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Clinical paper

Epinephrine in children receiving cardiopulmonary resuscitation for bradycardia with poor perfusion

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Abstract

Aim: To determine whether the use of epinephrine in pediatric patients receiving cardiopulmonary resuscitation for bradycardia and poor perfusion was associated with improved clinical outcomes.

Methods: Using the Get With The Guidelines–Resuscitation registry, we included pediatric patients (≤18 years) who received in-hospital cardiopulmonary resuscitation for bradycardia with poor perfusion (non-pulseless event) between January 2000 and December 2018. Time-dependent propensity score matching was used to match patients receiving epinephrine within the first 10 min of resuscitation to patients at risk of receiving epinephrine within the same minute.

Results: In the full cohort, 55% of patients were male and 39% were neonates. A higher number of patients receiving epinephrine required vasopressors and mechanical ventilation prior to the event compared to those not receiving epinephrine. A total of 3528 patients who received epinephrine were matched to 3528 patients at risk of receiving epinephrine based on the propensity score. Epinephrine was associated with decreased survival to hospital discharge (RR, 0.79 [95% CI, 0.74–0.85]; $p < 0.001$), return of spontaneous circulation (RR, 0.94 [95% CI, 0,91–0.96]; $p < 0.001$), 24-h survival (RR, 0.85 [95% CI, 0.81–0.90]; $p < 0.001$), and favorable neurological outcome (RR, 0.76 [95% CI, 0.68–0.84]; $p < 0.001$). Epinephrine was also associated with an increased risk of progression to pulselessness (RR, 1.17 [95% CI, 1.06–1.28]; $p < 0.001$).

Conclusion: In children receiving cardiopulmonary resuscitation for bradycardia with poor perfusion, epinephrine was associated with worse outcomes, although the study does not eliminate the potential for confounding.

Keywords: Epinephrine, Bradycardia, Poor perfusion, Heart arrest, Pediatrics

Introduction

Cardiopulmonary resuscitation (CPR) is provided for bradycardia with poor perfusion in more than 8000 children in the United States each year.[1] Outcomes remain poor, with an overall survival to hospital discharge of 70% in those maintaining a perfusing rhythm and 30% in the one third of patients who deteriorate into pulseless cardiac arrest despite resuscitation.[2]

The 2015 Pediatric Advanced Life Support (PALS) guidelines, published by the American Heart Association, recommend CPR for patients who have persistent bradycardia with poor perfusion despite

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https://doi.org/10.1016/j.resuscitation.2019.12.032
Available online xxx

Table 1 – Patient, event, and hospital characteristics in the full cohort before matching.

	No epinephrine (N = 2279)	Epinephrine (N = 4483)	Standardized difference
Demographics			
Sex			
Male	1277 (56)	2441 (54)	−0.03
Female	1002 (44)	2042 (46)	0.03
Age group			
Neonate (<1 month)	860 (38)	1780 (40)	0.04
Infant (1 month to <1 year)	976 (43)	1317 (29)	−0.28
Child (1 year to <12 years)	374 (16)	1064 (24)	0.18
Adolescent (>12 years)	69 (3)	322 (7)	0.19
Illness category			
Medical			
Cardiac	305 (13)	695 (16)	0.06
Non-cardiac	1083 (48)	1677 (37)	−0.21
Surgical			
Cardiac	193 (8)	802 (18)	0.28
Non-cardiac	307 (13)	549 (12)	−0.04
Newborn[a]	391 (17)	760 (17)	−0.01
Pre-existing conditions[b]			
Heart failure prior to admission	81 (4)	268 (6)	0.11
Heart failure this admission	93 (4)	344 (8)	0.15
Hypotension	326 (14)	1472 (33)	0.45
Respiratory insufficiency	1607 (71)	3104 (69)	−0.03
Hepatic insufficiency	65 (3)	203 (5)	0.09
Renal insufficiency	118 (5)	438 (10)	0.18
Metabolic/electrolyte abnormalities	197 (9)	821 (18)	0.29
Acute non-stroke CNS event	75 (3)	221 (5)	0.08
Baseline depression in CNS function	242 (11)	511 (11)	0.03
Metastatic/hematologic malignancy	34 (1)	132 (3)	0.10
Pneumonia	155 (7)	311 (7)	0.01
Septicemia	211 (9)	775 (17)	0.24
Location and time of arrest			
Location			
Emergency department	63 (3)	207 (5)	0.10
Intensive care unit	1836 (81)	3711 (83)	0.06
Floor			
Without telemetry	125 (5)	105 (2)	−0.16
With telemetry	45 (2)	31 (1)	−0.11
Other[c]	210 (9)	429 (10)	0.01
Time of week[d]			
Weekend	704 (31)	1291 (29)	−0.05
Weekday	1575 (69)	3192 (71)	0.00[f]
Time of day[e]			
Nighttime	678 (30)	1291 (29)	−0.02
Daytime	1601 (70)	3192 (71)	0.02
Year of arrest			
2000–2003	86 (4)	248 (6)	0.08
2004–2006	300 (13)	625 (14)	0.02
2007–2009	415 (18)	824 (18)	0.00[f]
2010–2012	460 (20)	893 (20)	−0.01
2013–2015	489 (21)	992 (22)	0.02
2016–2018	529 (23)	901 (20)	−0.08
Event characteristics			
Witnessed			
Yes	2190 (96)	4386 (98)	0.10
No	89 (4)	97 (2)	−0.10
Monitored			
Yes	2136 (94)	4366 (97)	0.18
No	143 (6)	117 (3)	−0.18
Interventions in place at arrest			
Vasopressors	277 (12)	1663 (37)	0.61
Antiarrhythmics	10 (0)	58 (1)	0.09
Mechanical ventilation	1510 (66)	3606 (80)	0.33
Arterial line	304 (13)	1339 (30)	0.41

Table 1 *(continued)*

	No epinephrine (N = 2279)	Epinephrine (N = 4483)	Standardized difference
Hospital characteristics			
Teaching status			
Major	1639 (72)	3193 (71)	−0.02
Minor	554 (24)	1090 (24)	0.00[f]
Non-teaching	86 (4)	200 (4)	0.04
Type of hospital			
Primary children	1222 (54)	2211 (49)	−0.09
Primary adult	1057 (46)	2272 (51)	0.09
Hospital location			
Rural	20 (1)	39 (1)	0.00[f]
Urban	2259 (99)	4444 (99)	0.00[f]
Hospital geographic location			
North-East	430 (19)	924 (21)	0.04
South-East	597 (26)	1312 (29)	0.07
North-Central	311 (14)	500 (11)	−0.08
South-Central	628 (28)	1240 (28)	0.00[f]
West	313 (14)	507 (11)	−0.07

[a] Defined as being born on the current admission. The newborn illness category was added to the GWTG-R registry in 2005 and removed in 2015.
[b] Definitions have been provided elsewhere.[43]
[c] Including ambulatory or outpatient clinics, diagnostic or interventional areas, operating room, post-anesthesia recovery room, rehabilitation unit, same-day surgical area, and delivery room.
[d] Friday 11 PM to Monday 7 AM.
[e] 11:00 PM to 6:59 AM.
[f] Standardized difference between −0.01 and 0.01.

adequate oxygenation and ventilation.[3] To prevent transition into pulseless cardiac arrest, epinephrine is advised after two minutes of CPR for patients who remain hemodynamically compromised.[3] However, to our knowledge, epinephrine has not been well-studied in this patient population and the association between epinephrine and outcomes remain unknown.

In this study, we aimed to determine whether the use of epinephrine in pediatric patients receiving CPR for bradycardia with poor perfusion was associated with clinical outcomes. We hypothesized that patients receiving epinephrine would have a higher probability of survival compared to those not receiving epinephrine, as well as a lower probability of progression to pulseless cardiac arrest.

Methods

Data source

This study was an analysis of the Get With The Guidelines-Resuscitation (GWTG-R) registry, which is a prospective quality-improvement registry of in-hospital cardiac arrest in the United States. The registry is sponsored by the American Heart Association. The design, data collection, and reliability of the GWTG-R registry has been described in detail elsewhere.[4,5] In the registry, non-pulseless events are defined as the presence of a pulse with inadequate perfusion for which chest compressions are provided with a hospital-wide or unit-wide response by acute care personnel. Hospital-level data were obtained from the 2013 American Hospital Association Annual Survey[6] and linked to the GWTG-R registry by the American Heart Association data management vendor.

IQVA (Cambridge, MA, USA) is the data collection coordination center for the American Heart Association/American Stroke Association Get With The Guidelines® programs. All participating hospitals in the GWTG-R registry are required to comply with local regulatory guidelines. Because data are used primarily at the local site for quality improvement, sites are granted a waiver of informed consent under the common rule.

Study population, exposure, and outcomes

We included pediatric patients (≤18 years of age) with an in-hospital non-pulseless event reported to the GWTG-R registry between January 1, 2000 and December 31, 2018. Patients with a non-index event, patients receiving <2 min of chest compressions, events in the delivery room, and hospital visitors, were excluded from the study, as were patients with missing and inconsistent data on the time to first epinephrine dose, time of progression to no pulse, time to termination of resuscitation, covariates (Table 1), and the primary outcome.

The exposure of interest was use of epinephrine within the first ten minutes of the event. Time to epinephrine was defined as the time interval in minutes from the start of chest compressions until the first administration of epinephrine. Times in the GWTG-R registry are registered as whole minutes, meaning that patients with a time to epinephrine of zero minutes received epinephrine within the same minute as the start of chest compressions. Due to changes in the GWTG-R case report form over the study period, events for which epinephrine was coded as missing were considered to be events for which epinephrine was not provided.

The primary outcome was survival to hospital discharge. The secondary outcomes included sustained return of adequate circulation (ROC), survival to 24 h, favorable neurological outcome at hospital discharge, and progression to pulseless cardiac arrest at any time during the event. Sustained ROC was defined as no further need for chest compressions for at least 20 min, including the initiation of cardiopulmonary bypass or extracorporeal membrane oxygenation. Favorable neurological outcome was defined as a Pediatric Cerebral

Please cite this article in press as: M.J. Holmberg, et al., Epinephrine in children receiving cardiopulmonary resuscitation for bradycardia with poor perfusion, Resuscitation (2020), https://doi.org/10.1016/j.resuscitation.2019.12.032

Performance Category (PCPC)[7] of 1 (normal or no cerebral disability) or 2 (mild cerebral disability) in accordance with the Pediatric Utstein criteria.[8]

Statistical analysis

Descriptive statistics were used to describe the study population. Categorical data are presented as counts with frequencies and continuous data are presented as medians with 1st and 3rd quartiles.

To provide the adjusted association between epinephrine and survival, we used a time-dependent propensity score with risk-set matching. Since the use of epinephrine is likely related to the length of resuscitation and prolonged resuscitation has been associated with worse outcomes,[9] not accounting for the timing of epinephrine is likely to bias the results toward a harmful effect of epinephrine.[10,11] A similar approach has been used in previous studies on cardiac arrest.[12–14]

The propensity score was calculated using a multivariable Cox proportional hazards model with the time to epinephrine as the dependent variable and the variables presented in Table 1 as the independent variables. The proportional hazards assumption was tested by including interaction terms between each independent variable and time. Variables not meeting the proportional hazards assumption (p-value from interaction below 0.01) were included as time-varying variables in intervals of two minutes. Patients were censored upon termination of chest compressions (with or without ROC) or at the time of progression to pulseless cardiac arrest. We performed 1:1 risk-set matching on the propensity score at any given minute using a nearest neighbor-matching algorithm and maximum caliper of 0.01 of the estimated propensity score.[15] Patients receiving epinephrine at any minute (from 0 to 10 min) were separately and sequentially matched to a patient at risk of receiving epinephrine within the same minute (patients undergoing resuscitation for a non-pulseless event who had not yet received

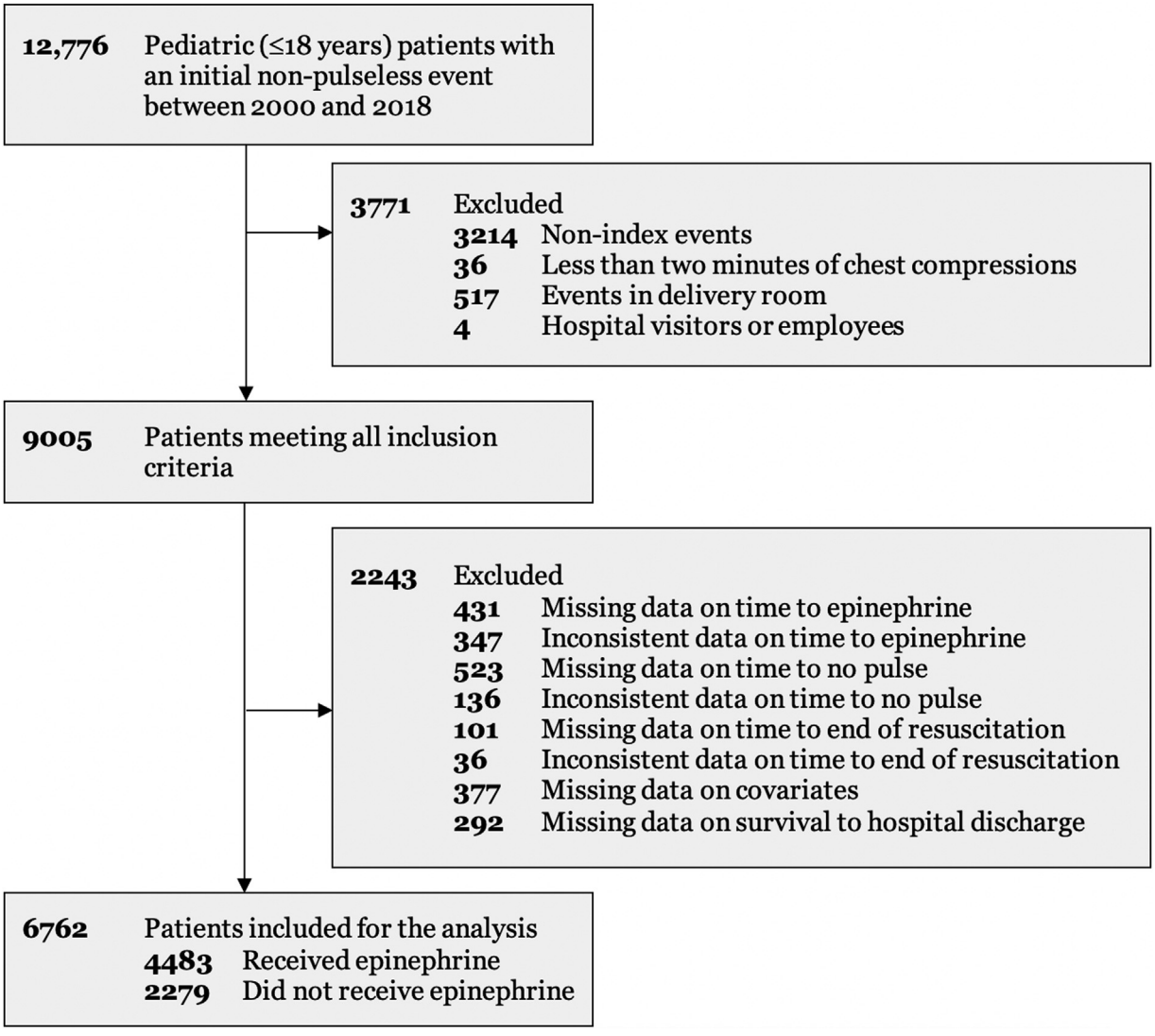

Fig. 1 – Inclusion and exclusion criteria for the primary analysis.
Out of 12,443 pediatric patients with an initial non-pulseless event between 2000 and 2018, we included 6762 patients for the primary analysis, of which 4483 (66%) patients received epinephrine and 2279 (34%) patients did not receive epinephrine at any time during the event.

Please cite this article in press as: M.J. Holmberg, et al., Epinephrine in children receiving cardiopulmonary resuscitation for bradycardia with poor perfusion, Resuscitation (2020), https://doi.org/10.1016/j.resuscitation.2019.12.032

Table 2 – Patient, event, and hospital characteristics in the matched cohort.

	No epinephrine (N = 3528)	Epinephrine (N = 3528)	Standardized difference
Demographics			
Sex			
Male	1916 (54)	1944 (55)	0.02
Female	1612 (46)	1584 (45)	−0.02
Age group			
Neonate (<1 month)	1514 (43)	1463 (41)	−0.03
Infant (1 month to <1 year)	1050 (30)	1072 (30)	0.01
Child (1 year to <12 years)	761 (22)	774 (22)	0.01
Adolescent (>12 years)	203 (6)	219 (6)	0.02
Illness category			
Medical			
Cardiac	564 (16)	561 (16)	0.00[f]
Non-cardiac	1241 (35)	1296 (37)	0.03
Surgical			
Cardiac	588 (17)	619 (18)	0.02
Non-cardiac	427 (12)	415 (12)	−0.01
Newborn[a]	708 (20)	637 (18)	−0.05
Pre-existing conditions[b]			
Heart failure prior to admission	205 (6)	220 (6)	0.02
Heart failure this admission	257 (7)	265 (8)	0.01
Hypotension	1166 (33)	1151 (33)	−0.01
Respiratory insufficiency	2553 (72)	2471 (70)	−0.05
Hepatic insufficiency	143 (4)	159 (5)	0.02
Renal insufficiency	325 (9)	341 (10)	0.02
Metabolic/electrolyte abnormalities	644 (18)	634 (18)	−0.01
Acute non-stroke CNS event	164 (5)	163 (5)	0.00[f]
Baseline depression in CNS function	357 (10)	376 (11)	0.02
Metastatic/hematologic malignancy	86 (2)	97 (3)	0.02
Pneumonia	226 (6)	227 (6)	0.00[f]
Septicemia	613 (17)	616 (17)	0.00[f]
Location and time of arrest			
Location			
Emergency department	132 (4)	143 (4)	0.02
Intensive care unit	3023 (86)	2997 (85)	−0.02
Floor			
Without telemetry	56 (2)	64 (2)	0.02
With telemetry	9 (<1)	18 (1)	0.04
Other[c]	308 (9)	306 (9)	0.00[f]
Time of week[d]			
Weekend	1004 (28)	1039 (29)	0.02
Weekday	2524 (72)	2489 (71)	0.00[f]
Time of day[e]			
Nighttime	1008 (29)	1020 (29)	0.01
Daytime	2520 (71)	2508 (71)	−0.01
Year of arrest			
2000–2003	192 (5)	195 (6)	0.00[f]
2004–2006	481 (14)	492 (14)	0.01
2007–2009	686 (19)	664 (19)	−0.02
2010–2012	758 (21)	730 (21)	−0.02
2013–2015	773 (22)	774 (22)	0.00[f]
2016–2018	638 (18)	673 (19)	0.03
Event characteristics			
Witnessed			
Yes	3449 (98)	3454 (98)	0.01
No	79 (2)	74 (2)	−0.01
Monitored			
Yes	3464 (98)	3451 (98)	−0.03
No	64 (2)	77 (2)	0.03
Interventions in place at arrest			
Vasopressors	1308 (37)	1295 (37)	−0.01
Antiarrhythmics	43 (1)	49 (1)	0.02
Mechanical ventilation	2909 (82)	2864 (81)	−0.03
Arterial line	1049 (30)	1044 (30)	0.00[f]

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Table 2 *(continued)*

	No epinephrine (N = 3528)	Epinephrine (N = 3528)	Standardized difference
Hospital characteristics			
Teaching status			
Major	2475 (70)	2501 (71)	0.02
Minor	921 (26)	900 (26)	−0.01
Non-teaching	132 (4)	127 (4)	−0.01
Type of hospital			
Primary children	1704 (48)	1777 (50)	0.04
Primary adult	1824 (52)	1751 (50)	−0.04
Hospital location			
Rural	26 (1)	29 (1)	0.01
Urban	3502 (99)	3499 (99)	−0.01
Hospital geographic location			
North-East	694 (20)	726 (21)	0.02
South-East	1106 (31)	1051 (30)	−0.03
North-Central	335 (9)	373 (11)	0.04
South-Central	974 (28)	972 (28)	0.00[f]
West	419 (12)	406 (12)	−0.01

[a] Defined as being born on the current admission. The newborn illness category was added to the GWTG-R registry in 2005 and removed in 2015.
[b] Definitions have been provided elsewhere.[43]
[c] Including ambulatory or outpatient clinics, diagnostic or interventional areas, operating room, post-anesthesia recovery room, rehabilitation unit, same-day surgical area, and delivery room.
[d] Friday 11 PM to Monday 7 AM.
[e] 11:00 PM to 6:59 AM.
[f] Standardized difference between −0.01 and 0.01.

epinephrine prior to or within the same minute).[16] Patients were matched up until 10 min after the start of chest compressions, because the use of epinephrine after 10 min was uncommon (Supplemental content). At risk patients also included patients who received epinephrine at a later time point, as sequential matching should not be conditioned on future events.[16,17] For example, a patient receiving epinephrine at minute 3 could be matched with a patient at risk of receiving epinephrine at minute 3, but never received epinephrine or received epinephrine at a later time. Patients at risk were resampled (allowed to be matched more than once) to reduce the number of unmatched exposed patients.

Characteristics of the matched cohorts were compared using descriptive statistics and standardized differences for which a difference between −0.1 and 0.1 was considered negligible.[18] To assess the association between epinephrine and survival, we used the propensity score matched cohort and performed modified Poisson regression (to obtain risk ratios) and linear regression (to obtain risk differences). Generalized estimating equations (GEE) was used to account for the matching of patients, the correlation between resampled patients, and clustering of patients within hospitals.[19] Results are reported as risk ratios and risk differences with 95% confidence intervals.[20,21] All analyses were repeated for the secondary outcomes.

An additional analysis was performed to examine whether the association between the use of epinephrine and survival to hospital discharge varied by the duration of chest compressions, by adding an interaction term to the modified Poisson regression model between the variable for epinephrine use and the time to matching. Separate analyses were performed with time to epinephrine included as a linear continuous variables and categorical variables (≤2 min and >2 min) in the model. We also conducted three predefined subgroup analyses based on age group, illness category, and event location. The subgroup analyses were performed by adding interaction terms between the variable for epinephrine use and the subgroup variable to the modified Poisson regression model in the propensity score matched cohort.

Five predefined sensitivity analyses were performed. First, multiple imputations were performed using the fully conditional specification method to account for missing data on the use of epinephrine, primary and secondary outcomes, and included variables (Table S1).[22] A total of 10 datasets were created.[23] Time to epinephrine, time to pulselessness, and time to end of resuscitation were imputed using Poisson distributions. Propensity score matching and modified Poisson regression was subsequently performed on each of the datasets and combined into one estimate. We did not account for clustering of patients within hospitals and resampling of patients for this analysis. Second, we repeated the analyses while accounting for competing risks using the Fine-Gray method.[24,25] Progression to pulseless cardiac arrest or termination of chest compressions with or without ROC were treated as competing events. The competing risk approach has been used previously with time-dependent propensity score matching.[26] Third, we repeated the primary analysis with ROC defined as no further need for chest compression for at least 20 min without including the initiation of cardiopulmonary bypass or extracorporeal membrane oxygenation. Fourth, we repeated the analysis with favorable neurological outcome defined as 1) a discharge PCPC score of 1, 2 or no increase from baseline, 2) a discharge PCPC score of 1, 2, or 3, and 3) a discharge PCPC score of 1, 2, 3, or no increase from baseline.[14,27] Lastly, we assessed the impact of potential unmeasured confounders not included in the analysis as has been described in detail elsewhere.[28,29]

All secondary analyses should be considered exploratory as no adjustments were made for multiple comparisons.[30] All analyses were two-sided, with a significance level of $p < 0.05$. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses.

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Results

Patient characteristics

A total of 6762 patients were included for the analysis (Fig. 1). In the full cohort, 3718 (55%) patients were male and 2640 (39%) patients were neonates (<1 month). Additional patient, event, and hospital characteristics are provided in Table 1. In the study population, 4483 (66%) patients received epinephrine while having a pulse and 2279 (34%) did not receive epinephrine. The median time to epinephrine from the start of chest compressions was 2 (quartiles: 1, 4) minutes (Fig. S1 in Supplementary content). There was a decrease in the proportion of patients receiving epinephrine over time (82% in 2000 and 66% in 2018; p = 0.01 for trend; Fig. S2 of Supplementary content).

Outcomes in the full cohort

A total of 3496 [52%] patients survived to hospital discharge. In the unadjusted analysis, the use of epinephrine at any time during CPR was associated with decreased survival to hospital discharge (1711 [38%] vs 1785 [78%]; RR, 0.49 [95% CI, 0.47−0.51]; p < 0.001). Epinephrine was also associated with decreased ROC (3039 [77%] vs 2076 [98%]; RR, 0.78 [95% CI, 0.77−0.80]; p < 0.001), survival to 24 h (2606 [58%] vs 2152 [94%]; RR, 0.62 [95% CI, 0.60−0.63]; p < 0.001), and favorable neurological outcome (795 [21%] vs 849 [54%]; RR, 0.39 [95% CI, 0.36, 0.42]; p < 0.001). In the 1883 (28%) patients who deteriorated into a pulseless cardiac arrest during CPR, epinephrine was associated with increased progression to pulselessness (1751 [39%] vs 132 [6%]; RR, 6.74 [95% CI, 5.69−7.99]; p < 0.001). Risk differences with 95% confidence intervals are provided in Table 3.

Outcomes in the matched cohort

Out of the 6762 patients in the full cohort, 4978 (74%) patients were matched with replacements based on the propensity score (Fig. S3). Patients were well-matched, with a standardized difference between −0.1 and 0.1 for all variables. Out of 3528 matched patients in the no epinephrine group, 2058 (58%) patients received the exposure at a later time point of which 297 (14%) patients received epinephrine after deteriorating into pulseless cardiac arrest. Patient, event, and hospital characteristics are provided in Table 2.

In the matched cohort, the use of epinephrine within the first 10 min of CPR was associated with decreased survival to hospital discharge (1353 [38%] vs 1707 [48%]; RR, 0.79 [95% CI, 0.74−0.85]; p < 0.001). For the secondary outcomes, epinephrine was associated with decreased ROC (2357 [78%] vs 2609 [83%]; RR, 0.94 [95% CI, 0,91−0.96]; p < 0.001), survival to 24 h (2083 [59%] vs 2441 [69%]; RR, 0.85 [95% CI, 0.81−0.90]; p < 0.001), and favorable neurological outcomes (642 [22%] vs 822 [29%]; RR, 0.76 [95% CI, 0.68−0.84]; p < 0.001). In those deteriorating into a pulseless cardiac arrest during CPR, epinephrine was associated with an increased progression to pulselessness (1067 [30%] vs 914 [26%]; RR, 1.17 [95% CI, 1.06−1.28]; p < 0.001). Risk differences with 95% confidence intervals are provided in Table 3.

Subgroup analyses

The interaction between the time of matching (duration of chest compressions) and epinephrine was statistically significant when

Table 3 – Risk ratios for the unadjusted analysis and propensity score-matched analysis.

Outcomes	Unadjusted analysis				Matched analysis			
	No epinephrine	Epinephrine	RR (95% CI)	RD (95% CI)	No epinephrine	Epinephrine	RR (95% CI)	RD (95% CI)
Survival to hospital discharge	1785/2279 (78.3%)	1711/4483 (38.2%)	0.49 (0.47, 0.51)	−40.1% (−42.4, −38.0)	1707/3528 (48.4%)	1353/3528 (38.4%)	0.79 (0.74, 0.85)	−10.0% (−12.9, −7.1)
Return of adequate circulation	2076/2120 (97.9%)	3039/3954 (76.9%)	0.78 (0.77, 0.80)	−21.0% (−22.5, −19.6)	2609/3147 (82.9%)	2357/3031 (77.8%)	0.94 (0.91, 0.96)	−5.1% (−7.2, −3.1)
Survival to 24 h	2152/2279 (94.4%)	2606/4483 (58.1%)	0.62 (0.60, 0.63)	−36.3% (−38.0, −34.6)	2441/3528 (69.2%)	2083/3528 (59.0%)	0.85 (0.81, 0.90)	−10.2% (−13.0, −7.3)
Favorable neurological outcome	849/1575 (53.9%)	795/3769 (21.1%)	0.39 (0.36, 0.42)	−32.8% (−35.6, −30.0)	822/2880 (28.5%)	642/2974 (21.6%)	0.76 (0.68, 0.84)	−6.9% (−10.0, −4.0)
Progression to cardiac arrest	132/2279 (5.8%)	1751/4483 (39.1%)	6.74 (5.69, 7.99)	33.3% (31.6, 35.0)	914/3528 (25.9%)	1067/3528 (30.2%)	1.17 (1.06, 1.28)	4.3% (1.7, 7.0)

RR denotes risk ratios; RD denotes risk difference.

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considering time as a continuous variable (p = 0.02 for interaction), with delayed use of epinephrine being more strongly associated with decreased survival to hospital discharge, but not when considering time as a categorical variable (p = 0.07 for interaction). There was also a statistically significant interaction between epinephrine and age group (p = 0.004), illness category (p < 0.001), and event location (p < 0.001). Epinephrine was generally more strongly associated with decreased survival to hospital discharge in younger age groups, those with a medical illness category, and events in locations without telemetry. The results from these subgroup analyses are provided in Fig. 2.

Sensitivity analyses

Data were missing or inconsistent for 2243 (25%) patients with a median number of missing variables of 4 (quartiles: 4, 4; mean: 3.9, SD: 2.9). A total of 9005 patients were included for the propensity score analysis. The 10 imputed datasets included between 9314 and 9446 patients. The results from the imputed analyses were similar to the primary analysis. Epinephrine was associated with a lower risk of survival to hospital discharge (RR, 0.80 [95% CI, 0.75−0.85]; p < 0.001), ROC (RR, 0.94 [95% CI, 0.92−0.96]; p < 0.001), survival to 24 h (RR, 0.86 [95% CI, 0.83−0.90]; p < 0.001), and favorable neurological outcome (RR, 0.83 [95% CI, 0.77−0.89]; p < 0.001). Epinephrine was also associated with a higher risk of progression to cardiac arrest (RR, 1.18 [95% CI, 1.11−1.26]; p < 0.001).

In the analysis accounting for competing risks, 3570 (50%) patients were matched on the propensity score. Patients were well-matched with a standardized difference between −0.1 and 0.1 for all variables. Similar to the primary analysis, the use of epinephrine in this cohort was associated with decreased survival to hospital discharge (RR, 0.81 [95% CI, 0.75−0.87]; p < 0.001), ROC (RR, 0.94 [95% CI, 0.92−0.96]; p < 0.001), survival to 24 h (RR, 0.87 [95% CI, 0.83−0.91]; p < 0.001), and favorable neurological outcome (RR, 0.77 [95% CI, 0.69−0.86]; p < 0.001), as well as increased progression to pulseless cardiac arrest (RR, 1.19 [95% CI, 1.09−1.30]; p < 0.001).

Extracorporeal cardiopulmonary bypass was used in 367 (5%) patients in the full cohort. When defining ROC without including cardiopulmonary bypass, the use of epinephrine remained associated with decreased ROC (RR, 0.94 [95% CI, 0.91−0.96]; p < 0.001).

The results for different definitions of favorable neurological outcome were similar to the primary analyses (Table S2) and the results from the analysis to assess the impact of a potential unmeasured confounder are provided in Fig. S4 of Supplementary content.

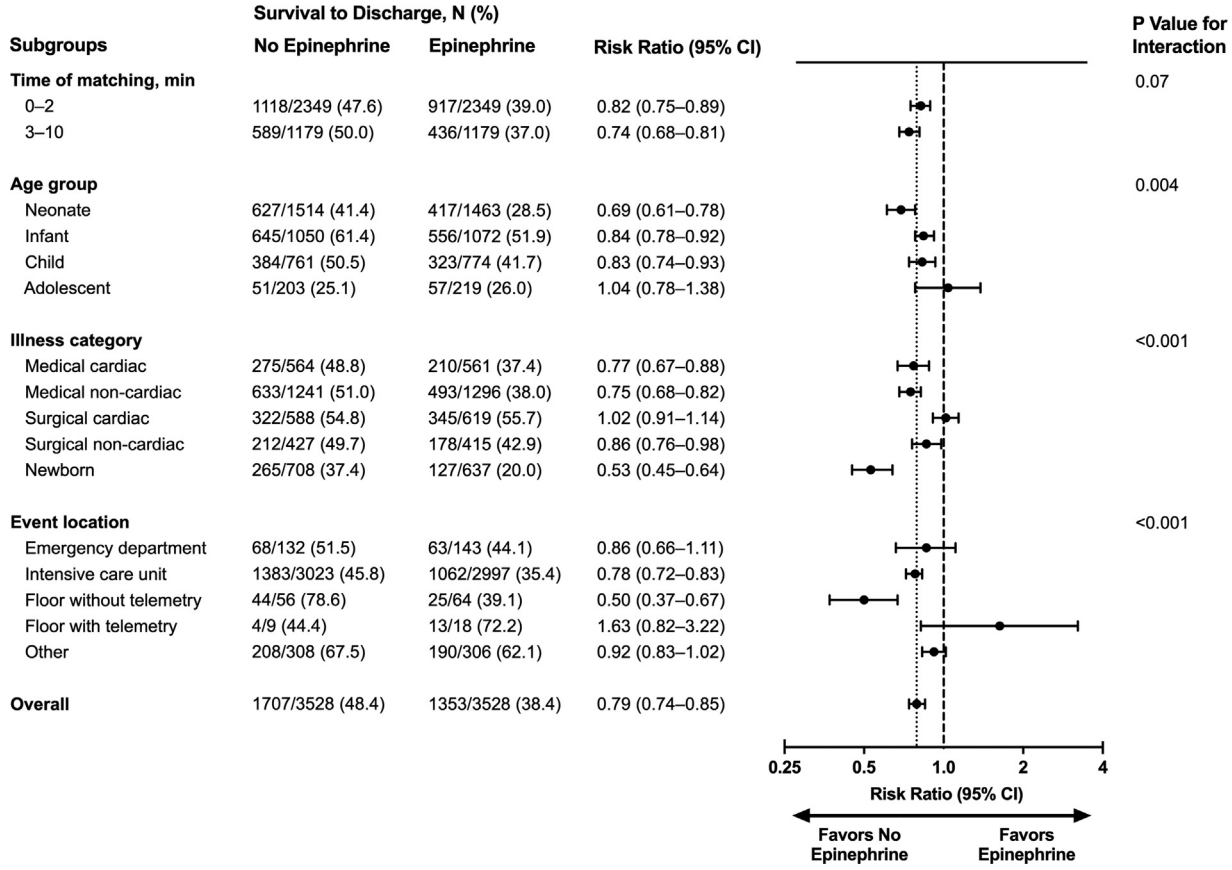

Fig. 2 – Subgroup analyses for survival to hospital discharge in the matched cohort.
Results are reported as risk ratios with 95% confidence intervals. The dotted vertical line (RR: 0.79) represents the risk ratio in the overall cohort and the dashed vertical line (RR: 1.0) represents the risk ratio for no association. The time of matching refers to the minute at which patients in the epinephrine group were matched to patients not receiving epinephrine before or within the same minute.

Discussion

In this study, we used a large in-hospital cardiac arrest registry to assess the association between the use of epinephrine and survival to hospital discharge in children receiving CPR for bradycardia and poor perfusion. We found that epinephrine was associated with decreased survival to hospital discharge, ROC, 24-h survival, and favorable neurological outcomes, as well as an increase in progression to pulseless cardiac arrest. The results remained consistent in multiple sensitivity analyses.

In the raw cohort of our study, approximately two thirds of patients received epinephrine at any time during resuscitation, with a median time to epinephrine of 2 (quartiles: 1, 4) minutes. Despite the wide use of epinephrine in pediatric patients with bradycardia and poor perfusion, there is little data to support or refute the use of epinephrine in this patient population and, to our knowledge, the available studies have largely been limited to animal models, the adult population, and pediatric patients with non-perfusing rhythms.[3,31] For example, one recent randomized controlled trial, including over 8000 adult out-of-hospital cardiac arrests, found improved ROSC and survival to 30 days with the administration of epinephrine compared to placebo.[32] Similar findings have been reported in earlier randomized controlled trials,[33,34] while observational studies have been more conflicting.[35] Studies addressing the use of epinephrine in pediatric pulseless cardiac arrest have been more limited, with the majority of studies comparing high-dose epinephrine to standard-dose epinephrine.[3,31] These previous studies have generally found a lack of benefit for higher dosages, which provided some support for the current dosing in the guidelines.[36–38] However, conducting randomized trials comparing epinephrine to placebo in the pediatric population is challenging and the potential benefit of using epinephrine for pediatric patients with bradycardia and poor perfusion remains uncertain.

The results of the present study were surprising, especially given the high frequency with which epinephrine was used. One potential explanation for these results is that the known detrimental effects of epinephrine outweighs the benefits in this population of patients with non-pulseless events. Epinephrine stimulates α-adrenergic and β-adrenergic receptors, where the α-adrenergic effects are of primary value in resuscitation as they increase peripheral vascular resistance and coronary perfusion pressure.[39] The β-adrenergic effects of epinephrine may increase myocardial oxygen demand, which could be particularly detrimental for children receiving CPR for bradycardia with poor perfusion caused by persistent hypoxia[40] — a common mechanism of cardiac arrest in young children.[2,5] There was some support for such a relationship in our subgroup analyses, where we found a stronger association with decreased survival to hospital discharge in neonates and newborns compared to older age groups, although this finding does not entirely explain the overall negative direction of our results.

Alternatively, there is a possibility that unmeasured or residual confounding could have influenced our results, despite adjustment for multiple patient, event, and hospital characteristics. We assessed the impact of potential unmeasured confounding in a sensitivity analysis, indicating that a single unmeasured confounder was unlikely to mask a null or positive association between epinephrine and survival to hospital discharge (Fig. S4). However, a combination of confounders such as quality of resuscitation and timing of other interventions (e.g., atropine, intravenous infusion of dopamine), both of which may be associated with the use of epinephrine and outcomes, could have confounded the results. There was also some data to support a greater severity of illness in patients receiving epinephrine with more patients requiring vasopressors and mechanical ventilation prior to the event (Table 1). While we adjusted for these characteristics in our analyses, residual or unmeasured confounding may have been present and more granular data could have improved the validity of our results. Moreover, patients deteriorating into pulseless cardiac arrest have a higher probability of receiving epinephrine and decreased survival to hospital discharge.[2] If patients deteriorated into pulseless cardiac arrest (or near pulseless cardiac arrest) prior to receiving epinephrine, reverse causation could bias the results towards a harmful effect of epinephrine. In our unadjusted analyses, there was some indication of this with a very strong and implausible association between epinephrine administration and progression to pulseless cardiac arrest (RR, 6.74 [95% CI, 5.69−7.99]). Although we tried to adjust for this in the main analysis by using time-dependent propensity score matching and censoring those progressing to pulseless cardiac arrest, misclassification of times, which is known to occur,[41,42] could reintroduce this bias. In comparison to traditional logistic models, our results should be interpreted as the risk of survival in a patient receiving epinephrine at a certain time point compared to a similar patient who had not already or not yet received epinephrine at that same time point.

In conclusion, we found that epinephrine was associated with worse outcomes in children receiving cardiopulmonary resuscitation for bradycardia with poor perfusion, although the study does not eliminate the potential for unmeasured and residual confounding. Further research, using more granular data, is warranted to address this research question.

Conflicts of interest

None of the authors have any conflicts of interest to report.

Sources of funding

There was no specific funding for this study.

Acknowledgements

Mathias J. Holmberg and Lars W. Andersen were responsible for the data acquisition, performed the statistical analyses, and drafted the manuscript. All authors contributed to the design of the study, interpreted the results, and critically revised the manuscript. All authors approved the final manuscript as submitted and agrees to be accountable for all aspects of the submitted work.

Appendix A

Get With The Guidelines®-Resuscitation Investigators

Besides the author Joan S. Roberts, M.D., members of the Get With The Guidelines®-Resuscitation Pediatric Research Task Force include:

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MD, FAAP; Jordan Duval-Arnould, MPH, DrPH; Melanie Bembea, MD, MPH, PhD; Michael Gaies, MD, MPH, MSc; Monica Kleinman, MD; Punkaj Gupta, MBBS; Robert M. Sutton, MD, MSCE, FAAP, FCCM; Taylor Sawyer, DO Med.

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.12.032.

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Please cite this article in press as: M.J. Holmberg, et al., Epinephrine in children receiving cardiopulmonary resuscitation for bradycardia with poor perfusion, Resuscitation (2020), https://doi.org/10.1016/j.resuscitation.2019.12.032

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