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Clinical paper

Adrenaline, ROSC and survival in patients resuscitated from in-hospital cardiac arrest

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Abstract

Objective: To describe how administration of adrenaline is associated with return of spontaneous circulation (ROSC) and 30-day survival in patients with in-hospital cardiac arrest (IHCA).

Design: Retrospective observational study.

Setting: Analysis of data extracted from a national cardiac arrest registry.

Study population: Patients >18 years old with IHCA from January 2015 up to June 2017.

Outcome measures: Primary outcomes were ROSC and 30-day survival. Secondary outcome was survival to hospital discharge with a good neurologic outcome defined as cerebral performance category (CPC) score 1–2.

Results: Of 6033 patients eligible for inclusion, 4055 (67%) received at least one dose of adrenaline. The rate of ROSC was lower in the adrenaline group (72 vs. 98% for shockable rhythm and 50% versus 65% for non-shockable rhythm; $p < 0.0001$ for both). Patients who had been treated with adrenaline showed a lower rate of 30-day survival (30 vs. 85% for shockable rhythm and 12 vs. 48% for non-shockable rhythm; $p < 0.0001$ for both). Survival to hospital discharge with a good neurological outcome was lower in the adrenaline group (22 vs. 80% for shockable rhythm and 8 vs. 41% for non-shockable rhythm; $p < 0.0001$ for both). There was a marked imbalance between the two groups in median duration of cardiopulmonary resuscitation. Stratification by duration of cardiopulmonary resuscitation attenuated the differences in outcomes between treatment groups and in patients with an initial non-shockable rhythm the association between adrenaline and ROSC was reversed to the benefit for adrenaline.

Conclusions: In our cohort of 6033 patients retrieved from a national cardiopulmonary resuscitation registry, administration of adrenaline during resuscitation from IHCA was associated with a lower rate of ROSC and 30-day survival.

Keywords: Cardiac arrest, Adrenaline, In-hospital cardiac arrest, Survival

Introduction

International guidelines for resuscitation from cardiac arrest include administration of adrenaline for an initial non-shockable rhythm and shockable rhythm refractory to defibrillation.[1] Adrenaline recommendations are mainly based on animal data and the association with positive short-term effects on ROSC and survival to hospital admission.[2] However, no sufficiently large clinical trial has established a clear beneficial effect on neurologically favorable survival from the

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https://doi.org/10.1016/j.resuscitation.2019.05.004
Received 24 August 2018; Received in revised form 31 March 2019; Accepted 12 May 2019

use of adrenaline for IHCA. Retrospective observation in patients with out-of-hospital-cardiac-arrest (OHCA) suggest that the use of adrenaline is associated with lower survival rates and worse neurologic outcome.[3–5] The PARAMEDIC2 trial in which patient with OHCA were randomized to adrenaline or placebo, demonstrated increased rates of ROSC and survival at 30 days with adrenaline but neurologically favorable survival was not significantly different between the groups.[6]

Extrapolating these findings to patients with IHCA is precarious as the distribution of prognostic factors such as age, co-morbidities, etiology and initial rhythm is different.[7] Importantly, time from collapse to initiation of cardiopulmonary resuscitation (CPR), defibrillation and drug administration are typically shorter for IHCA than for OHCA, a fact that could influence the effect of drugs administered during resuscitation. Despite such differences, the majority of studies of the use of adrenaline include only patients with OHCA. Because of the lack of data in the in-hospital population, the aim of this study was to describe the association between adrenaline administration and ROSC as well as 30-day survival in patients with IHCA.

Methods

Study design

We conducted a retrospective observational study using data from the Swedish Cardiopulmonary Resuscitation Registry. The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden (Dnr: 667-16).

Registry data

The Swedish Cardiopulmonary Resuscitation Registry is a national registry for in- and out of hospital cardiac arrest. Data on IHCA have been collected since 2006 and currently 98% of Swedish hospitals report to the registry. Patients are included if there is no breathing and no sign of circulation and if CPR, defibrillation, or both are started. Resuscitation data are collected by health care personnel in accordance with the Utstein style.[8] The registry includes characteristics such as age, sex, cardiovascular risk factors and comorbidities (diabetes mellitus, heart failure, stroke, myocardial infarction, estimated glomerular filtration rate <60 ml/min), location of arrest, initiating event, time from collapse to cardiopulmonary resuscitation (CPR), witnessed status, duration of CPR, initial cardiac rhythm (ventricular fibrillation, ventricular tachycardia, pulseless electrical activity or asystole). Data on interventions during CRP include type of airway management, medications administered, use of mechanical CPR and number of attempts with defibrillation. Hospital characteristics include hospital size and number of arrests per year. Survival status at 30 days was polled from the Swedish National Population Registry. Neurological outcome at hospital discharge is reported as CPC score. The CPC score is a 5-point scale depicting neurological status (1 = no major disability, 2 = moderate disability, 3 = severe disability, 4 = coma or vegetative state, and 5 = death).[9]

Study population

The study period ranged from January 1, 2015 to June 30, 2017. In-hospital cardiac arrest was defined as occurring in patients admitted to the hospital (including the emergency department) and where resuscitation was attempted. Eligible patients were those over 18 years of age with an IHCA. Since re-arrest is poorly defined in the register and registration of re-arrests vary between hospitals, only the first event was included for patients with multiple IHCAs during the study period. Patients were included regardless of whether the initial rhythm was known or not. Patients for whom adrenaline administration status or outcome status could not be determined were excluded.

Study variables

Adrenaline treatment was defined as adrenaline administered via an intravenous or intraosseous route during resuscitation. Data on timing and cumulative dose of adrenaline are not available from the registry data.

The primary outcomes were ROSC, defined as sustained spontaneous circulation assessed by the resuscitation team and registered during resuscitation, and survival at 30 days. The secondary outcome was survival to hospital discharge with a good neurologic outcome. A good neurologic outcome was defined as a CPC score of 1–2.

Statistical analysis

Baseline characteristics are presented as number (percentage) for proportions and median (10th, 90th percentile) for continuous variables. Due to the large number of subjects in our study we used the (absolute) standardized difference to assess the balance of baseline characteristics between the two groups. This measure is, in contrast to p-values and hypothesis testing, independent of sample size and thus avoids detecting differences that are clinically meaningless. Values of at least 0.10 were considered to indicate a clinically relevant difference.

For comparison of outcome, though, we applied Fisher's exact test and p-values <0.05 (two-sided test) were considered statistically significant.

In the analysis of ROSC and 30-day survival with patients stratified by initial rhythm and CPR duration we used logistic regression applying Firth's penalized likelihood method to calculate odds ratios with corresponding 95% confidence intervals for adrenaline administration in relation to no adrenaline.

To assess whether each of the baseline characteristics altered the association between adrenaline administration and outcome we used logistic regression, comparing the unadjusted odds ratio for those with non-missing of the specific variable with the odds ratio adjusted for the variable.

All analysis was performed using SAS v9.4 for Windows software.

Results

During the study period, 6623 cases of IHCA with initiation of resuscitation were recorded in the registry. Of these, 6033 could be assessed for eligibility and met the inclusion criteria and thus constituted our study population (Fig. 1).

Characteristics of the study population are listed in Table 1. The patients had a median age of 74 years and 38% were women. The arrest was witnessed in 81% of the patients and 23% had an identified initial shockable rhythm. For the entire group, the rate of ROSC and 30-day survival were 63% and 30%, respectively. Sixty-seven percent (4055 patients) received at least one dose of adrenaline. Patients in

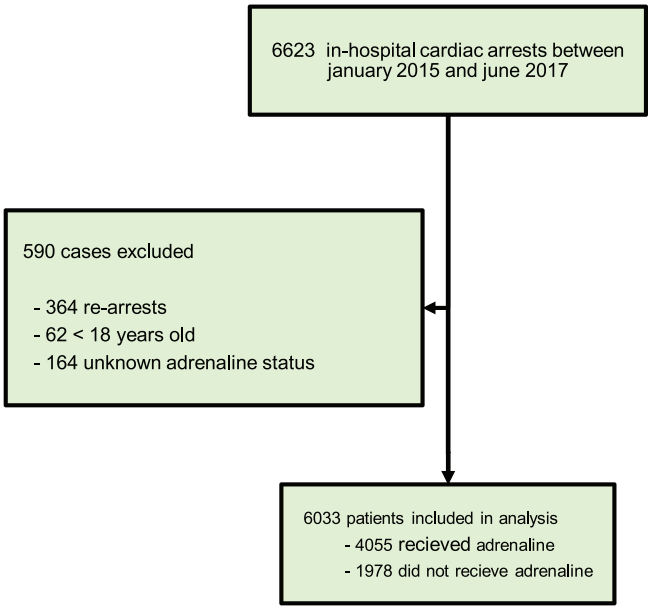

Fig. 1 – Inclusion of study patients.

Table 1 – Patient, hospital, and event characteristics among eligible patients in our cohort.

	Adrenaline			
	All patients (n = 6033)	Yes (n = 4055)	No (n = 1978)	Standardized difference
Year of IHCA				0.00
2015	2430 (40.3)	1627 (40.1)	803 (40.6)	
2016	2388 (39.6)	1615 (39.8)	773 (39.1)	
2017	1215 (20.1)	813 (20.0)	402 (20.3)	
Hospital incidence of IHCA per year				0.13
0–30	1371 (22.7)	973 (24.0)	398 (20.1)	
31–60	1427 (23.7)	984 (24.3)	443 (22.4)	
61–100	1979 (32.8)	1325 (32.7)	654 (33.1)	
>100	1256 (20.8)	773 (19.1)	483 (24.4)	
Age (years)	74 (55, 87)	74 (56, 87)	74 (54, 88)	0.02
Women	2305 (38.2)	1553 (38.3)	752 (38.0)	0.01
Previous history				
Heart failure (8.4)[a]	1811 (32.8)	1263 (34.2)	548 (29.9)	0.09
Diabetes (3.2)	1615 (27.7)	1165 (29.8)	450 (23.4)	0.14
Myocardial infarction (5.6)	1286 (22.6)	852 (22.4)	434 (23.1)	0.02
Stroke (3.4)	678 (11.6)	460 (11.7)	218 (11.4)	0.01
Respiratory insufficiency (5.1)	1362 (23.8)	1023 (26.6)	339 (18.0)	0.21
Malignancy (4.7)	1229 (21.4)	851 (22.0)	378 (20.0)	0.05
Renal dysfunction (eGFR < 60) (12.5)	3309 (62.7)	2356 (66.6)	953 (54.7)	0.24
Ongoing disease				
Myocardial infarction (9.8)	1319 (24.2)	821 (22.7)	498 (27.3)	0.11
Stroke (5.3)	182 (3.2)	125 (3.3)	57 (3.0)	0.02
Initiating event (22.4)				
Primary arrhythmia	1081 (23.1)	487 (15.9)	594 (36.8)	0.49
Myocardial ischemia/infarction	1360 (29.1)	861 (28.1)	499 (30.9)	0.06
Respiratory insufficiency	663 (14.2)	537 (17.5)	126 (7.8)	0.30
Hypotension	280 (6.0)	213 (6.9)	67 (4.2)	0.12
Acute pulmonary oedema	181 (3.9)	152 (5.0)	29 (1.8)	01.8
Location				
CCU/Cath lab/ICU/OR	1994 (33.1)	1205 (29.7)	789 (39.9)	0.21
Coronary care unit	881 (14.6)	480 (11.8)	401 (20.3)	0.23
Coronary laboratory	481 (8.0)	229 (5.6)	252 (12.7)	0.25
Intensive care unit	504 (8.4)	412 (10.2)	92 (4.7)	0.21
Operating room	128 (2.1)	84 (2.1)	44 (2.2)	0.01

Table 1 *(continued)*

	Adrenaline			
	All patients (n = 6033)	Yes (n = 4055)	No (n = 1978)	Standardized difference
Emergency department	717 (11.9)	492 (12.1)	225 (11.4)	0.02
General wards	2927 (48.5)	2105 (51.9)	822 (41.6)	0.21
Intermediary wards	26 (0.4)	14 (0.3)	12 (0.6)	0.04
Lab, X-ray, polyclinic,	256 (4.2)	174 (4.3)	82 (4.1)	0.01
Other	113 (1.9)	65 (1.6)	48 (2.4)	0.06
Witnessed (1.5)	4779 (80.5)	3113 (78.0)	1666 (85.5)	0.20
ECG monitored (1.5)	3127 (52.6)	1920 (48.2)	1207 (61.6)	0.27
Initial rhythm				
VF/VT	1356 (22.5)	541 (13.3)	815 (41.2)	0.66
PEA/Asystole	3410 (56.5)	2792 (68.9)	618 (31.2)	0.81
Unknown	1267 (21.0)	722 (17.8)	545 (27.6)	0.23
CPR duration (minutes) (17.7)	14 (2, 37)	19 (6, 44)	3 (1, 15)	1.69
Delay (minutes)				
Collapse to start of CPR (9.5)	0 (0,1)	0 (0,2)	0 (0,1)	0.06
Collapse to ECG recording (42.4)	0 (0,5)	0 (0,5)	0 (0,3)	0.33
Collapse to first defibrillation[b] (10.1)	1 (0,5)	2 (0,6)	1 (0,3)	1.19
No. of defibrillations[b] (2.8)	1 (1,5)	3 (1,7)	1 (1,3)	0.71
Treatment				
Intubation (1.5)	3049 (51.3)	2821 (71.1)	228 (11.6)	1.52
Antiarrhythmics (4.2)	804 (13.9)	584 (15.2)	220 (11.3)	0.11
Acidosis (4.5)	750 (13.0)	728 (19.1)	22 (1.1)	0.62
Defibrillation				
Of all patients (1.5)	1833 (30.8)	1041 (26.2)	792 (40.3)	0.30
Of VF/VT patients (0.3)	1272 (94.2)	521 (96.8)	751 (92.4)	0.20
Of PEA/Asystole patients (0.8)	403 (12.0)	393 (14.3)	10 (1.3)	0.48
Of patients with unknown rhythm (2.6)	158 (12.8)	127 (18.3)	31 (5.7)	0.39

Results presented as number (percentage) or median (10th, 90th percentile).
[a] Percentage of patients where information was missing.
[b] Of defibrillated patients with VF/VT as initial rhythm.

the adrenaline group were less prone to have a primary arrhythmia as the initiating event and were less monitored on telemetry. Delays from collapse to start of CPR, to ECG recording and to first defibrillation were short in both groups, although there was an imbalance between the groups regarding the latter, with longer delay in the adrenaline group. Defibrillation in patients with an initial rhythm of asystole or PEA was significantly more common in the adrenaline group. The largest imbalance between the two groups was found for duration of CPR (Fig. 2), which was substantially longer in the adrenaline group, and for intubation treatment, which was much more common in the adrenaline group.

Outcome variables are displayed in Table 2. The rate of ROSC and 30-day survival as well as discharge with a good neurological outcome were all significantly lower in the adrenaline group, regardless of initial rhythm. Among the patients who survived to discharge, a majority had a good neurological outcome.

In the secondary analysis, adjusting for baseline characteristics one at the time, only initial rhythm and CPR duration altered the

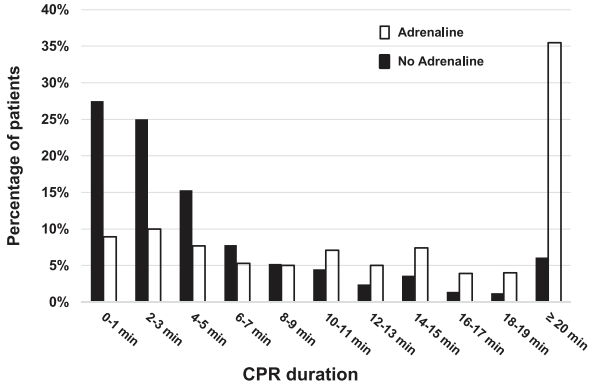

Fig. 2 – Distribution of CPR duration in patients receiving adrenaline (□) and not receiving adrenaline (■).

Table 2 – Primary and secondary outcomes in our cohort.

	VF/VT Patients				PEA/asystole patients				Patients with unknown rhythm			
	Adrenaline				Adrenaline				Adrenaline			
	All (n = 1356)	Yes (n = 541)	No (n = 815)	p*	All (n = 3410)	Yes (n = 2792)	No (n = 618)	p*	All (n = 1267)	Yes (n = 722)	No (n = 545)	p*
ROSC any time	87.6	72	97.8	<0.0001	52.7	50.0	64.7	<0.0001	65.2[1]	59.4[1]	72.8	<0.0001
Discharged alive	63.2[1]	29.8[1]	85.7[1]	<0.0001	17.6[1]	11.1	47.5[1]	<0.0001	28.5[1]	14.6[1]	47.1[1]	<0.0001
Discharged with CPC score 1–2												
Of those discharged alive	94.4[3]	86.6[3]	96.1[3]	0.0001	90.5[3]	86.4[3]	94.6[3]	0.003	85.5[3]	83.8[4]	86.1[3]	0.003
Of all patients	56.2[3]	22.0[2]	80.1[3]	<0.0001	13.2[1]	7.5[1]	40.7[3]	<0.0001	20.6[2]	9.1[2]	36.6[2]	<0.0001
30-day survival	63	30.5	84.7	<0.0001	18.1	11.6	47.8	<0.0001	28.9	15.1	47.1	<0.0001

Results presented as percentage.
[1]1–5% missing; [2]5–10% missing; [3]10–25% missing; [4]>25% missing.
* p-Value for difference between adrenaline and no adrenaline.

association between adrenaline treatment and the two primary outcomes to more than a slight degree (Supplemental Table S1).

When grouping the patients according to initial rhythm and intervals of CPR duration, we observed a lesser difference between the treatment and non-treatment groups in almost all intervals for both primary outcomes. For patients with initial asystole or PEA, the relation between the groups was even reversed in all but one interval and their weighted average showed a significant association between adrenaline administration and a higher rate of ROSC (Fig. 3 and Supplemental Table S2).

Discussion

In the present study, our principal finding was that administration of adrenaline during resuscitation from IHCA was associated with a lower rate of ROSC, 30-day survival and hospital discharge with good neurological outcome defined as CPC 1–2. However, in a secondary analysis with patients stratified according to CPR duration, adrenaline administration was associated with a higher likelihood for ROSC in patients with an initial non-shockable rhythm.

Earlier randomized clinical trials in OHCA patients,[2,10] have demonstrated an association between adrenaline and a higher rate of ROSC, especially for patients with a non-shockable rhythm. In our cohort patients with an initial non-shockable rhythm, in whom adrenaline was administered, were more likely to receive defibrillations, suggesting that they converted to a shockable rhythm during resuscitation, and also had a higher rate of ROSC when stratified by duration of CPR. Contrary to this, in patients with an initial shockable rhythm, adrenaline was associated with lower rate of ROSC also when we stratified patients by duration of CPR. This is of special concern since these patients should have a good prognosis as delay to CPR and defibrillation is short in the hospital setting. In line with these findings is a recent study by Andersen et al. on IHCA patients suggesting that early administration of adrenaline to patients with an initial shockable rhythm was associated with worse outcome.[11] As previously demonstrated, initial rhythm correlates with the etiology in IHCA which could explain the interaction between adrenaline and initial rhythm on ROSC in patients with IHCA.[12] Patients in our cohort in whom adrenaline was administered had a lower 30-day survival, regardless of initial rhythm. This is consistent with many,[13–15] although not all,[16] retrospective observational studies on adrenaline in OHCA. However, the PARAMEDIC2 trial refuted the belief that adrenaline is casually linked with lower survival in OHCA.[6] As with prior observational trials, the negative association we found between adrenaline and survival can be questioned as the propensity for receiving adrenaline is difficult, if not impossible, to match between groups. The administration of adrenaline is inherently linked with longer duration of CPR, which is strongly associated with worse outcomes.[17,18] Patients who do not get ROSC quickly will have continued CPR and will be increasingly likely to receive adrenaline. Furthermore, adrenaline could alter the duration of CPR as it could increase (or decrease) the likelihood of achieving ROSC. This issue with retrospective analysis of intra-cardiac arrest interventions has been termed “resuscitation time bias” and is demonstrated in our cohort where duration of CPR was the covariate with the largest effect on the association between adrenaline exposure and outcome (Supplementary Table S3).[19]

Despite guideline recommendations, there is a scarcity of data on adrenaline in patients with IHCA, particularly in prospective clinical trials. Van Walraven et al. evaluated the association between administration of adrenaline and short-term survival in patients with IHCA, showing that adrenaline was associated with lower chance of survival at one hour.[20] More recently, observational studies have evaluated timing of and dosing intervals of adrenaline administration in adult and pediatric IHCA. For both adult and pediatric patients with an initial non-shockable rhythm, shorter time to administration of adrenaline has been associated with a higher probability of survival with a favorable neurological outcome.[21,22] Warren et al. found a correlation between increasing interval between adrenaline dosing and increased survival, raising the question of the most appropriate interval and dosing of adrenaline during in-hospital resuscitation.[23]

With PARAMEDIC2 there is now high quality data on the use of adrenaline in OHCA. However, patients with IHCA constitute a more heterogeneous group in terms of systemic illness and etiology to the

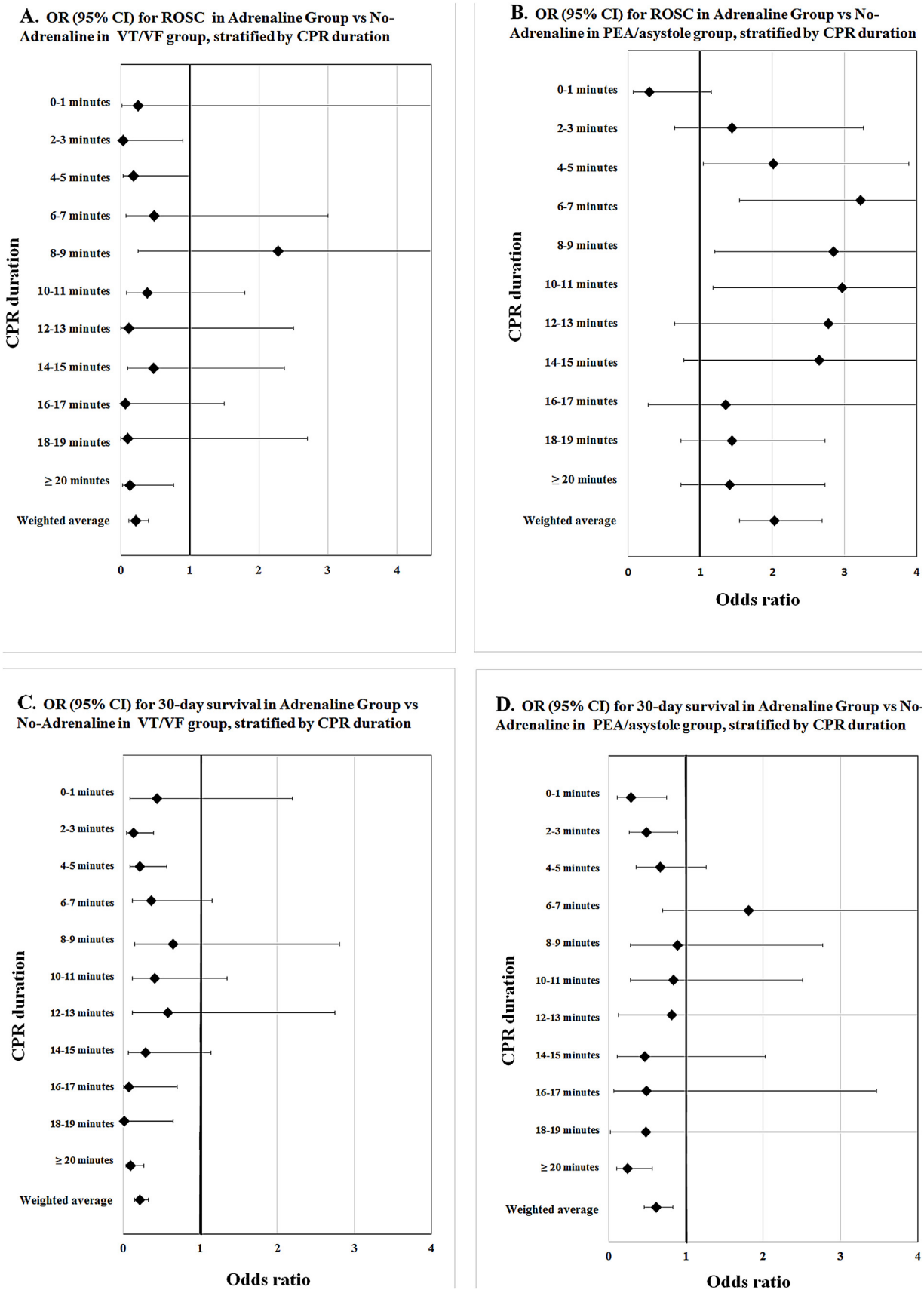

Fig. 3 – Unadjusted odds ratio of major outcomes stratified by CPR duration. Return of spontaneous circulation in adrenaline vs. no-adrenaline group in patients with (A) VT/VF and (B) PEA/Asystole. Survival at 30 days in patients with (C) VT/VF and (D) PEA/Asystole.

arrest.[7,12] Furthermore, both basic and advanced cardiac life support, including defibrillation and drug administration, are provided more rapidly in IHCA. Shorter time to drug administration could have implications as animal data and observational studies suggest a time-sensitive effect of adrenaline administration on survival.[21,22,24] Intuitively, any intervention (even if beneficial) would be likely to fail to improve outcome if the time from collapse to intervention is sufficiently prolonged.[25] In the PARAMEDIC2 trial, the median delay from emergency call until treatment with adrenaline was 21.5 min.[6] For comparison, the median duration of CPR in our study, among patients in the adrenaline group, was 19 min (Table 1). It is also unclear whether long-term survival following IHCA depends on neurological outcome to the same degree as it does in OHCA.[26]

Limitations

Our data highlight the essential problem with observational studies in patients with cardiac arrest, that of confounding by indication. Patients in whom adrenaline is not administered are, at group level, clearly different from patients that receive adrenaline and the propensity of receiving adrenaline is difficult to match.

Furthermore, we did not have information on timing and cumulative dosing of adrenaline, both of which have been previously implicated as important for outcome in IHCA.[11,12,27] We could not determine the reason why some patients did not receive adrenaline despite an assumed indication. Reasons for deviations from guidelines include; inability to establish intravenous or intraosseous access; ethical concerns or perceived futility of further advanced cardiac life support by the resuscitation team. In a hospital setting a deliberate decision not to administer adrenaline could be based on the hemodynamic status of the patient as assessed by the presence of invasive monitoring (e.g. arterial pressure or end-tidal carbon dioxide measurement). However, overall poor adherence to guidelines has previously been found to be associated with worse outcomes in patients with cardiac arrest.[28]

Conclusion

In our cohort of 6033 patients retrieved from a national cardiopulmonary resuscitation registry, administration of adrenaline during resuscitation from IHCA was associated with a lower rate of ROSC and 30-day survival. Given the inherent limitations of our and other observational studies we believe that a prospective trial of adrenaline in IHCA is warranted.

Conflicts of interest

The authors declare that they do not have any conflicts of interest.

Acknowledgement

The authors are indebted to Jonny Lindqvist at Institute of Medicine, Center for Cardiovascular and Metabolic Research, Sahlgrenska University Hospital, for data retrieval from the Swedish Cardiopulmonary Resuscitation registry.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.05.004.

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