Correlation of Adrenaline Doses With the Outcome of Paediatric Out-of-hospital Cardiac Arrest: Secondary Analysis of the SOS-KANTO 2012 Study

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Abstract

Background Out-of-hospital cardiac arrest (OHCA) is very rare in the paediatric population, with an annual incidence of 2-9 cases per 1,000,000 children. The predictive factors for survival included a shorter interval between the time of arrest and hospital arrival, a palpable pulse on presentation in the emergency department (ED), a shorter duration of resuscitation in the ED, and the administration of fewer doses of adrenaline in the ED. This study was conducted to evaluate the interrelationship between the paediatric OHCA outcome and the number of adrenaline doses administered during resuscitation.

Methods The SOS-KANTO 2012 study had enrolled all OHCA patients who were transported to the participant hospitals by emergency medical service personnel. After screening the available data, we included paediatric OHCA patients (aged ≤ 18 years) in this study. The primary outcome was the return of spontaneous circulation (ROSC) and the number of adrenaline doses that were administered, and the secondary outcome was the neurological outcome at 1 month after the OHCA in relation to the number of adrenaline doses.

Results Two hundred sixty-seven patients were included in the final analyses. During CPR, 62 and 205 paediatric patients did and did not achieve ROSC, respectively. Patients who survived to one month after the OHCA received fewer adrenaline doses than patients who died, although there was no significant intergroup difference (3 [1.75-5.25], vs. 4 [2.5-6], $p=0.319$). Patients with a good neurological outcome (PCPC 1-2) received fewer doses of adrenaline than those with an unfavourable neurological outcome (PCPC 3-6), but intergroup difference was not significant. Fewer doses of adrenaline were associated with an improved rate of successful ROSC (odds ratio = 0.80, 95% confidence interval = 0.69-0.92, $p<0.01$).

Conclusion The present study reports associations of the neurological outcomes with adrenaline doses in paediatric patients with OHCA. More than three adrenaline doses were associated with poor neurological outcome, and a favourable outcome occurred infrequently. By using information that was only available up to 1 month after the OHCA, we found that a higher number of adrenaline doses was associated with poor neurological outcome.

Background

Out-of-hospital cardiac arrest (OHCA) is very rare in the paediatric population, with an annual incidence of 2-9 cases per 1,000,000 children (1-5). There are several guidelines on paediatric cardiac arrest, such as the Pediatric Advanced Life Support issued by the American Heart Association: however, the outcome of OHCA in paediatric patients is very poor, with survival rates ranging from 2% to 22% (1-6). In a recent literature review of the science of paediatric resuscitation, Topjian et al reported that 5-10% of paediatric OHCA victims survive to hospital discharge, and only 0-12% of those have a good neurological outcome (7).

The indicators of potentially for successful outcomes in OHCA pediatric patients include a witnessed arrest, the initiation of early bystander cardiopulmonary resuscitation (CPR), an initial shockable rhythm,

and return of spontaneous circulation (ROSC) within 20 minutes (8). However, the outcome for paediatric out-of-hospital resuscitation is substantially worse, because OHCA in children is more commonly caused by severe trauma, prolonged respiratory arrest, or septic shock rather than by a primary cardiac aetiology. Moreover, these etiologies possibly imply a longer hypoxia duration before the actual arrest, and resultant brain and other organ damage (7).

Adrenaline is an essential drug for the resuscitation of OHCA patients. Previous studies have reported that the earlier use of adrenaline in OHCA patients resulted in a better OHCA outcome. Nonetheless, the neurological outcome of OHCA patients who needed more than three doses of adrenaline was poor. There is a substantial amount of research on adrenaline doses and the paediatric OHCA outcome. The predictive factors for survival until hospital discharge included a shorter interval between the time of arrest and hospital arrival, a palpable pulse on presentation in the emergency department (ED), a shorter duration of resuscitation in the ED, and the administration of fewer doses of adrenaline in the ED (9). A recent survey revealed the lack of a set of clear termination criteria and consensus among clinicians on the optimal duration of resuscitative efforts in paediatric patients (10).

Therefore, this study was conducted to evaluate the interrelationship between the paediatric OHCA outcome and the number of adrenaline doses administered during resuscitation.

Methods

Study design and setting

The study undertook a post hoc analysis of the data from the Surveys of Survivors after Out-of-Hospital Cardiac Arrest in Kanto Area (SOS-KANTO) 2012 study that was conducted in 2012 (11-13). The SOS-KANTO 2012 study was a prospective multicenter study that included OHCA patients who were transported to one of the 67 critical care centres in the Kanto area of Japan. The data collection in the SOS-KANTO 2012 study was conducted between January 2012 and March 2013, and the study design and data collection methods of the study have been previously described (12). This study was approved by the relevant institutional review boards of all participating hospitals. As the database used for this study included only anonymised data, the need for written informed consent was waived.

Patients

The SOS-KANTO 2012 study had enrolled all OHCA patients who were transported to the participant hospitals by emergency medical service (EMS) personnel. After screening the available data, we included paediatric OHCA patients (aged ≤ 18 years) in this study. Patients with missing data for the neurological outcome were excluded from the final analysis dataset.

Data collection

The EMS personnel collected prehospitalisation information, including age, sex, initial rhythm, witnessed cardiac arrest, time interval, and prehospital management, in an Utstein-style reporting template.

Physicians collected in-hospital data on resuscitation, aetiology of cardiac arrest, survival, and good neurological outcome at 1 month after the OHCA.

Measurements and definitions

The primary outcome was the ROSC after the cardiopulmonary resuscitation and the number of adrenaline doses that were administered, and the secondary outcome was the neurological outcome at 1 month after the OHCA in relation to the number of adrenaline doses that were administered, as reported in previous study (1, 14-17).

The aetiology of the OHCA was classified as cardiogenic, trauma, and others. The initial cardiac rhythm was categorised as ventricular tachycardia (VT)/ventricular fibrillation (VF) and pulseless electrical activity/asystole. The arrest location was stratified as the residence, school, and others. The neurological outcome was classified on the basis of the paediatric cerebral performance category (PCPC) as 1; good, 2; mild disability, 3; moderate disability, 4; severe disability, 5; coma or vegetative state, and 6; brain death. The number of adrenaline doses that were administered was divided from 0 to more than 10 times.

Statistical analysis

We compared demographic factors, patient characteristics, as well as the prehospital and in-hospital treatment or procedures. The patients were assigned to two groups as those with or without successful ROSC. The relationship between the ROSC and favourable neurological outcome and with the number of adrenaline doses that were administered were evaluated. The age, frequency of adrenaline administration, and time to resuscitation were clearly skewed and, therefore, medians with interquartile ranges were used for numerical variables. The intergroup differences in numerical variables were compared with the Mann-Whitney *U* test. The chi-square test was used to compare the frequencies with regard to the gender, aetiology of cardiac arrest, initial rhythm, witnessed OHCA, bystander CPR, and arrest location. To assess the independent effect of adrenaline doses on study endpoints, a multivariate logistic regression analysis of the ROSC was undertaken. Covariates were carefully selected on the assumption that they were not directly affected by the intervention. Both bystander CPR and the time from the emergency call to the initial adrenaline administration were included as variables in the multivariable logistic analysis. The data management and statistical analyses were undertaken in EZR software (Y Kaneda, Saitama, Japan). A *p*-value of < 0.05 was considered statistically significant.

Results

A total of 17,098 OHCA patients were enrolled in the SOS-KANTO 2012 study, and the study included 307 patients who were younger than 18 years. After 40 patients with missing data on ROSC or adrenaline administration were excluded, 267 patients were included in the final analyses. During CPR, 62 and 205 paediatric patients did and did not achieve ROSC, respectively.

Table 1 presents the demographics of the study population. There were seven patients (11.3%) with VF/VT as the initial cardiac rhythm in the ROSC group, and none with VF/VT in the non-ROSC group. Thirty-nine (62.9%) and 131 (37.1%) patients with of witnessed OHCA in the ROSC and no ROSC groups, respectively. There were significant differences between the two groups in the initial rhythm, witnessed OHCA, and arrest locations.

Table 2 lists the interventions at the prehospitalisation scene, wherein 11 patients (17.7%) and two patients (1.0%) underwent defibrillation in the ROSC and no ROSC group, respectively. There was a significant intergroup difference with regard to the defibrillation at the prehospitalisation scene.

Table 3 shows the at-hospital interventions in the study group. In the ROSC and no ROSC groups, respectively, 54 (87.1%) and 151 (73.7%) were intubated, 7 (11.3%) and 4 (2.0%) were defibrillated. There were significant between-group differences in the rates of intubation and defibrillation. Furthermore, significantly fewer adrenaline doses were administered in the ROSC than in the no ROSC group (4 [2-6] vs 6 [3-10], $p < 0.05$).

Table 4 shows the timeline of resuscitative activity. The time from the emergency call to the initial administration of adrenaline was significantly shorter in the ROSC group than in the no ROSC group (31 min [26.75-35.25 min] vs. 35 min [30-44 min], $p < 0.05$).

Table 5 lists the number of adrenaline doses that were administered in the ROSC group. Patients who survived to one month after the OHCA received fewer adrenaline doses than patients who died, although there was no significant intergroup difference (3 [1.75-5.25], vs. 4 [2.5-6], $p = 0.319$). Moreover, patients with a good neurological outcome (PCPC 1-2) received fewer doses of adrenaline than those with an unfavourable neurological outcome (PCPC 3-6), but intergroup difference was not significant.

The results of multivariate logistic regression analysis for the survival outcome are specified in Table 6, and showed that fewer doses of adrenaline were associated with an improved rate of successful ROSC (odds ratio = 0.80, 95% confidence interval = 0.69-0.92, $p < 0.01$).

Discussion

This study reviewed the data of the SOS-KANTO 2012 study, a multicenter, retrospective, cohort population-based study, and revealed the interrelationship between the outcome of paediatric patients with OHCA and the number of doses of adrenaline that was administered during resuscitation. The results revealed that the median number of adrenaline doses in paediatric OHCA patients with ROSC was three, and none of the OHCA paediatric patients with good neurological outcome had received more than three doses of adrenaline.

The predictors of survival to hospital discharge included a shorter interval between the OHCA and hospital arrival, a palpable pulse on presentation, comparatively fewer doses of adrenaline, and a relatively shorter duration of resuscitation in the ED (18). In the present study, the rate of successful ROSC

was 23% (62/267), and 11.3% (7/62) of the survivors had a favourable neurological outcome. In previous reports, survival rates of paediatric OHCA patients have ranged from 2% to 22%, and 5-10% have survived to hospital discharge, with a good neurological outcome in 0-12% of the survivors (7, 10, 19). Multivariate logistic regression analysis of the ROSC and adrenaline administration showed that fewer adrenaline doses were associated with an improved rate of ROSC. Therefore, similarly as in the previous reports, shorter duration of resuscitation and fewer doses of adrenaline were related to the rate of successful ROSC (18).

Previous reports have described a specific number of adrenaline doses wherein the outcome was universally poor, such that the futility of the resuscitative intervention could be assured. More than two or three doses of adrenaline have been previously reported as cutoff points (18, 19). In 1996, Schindler reported that there were no survivors of paediatric cardiac arrest if more than two doses of adrenaline were required (18). Young et al more recently reported in 2004 greater than 3 adrenaline doses to be universally associated with poor survival outcome (19, 20). In Moler's cohort, 46 patients received more than three doses of adrenaline, and only seven of these 46 children survived to hospital discharge, and only one of these seven children was discharged from the hospital with a good neurological outcome. Overall, 45/46 (98%) of their patients had a poor outcome, defined as death or PCPC >2. Therefore, the cutoff point of four or more doses of adrenaline is usually, but not always, associated with a poor clinical outcome (10). In another report, patients who needed comparatively fewer doses of resuscitative drugs had improved survival outcomes. However, none of the patients who were given more than three doses of adrenaline survived to hospital discharge (10, 18). The results of the present study are similar to those mentioned in previous reports, and none of the children who were received more than three doses of adrenaline had a good neurological outcome.

Several observational studies have demonstrated that the effects of adrenaline may be time dependent, with earlier adrenaline administration associated with improved outcomes in OHCA with a shockable initial cardiac rhythm (21-23). Adrenaline is thought to be beneficial for patients in cardiac arrest through increased coronary perfusion pressure, which potentially enhances cardiac function; however, adrenaline may reduce cerebral blood flow and can cause increased myocardial oxygen demand (24, 25). Previous studies have consistently found that adrenaline improves the rate of ROSC during cardiac arrest (21, 26-29). The primary physiological mechanism for the improved rate of ROSC is attributed to the alpha-adrenergic effect of adrenaline to improve the aortic diastolic pressure, which leads to an increased blood flow to the left ventricle that is mediated by an increase in the coronary perfusion pressure (30-33). However, vital organs such as the brain and heart sustain more ischaemic damage with longer CPR times and frequent administration of adrenaline, and the beneficial effects of adrenaline on the left ventricular blood flow may be countered by a reduction in the cerebral blood flow, worsening of brain ischaemia, reduction of microcirculatory flow, and an increased myocardial oxygen demand (24, 25). In this study, the patients with prolonged resuscitation or more than three doses of adrenaline were unable to achieve a favourable neurological outcome. Similarly as in a previous report, the results of this study suggest that the rate of successful ROSC and favourable neurological outcome in paediatric OHCA patients are related to fewer doses of adrenaline and the duration of resuscitation time (10, 19, 20). Thus, it is important to

discuss the termination criteria with regard to the resuscitation time or doses of adrenaline in the paediatric OHCA patient, because the rates of ROSC and favourable neurological outcome do not change with an increasing number of adrenaline doses. Moreover, resuscitative efforts that involve many doses of adrenaline do not produce survivors with good neurological outcomes.

Several limitations should be considered when interpreting the results of the present study. First, a major limitation of this study concerns the long-term neurological outcome of survivors. In this study, neurological outcome could only be ascertained at 1 month after the OHCA with the simple clinical score of the PCPC. Optimally, outcome should be assessed at follow-up periods for at least a year and with a more extensive range of neurobehavioral assessment tools. Second, this study is a secondary analysis of the SOS-KANTO study 2012 and, because the original study was not specifically designed for the stated purpose of the present study, some of the study patients were missing data for the specific parameters evaluated in this study. Therefore, we are only able to comment on the association rather than the causation. Third, we do not have information on specific hospital factors, such as staff ratios or the presence of an intensivist in the intensive care unit or the paediatric intensive care unit. Furthermore, the emergency medical system and the procedures which are permissible for EMS personnel to carry out differs in the various subareas. The prehospitalisation procedures performed at the scene of the OHCA differed by the emergency medical system or patient's age, and they might have affected the outcome to some extent. Fourth, these results may not be generalisable to different paediatric populations who suffer an OHCA. An important limitation of this study is the number of paediatric patients included in the study. In the original SOS-KANTO 2012 study, the OHCA paediatric patients compared only 1.6% of the total study population. This constitutes a very small proportion of the study sample compared with the population of adult patients. Finally, this study is also limited by its retrospective nature. Demographic and clinical data were obtained from medical records, which may have been incompletely or erroneously filled out, and there were several patients with missing data.

Conclusions

In conclusion, this multicenter study is one of the largest studies in the paediatric OHCA population thus far, and reports associations of the neurological outcomes with adrenaline doses in paediatric patients with OHCA. More than three adrenaline doses were associated with poor neurological outcome, and a favourable outcome occurred infrequently. By using information that was only available up to 1 month after the OHCA, we found that a higher number of adrenaline doses was associated with poor neurological outcome. In the future, studies to reveal the appropriate doses of adrenaline administration with regard to a favourable neurological outcome need to be undertaken to define the cutoff points for the termination criteria for CPR in paediatric OHCA patients.

Abbreviations

OHCA: out-of-hospital cardiac arrest; PCPC: paediatric cerebral performance; CPR: cardiopulmonary resuscitation; ED: emergency department; ROSC: return of spontaneous circulation; VT/VF: ventricular

tachycardia/ventricular fibrillation

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (1-022, in the Juntendo University Urayasu Hospital, Chiba, Japan), whichh waived the need for informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed during the current study are not publicly available due to contain each patient's characteristics of participated hospital, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

All authors contributed to the study conception and design. Data collection and analysis and writing of the manuscript-first draft were undertaken by TI. YK, KS, SM, KO and HT critically reviewed the manuscript. All authors read and approved the final manuscript.

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Competing interest:

The authors declare no competing of interest.

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Tables

Table 1. Demographics of study population

Characteristics	ROSC group (n=62)	No ROSC group (n=205)	p-values
Age, median (IQR)	2 (0-10.75)	1 (0-12)	0.31
Gender (male, %)	27 (43.5)	120 (58.5)	0.65
<u>Initial rhythm</u>			
VT/VF	7 (11.3)	0 (0)	< 0.05*
Asystole/PEA	55 (88.7)	205 (100)	
<u>Etiology of CPA</u>			
Cardiogenic	12 (19.4)	45 (22.0)	0.05
Trauma	10 (16.1)	40 (19.5)	
Others	40 (64.5)	120 (58.5)	
<u>Witnessed CPA</u>			
Family (%)	25 (40.3)	51 (24.9)	< 0.05*
Non-family (%)	14 (22.6)	23 (11.2)	
None (%)	23 (37.1)	131 (63.9)	
<u>Bystander CPR</u>			
Medical staff (%)	2 (3.2)	9 (4.4)	0.67
Citizen (%)	27 (43.5)	77 (37.6)	
None (%)	33 (53.2)	119 (58.0)	
<u>Arrest location</u>			
Home (%)	37 (59.7)	148 (72.2)	< 0.05
School (%)	5 (8.1)	4 (2)	
Others (%)	20 (32.2)	53 (25.9)	
1month survival (%)	27 (43.5)	0	
PCPC 1-2 (%)	7 (11.3)	0	

* p < 0.05

ROSC: return of spontaneous circulation, VT: ventricular tachycardia,

VF: ventricular fibrillation, CPA: cardiopulmonary arrest,

CPR: cardiopulmonary resuscitation, PCPC: pediatric cerebral performance category

Table 2. Interventions at prehospitalisation scene

Intervention	ROSC group (n=62)	No ROSC group (n=205)	p-values
<u>Advanced airway management (%)</u>	53 (85.5)	193 (94.1)	0.05
BVM (%)	41 (77.4)	168 (87.0)	
LMA (%)	1 (1.9)	5 (2.6)	0.13
Intubation (%)	11 (17.7)	20 (10.4)	
Adrenaline administration (%)	4 (6.5)	6 (2.9)	0.37
Defibrillation (%)	11 (17.7)	2 (1.0)	< 0.05*

* p < 0.05

ROSC: return of spontaneous circulation, BVM: bag valve mask,

LMA: laryngeal mask airway

Table 3. Interventions at hospital

Intervention	ROSC group (n=62)	No ROSC group (n=205)	p-values
Advanced life support (%)	58 (93.5)	178 (86.8)	0.18
Intubation (%)	54 (87.1)	151 (73.7)	< 0.05*
Defibrillation (%)	7 (11.3)	4 (2.0)	< 0.05*
Adrenaline administration (%)	50 (80.1)	165 (80.5)	1
Adrenaline administration, doses median (IQR)	4 (2-6)	6 (3-10)	< 0.05*

* p < 0.05

ROSC: return of spontaneous circulation

Table 4. Time of activity

Activity	ROSC group (n=62)	No ROSC group (n=205)	p- values
Time from the emergency call to contact the patient, min (IQR)	8 (7-10)	8 (7-11)	0.433
Time from the emergency call to arrival at the hospital, min (IQR)	27.5 (22.25-36)	30 (24-37)	0.243
Time from the emergency call to initial adrenaline administration, min (IQR)	31 (26.75- 35.25)	35 (30-44)	< 0.05
Time from the emergency call to ROSC, min (IQR)	44 (38-55)	nd	-

* p < 0.05

ROSC: return of spontaneous resuscitation

Table 5. Number of adrenaline doses in ROSC group

One-month survival (IQR)	Survival (n=27)	Not survival (n=35)	p-values
Adrenaline administration, doses median, (IQR)	3 (1.75-5.25)	4 (2.5-6)	0.319
One-month PCPC1-2 (IQR)	PCPC 1-2 (n=7)	PCPC 3-6 (n=55)	p-values
Adrenaline administration, doses median, (IQR)	2 (2-2)	4 (2-6)	0.392

ROSC: return of spontaneous circulation

Table 6. Logistic regression analysis

	ROSC OR	95% CI	p-value
ROSC (unmatched)	0.83	0.74 to 0.93	<0.05*
ROSC (matched)	0.80	0.69 to 0.92	<0.05*

P<0.05*

ROSC: return of spontaneous circulation, OR: odds ratio, CI: confidence interval

Figures

Figure 1

Inclusion criteria of the study