PEA arrest [4]. Although the study did not dismiss the potential role for fibrinolytic agents in cardiac arrest, their results suggested that t-PA administration offered no significant benefit to patients with cardiac arrest from undifferentiated PEA [4]. This population differs greatly from our patient cohort who arrested in-hospital. Although Abu-Laban and colleagues did not statistically evaluate time from arrest onset to alteplase administration and the effect on survival, the median interval between time of collapse of the patient in the field to the start of the fibrinolytic infusion was 35 minutes [4]. Fibrinolytic infusion was delayed and a high mortality rate observed. With the code survivors in our analysis, the average time from code onset to alteplase administration was 19 minutes versus 30 minutes in non-survivors. Although our primary outcome did not prove to be statistically significant, we observed a trend towards potential improved survival with earlier alteplase administration.

Unlike the use of t-PA in the treatment of MI and PE, the pharmacokinetics and use of t-PA in cardiac arrest patients is poorly understood. In the previous out-of-hospital arrest study described, 100 mg of t-PA was administered over a 15 minute period during CPR and resuscitative efforts were continued for a minimum of 15 minutes. The authors found no difference in their primary endpoint of survival to hospital discharge with alteplase administration [4]. The first prospective observational study evaluating the efficacy and safety of t-PA following unsuccessful initial resuscitation efforts used an intervention similar to the alteplase protocol utilized in cardiac arrest patients at our institution [15]. A total of 50 mg of t-PA was administered over two minutes following 15 minutes of unsuccessful CPR, with an optional 5,000 unit heparin bolus administered if ROSC was not achieved within 30 minutes. There was a statistically significant increase in ROSC and 24-hour survival in the treatment versus control group. The average duration of CPR in patients with ROSC was 40 minutes in those who received t-PA [15]. Our institution's protocol recommends an optional 50 mg bolus of alteplase to be administered over five minutes in cases of undifferentiated cardiac arrest. It does not recommend adjunct heparin therapy, nor the administration of a second t-PA bolus. The decision to proceed with the aforementioned is left to the discretion of the treating physician. In our study, we observed a nine-minute duration of CPR post-alteplase administration in code survivors. Although better outcomes were observed in the out-of-hospital arrest population described by Bottiger et al., with substantially longer CPR efforts following t-PA than was observed in both our study and the population described by Abu-Laban et al, it is difficult to ascertain if longer CPR efforts post-fibrinolysis improves survival. A larger randomized control trial is needed for validation of such a conclusion.

Bottiger et al reported that one of their most important findings focused on the safety of fibrinolytic therapy during CPR [15]. CPR-related bleeding complications were negligible; however, complications due to bleeding, including gastrointestinal hemorrhage in two patients who received t-PA, necessitated transfusion. The authors questioned whether these complications were causally related to administration of fibrinolytics given that bleeding occurred days following t-PA administration [15]. A larger incidence of major hemorrhage was reported by Abu-Laban and colleagues with the administration of 100 mg of t-PA [4]. With our institution mirroring fibinolytic prescribing patterns most similar to Bottiger et al., our results contrasted more than expected. It is, however, difficult to make such a comparison given bleeding events were only assessed in code survivors in our study. Three of the five patients who survived the code had a major bleeding event requiring significant transfusions, and only one of the three survived to discharge. Concern therefore surfaces regarding the safety fibrinolytic therapy, even with smaller dosing protocols, in this patient population.

Our results support the findings of previous studies in that t-PA should be considered in cardiac arrest patients, including those with undifferentiated PEA, when an acute thrombus (e.g. PE or MI) is known or highly suspected. Other risk factors for post-administration bleeding complications should also be considered, however, the presence of multiple risk factors should not entirely preclude its use given the potential for a life saving opportunity.

Limitations and future research

It is important that the limitations of this study be recognized. We conducted a single center analysis that was retrospective in nature, and the small sample size and highly selective group who received alteplase limited the statistical significance of the results. It is worth noting that the authors retrospectively reviewed five years of data at a large academic medical center and were only able to identify 27 patients who received alteplase during an episode of PEA arrest. This highlights the rarity of PEA arrest events and supports the limited availability of reports assessing the survival margin for arrests specific to a PEA rhythm. Additionally, lack of documentation during codes may have lent itself to missed arrest cases where alteplase was administered, further restricting our sample size. Given the aforementioned and lack of statistical significance of the results, with both primary and secondary outcomes, no definitive conclusions can be drawn from the data described. A larger study, designed with an increased sample size and smaller effect size, would have to be conducted to verify the conclusions drawn by the authors of this manuscript.

Next steps for research include looking into efficacy, both in terms of survival and neurologic outcomes, versus safety of administering a second bolus dose of alteplase in cardiac arrest patients unresponsive to an initial bolus and resuscitative efforts. There is a paucity of evidence evaluating administration of alteplase doses greater than 100 mg and the associated incidence of major bleeding events. Bleeding was assessed only in code survivors in our study, limiting assessment of overall bleeding event rates. Additionally, it would be of interest to

further evaluate the effects of longer CPR efforts, post-alteplase administration, in in-hospital cardiac arrest cases on both ROSC and survival.

Conclusion

In summary, we found a high mortality rate in patients with PEA during cardiac arrest. Early alteplase administration was not associated with a statistically significant improvement in patient outcomes including ROSC and code survival. Future studies with larger sample sizes are needed to detect smaller clinically significant differences in code survival with earlier administration. Further investigation is also warranted to determine the potential benefit from prolonged CPR efforts following alteplase administration in this patient population. We observed a high incidence of major bleeding in our code survivors, with only one major bleed patient surviving to hospital discharge, suggesting that individual bleeding risk should be assessed prior to alteplase administration even in a cardiac arrest patient population where predicted post-arrest prognosis is poor.

Declarations

Ethics approval and consent to participate

This study was approved by Brigham and Women's Hospital Institutional Review Board (reference number: 2014P002009)

Consent for publication

Not applicable

Availability of data and material

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

Competing Interests

The authors declare that they have no competing interests

Funding

There are no sources of funding for the research reported

Author's Contributions

JD performed data collection, analyzed/interpreted the data and was a major contributor in writing the manuscript. IR analyzed/interpreted the data and contributed to manuscript revision. PK analyzed/interpreted the data and contributed to manuscript revision. JF analyzed/interpreted the data and contributed to manuscript revision. KS analyzed/interpreted the data and was a major contributor in writing the manuscript. All authors read and approved the final manuscript

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