Original Article

Early endotracheal intubation improves neurological outcome following witnessed out-of-hospital cardiac arrest in Japan: a population-based observational study

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Aim: It is unclear whether endotracheal intubation in the prehospital setting improves outcomes following out-of-hospital cardiac arrest. The purpose of this study was to evaluate the association between endotracheal intubation time (time from patient contact to endotracheal intubation) and favorable neurological outcomes on out-of-hospital cardiac arrest.

Methods: We extracted patients who underwent endotracheal intubation on the scene from a nationwide out-of-hospital cardiac arrest database registered between 2014 and 2017 in Japan. We included 14,969 witnessed and intubated adult out-of-hospital cardiac arrest cases. Patients were divided into Shockable (n = 1,102) and Non-shockable (n = 13,867) cohorts. We first drew the logistic curve due to predicting the association between endotracheal intubation time and favorable neurological outcome defined as Cerebral Performance Category (CPC) 1 or 2. Secondary, multivariable logistic regressions were used to estimate the association between the endotracheal intubation time (1-min unit increase), CPC 1 or 2.

Results: The logistic curve for CPC 1 or 2 showed similar shapes and indicated a decreasing outcome over time. From the results of multivariable logistic regression, in the Shockable cohort, endotracheal intubation time delay was correlated with decreasing favorable outcomes: CPC 1 or 2 (adjusted odds ratio, 0.89; 95% confidence interval, 0.82–0.87). Results were the same for the Non-shockable cohort: CPC 1 or 2 (adjusted odds ratio, 0.94; 95% confidence interval, 0.89–0.99).

Conclusion: Early endotracheal intubation was correlated with favorable neurological outcome. Training for intubation skills and improving protocols are needed for carrying out early endotracheal intubation.

Key words: Advanced life support, airway management, endotracheal intubation, out-of-hospital cardiac arrest, prehospital care

INTRODUCTION

IN JAPAN, MORE than 13 million cases of out-of-hospital cardiac arrest (OHCA) occur per year. Even in cases of cardiogenic cardiac arrest, which reported a high probability of resuscitation, it is less than 10% and less than 5% for non-cardiogenic cardiac arrest,[1] which is a social issue. In particular, prior to cardiac arrest of non-cardiogenic origin, hypoxemia, hypercapnia, and acidosis are produced.[2] To manage the problem, high-quality chest compressions and advanced life support (ALS), including endotracheal intubation (ETI), are carried out.[3,4]

Endotracheal intubation is used for advanced airway management in the field of resuscitation all over the world, but evidence of its effectiveness is limited.[5–14] In recent randomized control trials (RCTs) on advanced airway management, ETI was not correlated with improving long-term outcomes compared to supraglottic airway devices (SGA) or bag-valve-masks (BVM).[7–9] In addition, the use of ETI has been questioned in recent observational studies, because outcomes in OHCA have not improved, compared to SGA and BVM.[10,12–14] Previous studies have reported that ETI is associated with poor long-term outcomes because ETI takes longer to complete airway management compared to SGA.[14]

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According to the airway management protocol in Japan, BVM is selected to provide artificial ventilation to patients with cleared airways. Supraglottic airway devices are used in patients who require advanced airway management; ETI is used in cases of asphyxia-related cardiac arrest or insufficient airway management with SGA. For that reason, the background of the patient differs depending on airway management devices. It is difficult to prove the effectiveness of ETI by comparing between ETI and another airway management device. We highlight cases in which early ETI was used and hypothesize that early oxygenation by ETI would improve outcomes in OHCA.

We included OHCA cases with ETI, and evaluated the correlation between ETI time (time from patient contact to ETI) and neurological outcome at 1 month.

METHODS

Study design and setting

THIS WAS A retrospective cohort study of nationwide OHCA cases registered with the Utstein style between 1 January, 2014 and 31 December, 2017. We evaluated the correlation between ETI time and neurological outcome with witnessed OHCA. This study was approved by the Ethics Committee at Kokushikan University (#19018).

Emergency medical service system in Japan

As of 2017, the national land area of Japan was approximately 378,000 km^2, with a population of 130 million. Our prehospital emergency medical system (EMS) is based on the fire department and city, and it runs 24 h a day, 7 days a week. Each ambulance has three emergency medical technicians. At least one of them is an emergency life support technician (ELST); they can carry out i.v. injections, adrenaline administration, and advanced airway management for OHCA patients. According to the standard airway management protocol in Japan, BVM is selected to provide artificial ventilation on patients with airways cleared. If not, SGA is undertaken to maintain airways. When ELSTs made a decision not to maintain airways by either BVM or SGA, ventilation through ETI would be carried out.

Although all ELSTs can use SGA, such as laryngeal tubes or laryngeal masks, only certified ELSTs are permitted to carry out ETI under the direction of online medical control. In order to be certified, ELSTs need to carry out at least 30 successful ETIs under the supervision of an anesthesiologist, as well as attend lectures for 62 h. In 2017, there were 13,943 certified ETI-ELSTs in Japan, accounting for 40% of ELSTs who work at the Fire Departments. In Japan, ELSTs may only carry out ETI on OHCA patients aged over 15 years and meet one of the following criteria: (i) choking by a foreign body obstruction, (ii) difficult to maintain airway by SGA, (iii) the medical director orders them to do so. Endotracheal intubation by an ELST must not be carried out in patients who achieve the return of spontaneous circulation (ROSC). ETI by an ELST is followed by the 2015 Japan Resuscitation Council Guidelines, as well as the standard ALS protocol has been shown by the Fire and Disaster Management Agency of the Ministry of Internal Affairs and Communications. In addition, the ALS protocol has been established by local medical control. These were created based on the International Liaison Committee on Resuscitation consensus.[15] Interruption of resuscitation in the field is not permitted, so patients are transported to hospitals. The ELST does not treat cases with obvious death, such as cutting off the trunk, traumatic brain injury with extreme cerebral prolapse, skeletonization, or early postmortem changes.

Data collection

This study used Utstein data. Japan's Utstein data, an OHCA registry, was initiated in January 2005 by the Fire and Disaster Management Agency, recording data as per the international Utstein style.[16,17] The definition of cardiac arrest followed this standard as well. The collection of Utstein data includes sex, age, and cause of cardiac arrest. Cardiac arrest is categorized into cardiogenic or non-cardiogenic; non-cardiogenic includes trauma, drowning, drug overdose, respiratory disease, cerebrovascular disease, malignant tumor, and something caused by exogenous issues. The presence of a witness or bystander also involves who it was (family, friend, colleague, passerby, firefighter, EMS crew, or other), the presence and type of CPR done by the bystander (hands-only CPR or conventional CPR), the presence of dispatcher assistance, the presence of defibrillation, adrenalin administration, and the method of airway management. The time courses were recorded for: emergency activation, arrival at the scene, contact with patient, initiating CPR, arrival at hospital, adrenaline administration, and advanced airway devices insertion time. The outcomes include ROSC before hospitalization, survival at 1 month, and cerebral function at 1 month. Cerebral function at 1 month after OHCA is evaluated by the Cerebral Performance Category (CPC): 1, good cerebral performance; 2, moderate cerebral disability; 3, severe cerebral disability; 4, coma or vegetative state; 5, death. The patient's neurological function was determined by the treating physician. The EMS in charge of OHCA calls the hospital to collect followup data at 1 month. The CPC is scored by the physician in charge. The EMS receives a written answer and tracks the situation if patients do not show up.

Study participants

Data were accessed for OHCA patients registered between 1 January, 2014 and 31 December, 2017 in Japan's nationwide database. Inclusion criteria were patients aged 15 years or older with OHCA witnessed by laypersons, and ETI undertaken in the prehospital settings. Exclusion criteria were as follows: unknown initial electrocardiogram (ECG) rhythm, missing or negative values (from call to patient contact, from patient contact to hospital arrival, from patient contact to ETI, and ROSC before ETI), and outlying values. Outlying values were defined as time interval above the 99th percentile. Patients were divided into the Shockable (ventricular fibrillation and pulseless ventricular tachycardia) and Non-shockable (pulseless electrical activity and Asystole) cohorts because the treatment would differ depending on the initial ECG rhythm.

Outcomes

The primary outcome was a favorable neurological outcome, defined as CPC 1–2 at 1 month after OHCA. The secondary outcome was ROSC in the prehospital setting.

Statistical analysis

In the patients' characteristics, continuous variables are shown as mean (standard deviation) or median (interquartile range), and categorical variables were shown as number (%). First, we drew logistic curve and 95% confidence intervals (CI) to predict the association between ETI time and outcomes.

Second, we used multivariable logistic regression analysis to estimate the adjusted odds ratio (AOR) and 95% CI for the correlation between ETI time (1-min unit increase) and outcomes. In order to adjust potential confounders, we included the following variables in the model: age, gender, family bystander (yes [y]/no [n]), type of bystander CPR (hands-only CPR, conventional CPR, or not), public access defibrillation (y/n), adrenaline administration (y/n), etiology (cardiogenic or non-cardiogenic), time from call to contact, and time from contact to arrival at hospital. Based on assessment of the fitting model, the goodness-of-fit test, R^2 value, and area under the receiver operating characteristic curve were used. The significance level was 0.05 (two-tailed). We used R Studio version 1.2.1335 (R Studio, Inc., Boston, MA, USA) for drawing the logistic curve, and JMP Pro 13.2.1 (SAS Institute, Cary, NC, USA) for statistical analysis.

RESULTS

Flowchart of OHCA patients

EXCLUSION CRITERIA OF OHCA cases and cohort allocation are shown in Figure 1. A total of 499,944 OHCA cases were registered, of which 37,748 (7.6%) received ETI and 462,196 (92.4%) did not. Witnessed cases consisted of 17,124 (45.4%), and the initial ECG rhythm consisted of 16,415 (43.5%) cases. Finally, 14,969 cases were included (1,102 cases were Shockable and 13,867 cases were Non-shockable).

Patients' characteristics

We divided all intubated cases into two cohorts, Shockable and Non-shockable, based on the initial ECG rhythm, with patient characteristics of each subcohort shown in Table 1. Average age in the Shockable cohort was lower than the Non-shockable cohort (Shockable vs. Non-shockable, 68.6 vs. 78.9 years old) and sex difference was found (Shockable vs. Non-shockable, 75.7% vs. 54.7%). The incidence of cardiogenic cardiac arrest was higher in the Shockable cohort (Shockable vs. Non-shockable, 86.2% vs. 43.5%) and respiratory-related pathology was higher in the Non-shockable cohort (Shockable vs. Non-shockable, 5.9% vs. 36.3%). In the bystander interventions, there were no differences in terms of family bystander or type of CPR. In the Shockable cohort, the rate of public access defibrillation was higher (Shockable vs. Non-shockable, 3.5% vs. 1.0%). For EMS treatments, defibrillation was higher in the Shockable cohort (Shockable vs. Non-shockable, 95.6% vs. 5.0%), as well as adrenaline administration (Shockable vs. Non-shockable, 54.7% vs. 45.0%).

Endotracheal intubation time and favorable outcomes

The logistic curve for the relationship between the ETI time, CPC 1-2, and ROSC of each cohort are shown in Figure 2. In the logistic curve, the rate of CPC 1-2 tended to decrease with ETI time delay. Compared to the Shockable cohort, the Non-shockable cohort had very low CPC 1–2 rate and showed the tendency of poor outcome. Return of spontaneous circulation also showed a tendency to decrease with ETI time delay as well as CPC 1–2. There was no significant difference in the rate of ROSC between the Shockable and Non-shockable cohort.

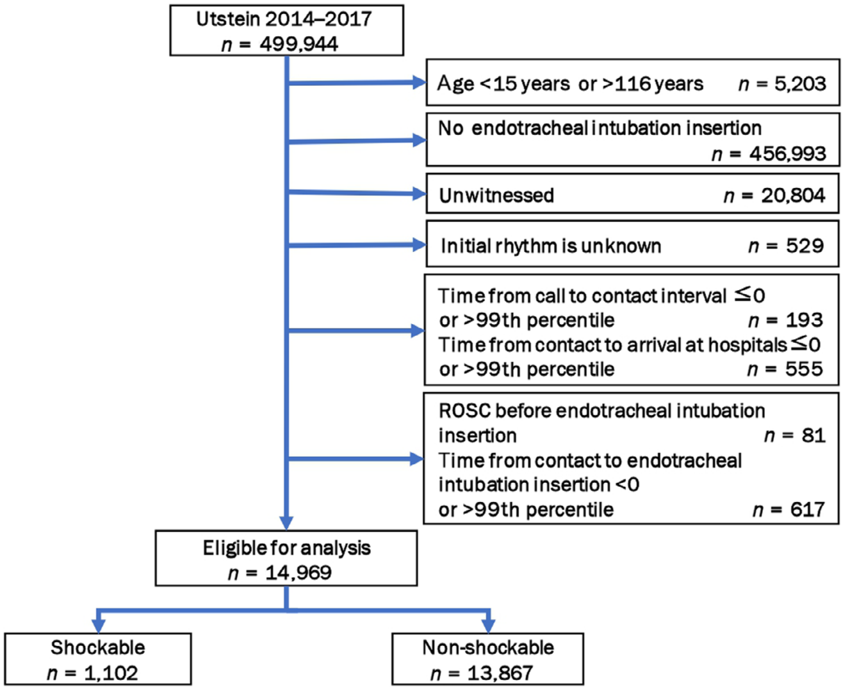

Fig. 1. Flowchart for patient enrollment in the study. ROSC, return of spontaneous circulation.

The results of the multivariable logistic regression analysis are shown in Table 2. In the Shockable cohort, delayed ETI time (1-min unit increase) had a negative correlation with CPC 1–2 (AOR, 0.91; 95% CI, 0.86–0.96) and ROSC (AOR, 0.90; 95% CI, 0.87–0.93). Also, in the Non-shockable cohort, delayed ETI time (1-min unit increase) had a negative correlation with CPC1–2 (AOR, 0.92; 95% CI, 0.89–0.96) and ROSC (AOR, 0.91; 95% CI, 0.90–0.92).

DISCUSSION

IN THIS STUDY, we evaluated the correlation between ETI time (1-min unit increase) and favorable neurological outcomes from 14,969 nationwide OHCA patients in Japan. Along with ETI time delay, decreasing favorable neurological outcomes and ROSC was shown.

There was no significant difference in the rate of ROSC between the Shockable cohort and the Non-shockable cohort. However, the Non-shockable cohort showed a very low rate of CPC 1–2, irrespective of over time, compared to the Shockable cohort. In the shockable rhythm, it has been reported that treatment such as early defibrillation greatly influences the favorable neurological function.[18,19] As defibrillation is extended every minute, the rate of ROSC decreases by approximately 2.5%.[20] In this study, the logistic curve showed the time-dependent tendency as ETI time extends, which was similar to decreasing CPC 1-2 in a delay of defibrillation. From the results of multivariable logistic regression analysis, there was a significant negative correlation between CPC 1–2 and delaying ETI time every minute. Therefore, it was shown that it is important to carry out ETI in the prehospital setting as soon as possible in order to maintain cerebral and cardiac oxygenation as early as possible. Respiratory-caused OHCA occupied much in Non-shockable rhythm. This might already progress hypoxemia, so the CPC 1–2 rate was low regardless of ETI time. However, from the multivariable logistic regression analysis, there was a significant negative correlation between CPC 1–2 and extending ETI time every minute. This indicated that early ETI is important. In order to gain favorable neurological outcomes, patients should achieve ROSC in the early phase.[21,22] Thus, it is important to perform high-quality chest compressions and ETI as early as possible. According to the study by Ahn *et al.*, maintaining regional cerebral oxygen saturation was thought to be related with ROSC in Non-shockable rhythm,[23] so ETI was carried out to prevent prolonged hypoxemia, and was required to achieve early ROSC.

Previous observational studies on ETI reported that a “resuscitation time bias” existed and might have not been considered properly.[24] The time difference in providing ETI is a major barrier to evaluate the effectiveness of ALS in the

Table 1. Characteristics of patients with out-of-hospital cardiac arrest who underwent endotracheal intubation

Characteristics *n* (%)	All cases *n* = 14,969		Initial rhythm Shockable *n* = 1,102		Initial rhythm Non-shockable *n* = 13,867	
Year						
2014	3,631	(24.3)	264	(24.0)	3,367	(24.3)
2015	3,761	(25.1)	256	(23.2)	3,505	(25.3)
2016	3,660	(24.5)	285	(25.9)	3,375	(24.3)
2017	3,917	(26.2)	297	(27.0)	3,620	(26.1)
Age, years; mean (SD)	78.1	(13.6)	68.6	(15.3)	78.9	(13.1)
>65 years	12,910	(86.2)	728	(66.1)	12,182	(87.9)
Sex, male	8,420	(56.2)	834	(75.7)	7,586	(54.7)
Bystander interventions						
Family bystander	8,540	(57.1)	674	(61.2)	7,866	(56.7)
CPR by bystander						
Conventional CPR	1,133	(7.6)	83	(7.5)	1,050	(7.6)
Hands-only CPR	6,802	(45.4)	503	(45.6)	6,299	(45.4)
Public access defibrillation	178	(1.2)	38	(3.5)	140	(1.0)
Etiology						
Cardiogenic	6,975	(46.6)	950	(86.2)	6,025	(43.5)
Non-cardiogenic						
Stroke	333	(2.2)	12	(1.1)	321	(2.3)
Respiratory disease	5,092	(34.0)	65	(5.9)	5,027	(36.3)
Malignant tumor	283	(1.9)	7	(0.6)	276	(2.0)
Extrinsic	399	(2.7)	11	(1.0)	388	(2.8)
Poisoning	16	(0.1)	1	(0.1)	15	(0.1)
Drowning	149	(1.0)	13	(1.2)	136	(1.0)
Traffic injury	166	(1.1)	4	(0.4)	162	(1.2)
Hypothermia	6	(0.0)	0	(0.0)	6	(0.0)
Anaphylaxis	5	(0.0)	1	(0.1)	4	(0.0)
Other	1,546	(10.3)	38	(3.4)	1,508	(10.9)
Unknown	7	(0.0)	0	(0.0)	7	(0.1)
EMS interventions						
Dispatcher-assisted	8,364	(55.9)	612	(55.5)	7,752	(55.9)
Defibrillation by EMS	1,743	(11.6)	1,054	(95.6)	689	(5.0)
Number of defibrillations						
1	842	(5.6)	307	(27.9)	535	(3.9)
2	361	(2.4)	230	(20.9)	131	(0.9)
3	288	(1.9)	217	(19.7)	71	(0.5)
>4	672	(4.5)	300	(27.2)	372	(2.7)
Adrenaline administration	6,842	(45.7)	603	(54.7)	6,239	(45.0)
Number of adrenaline administrations						
1	2,766	(18.5)	206	(18.7)	2,560	(18.5)
2	1,946	(13.0)	155	(14.1)	1,791	(12.9)
>3	2,368	(15.8)	253	(23.0)	2,115	(15.3)
Time data						
Call to contact interval, median (IQR), min	9	(7–11)	8.5	(7–10)	9	(7–11)
Contact to hospital arrival, median (IQR), min	27	(22–34)	27	(22–33)	27	(20–29)
Contact to adrenaline administration, median (IQR), min	15	(10–21)	13	(9–18)	15	(8–17)

Table 1. (Continued)

Characteristics *n* (%)	All cases *n* = 14,969		Initial rhythm			
			Shockable *n* = 1,102		Non-shockable *n* = 13,867	
Outcomes						
ROSC	2,916	(19.5)	242	(22.0)	2,674	(19.3)
Favorable neurological outcome at 1 month	252	(1.7)	102	(9.3)	150	(1.8)

CPR, cardiopulmonary resuscitation; EMS, emergency medical service; IQR, interquartile range; ROSC, return of spontaneous circulation; SD, standard deviation.

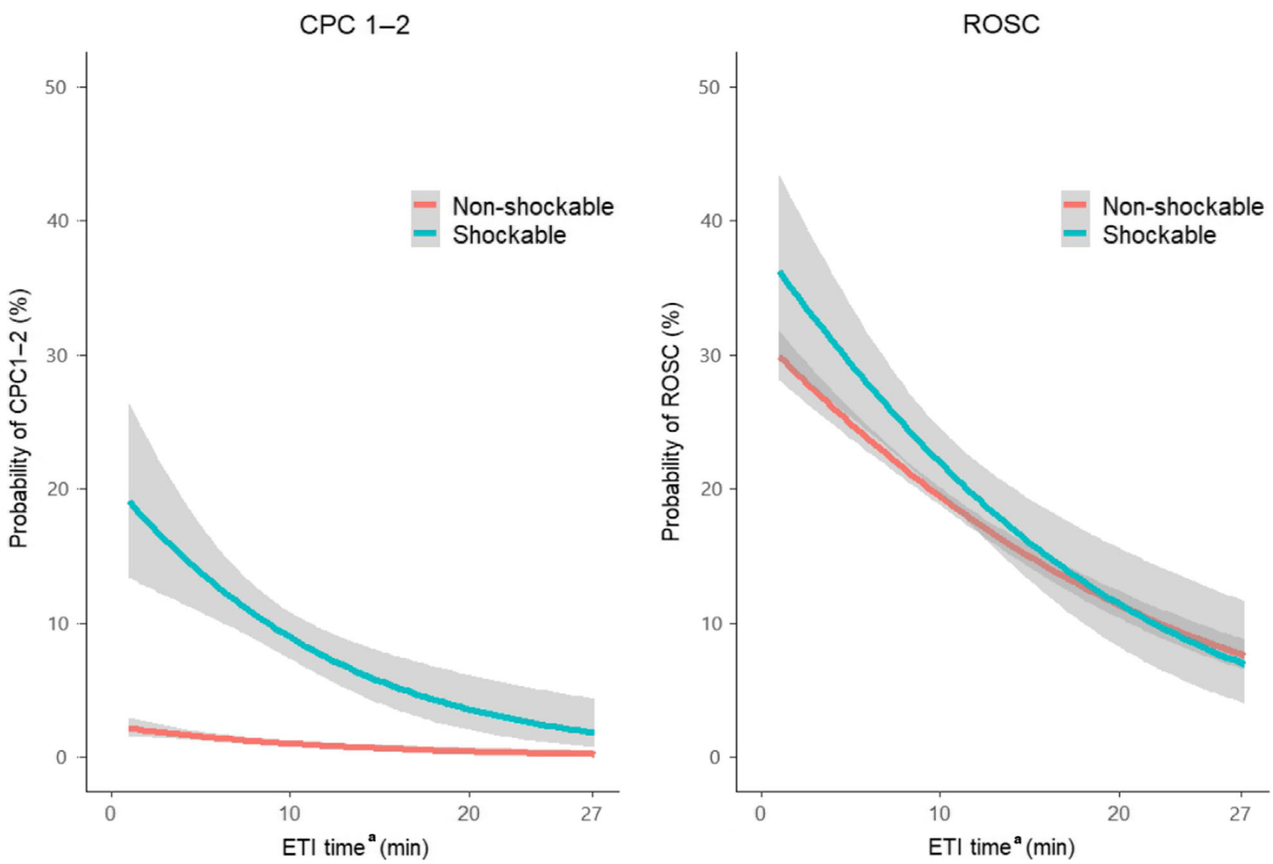

Fig. 2. Logistic curves of endotracheal intubation (ETI) time, Cerebral Performance Category (CPC) 1–2, and return of spontaneous circulation (ROSC) in patients with out-of-hospital cardiac arrest, categorized as Shockable or Non-shockable, who underwent endotracheal intubation. [a]Time from patient contact to ETI.

prehospital setting. In OHCA, each patient's pathology differs and the time depends on the treatment, so analysis taking into account time factors is indispensable. According to the previous observational studies where Utstein data were used, advanced airway management in the prehospital setting was reported as a poor outcome when compared to BVM. These results have been believed blindly nationwide.[5–14] However, patients who received advanced airway management were in poor condition and underwent extended treatment time, in which "resuscitation time bias"

Table 2. Odds ratios (OR) of outcomes in patients with out-of-hospital cardiac arrest according to endotracheal intubation time interval

	OR (95% CI)	CPC 1–2		ROSC	
Shockable†	Unadjusted	0.91	(0.87–0.95)	0.92	(0.90–0.95)
	Adjusted§	0.91	(0.86–0.96)	0.90	(0.87–0.93)
Non-shockable‡	Unadjusted	0.92	(0.89–0.96)	0.94	(0.93–0.95)
	Adjusted§	0.92	(0.89–0.96)	0.91	(0.90–0.92)

CI, confidence interval.
†Goodness-of-fit test, $P = 1.00, 0.38$; $R^2 = 0.11, 0.05$; area under the receiver operating characteristic curve (AUROC) = 0.74, 0.66 in Cerebral Performance Category (CPC) 1–2 and return of spontaneous circulation (ROSC) groups, respectively.
‡Goodness-of-fit test, $P = 1.00, 1.00$; $R^2 = 0.06, 0.17$; AUROC = 0.72, 0.78 in CPC 1-2 and ROSC groups, respectively.
§Logistic regression analyses were calculated controlling for age, sex, year of occurrence, family bystander, type of bystander cardiopulmonary resuscitation, public access defibrillation, adrenaline administration, etiology, time from call to contact, and time from contact to arrival at hospital.

occurred. In their study about advanced airway management for OHCAs, Izawa *et al*. used time-dependent propensity score matching to address the time bias,[5] and reported that ETI in the Non-shockable cohort correlated with favorable neurological outcomes. Kajino *et al*. reported that early advanced airway management influenced long-term neurological outcomes for OHCA cases in Osaka Prefecture.[14] In our study, we focused on the ETI time and evaluated the correlation with the neurological outcome as an object only in patients who underwent ETI. As a result, early ETI time correlated with favorable neurological outcome.

Recently, several RCTs on advanced airway management have been published, but the correlation between ETI and outcome has not been reported.[7–9] Randomized controlled trials represent an important analysis method to examine effectiveness. However, there is a possibility of having differences in the time to perform ETI due to the differences in protocols across multiple facilities. As we focused on ETI time, we found that early ETI was correlated with favorable neurological outcomes. Unlike the in-hospital environment, ETI undertaken in the prehospital setting can be more difficult because of the influence of the on-site environment. Therefore, failure of ETI and prolonged interruption of chest compressions have been considered major issues. Continuous training is important to carry out ETI quickly and accurately. The effectiveness of early ETI should be emphasized; thus, it is necessary to consider introducing a protocol for early ETI because the protocol is different depending on the region in Japan.

Limitations

This was an observational study by secondary use of Utstein data. Therefore, it was unclear whether the influence of the following exposures had been measured.

1. Failed intubation; a number of ETI trials and skill difference of ELSTs, reported to correlate with poor outcomes.[25]
2. Interruption time of chest compressions; intubation for OHCA made a difference in lengthening the interruption time of chest compressions. Therefore, there was a possibility that favorable outcomes were not obtained due to CPR interruption.[26,27]
3. The order of ALS procedure; early adrenaline administration could be a factor in improving outcomes for OHCA.[28–30]

We analyzed data including witnessed OHCA patients aged 15 years and over who underwent ETI. Therefore, our results cannot be generalized to the population under the age of 15 years, unwitnessed OHCA cases, and communities with different EMS systems. This study did not determine the effectiveness ETI compared with SGA or BVM.

CONCLUSION

WE EVALUATED THE correlation between ETI time and favorable neurological outcomes in witnessed OHCA cases. Due to the negative correlation between delayed ETI time (1-min unit increase) and favorable neurological outcomes, it was clarified that early ETI was associated with improving neurological outcomes in OHCA.

DISCLOSURES

Approval of the research protocol: N/A.
Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None.

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