임상의과학석사 학위논문

The comparison of the Effect of Mild Therapeutic Hypothermia on Good Neurological Recovery of Out-of-hospital Cardiac Arrest victims according to the locations of ROSC: Pre-hospital vs. Emergency department

자발순환회복 위치에 따른 병원 밖 심정지 환자의 양호한 신경학적 회복에 대한 치료적 저체온요법의 효과: 병원 전단계 vs. 응급실

2015년 2월

서울대학교 대학원

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임상의과학과
배 광 수

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The comparison of the Effect of Mild Therapeutic Hypothermia on Good Neurological Recovery of Out-of-hospital Cardiac Arrest victims according to the locations of ROSC: Pre-hospital vs. Emergency department

by

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A thesis submitted to the Department of Clinical Medical Sciences in partial fulfillment of the requirements for the Degree of Master in Clinical Medical Sciences at Seoul National University College of Medicine

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ABSTRACT

Introduction: Mild therapeutic hypothermia (MTH) has been known to be associated with good neurological recovery after out-of-hospital cardiac arrest (OHCA). Prehospital return of spontaneous circulation (P-ROSC) is associated with better hospital outcomes than ROSC at emergency department (ED-ROSC). It is unclear whether MTH has an interaction with location of ROSC (Prehospital vs. ED) for good neurological recovery. The study aims to examine the association between MTH by of ROSC and good neurological recovery after OHCA.

Methods: Adult OHCA cases with presumed cardiac etiology who survived to hospital admission were collected from a nationwide cardiac registry between 2008 and 2013. Study variables included age, gender, place of OHCA occurrence, witness, bystander cardiopulmonary resuscitation (CPR), metropolitan, emergency medical services (EMS) response time, prehospital defibrillation, levels of ED, reperfusion therapy, primary ECG, and P-ROSC versus ED-ROSC. MTH was defined as a case receiving hypothermia procedure regardless of procedure method. Primary outcome was good neurological recovery with cerebral performance category score of 1 and 2 measured by hospital medical record review. Multivariable logistic regression analysis was performed adjusting for potential confounders with an interaction term between MTH and location of ROSC to calculate adjusted odds ratios (AORs) and 95% confidence intervals (CIs).

Results: Of 138,410 adult OHCAs with cardiac etiology, 11,158(8.1%) patients survived to admission. Among such cases, good neurological recovery was 23.6% (399/1,691) in MTH vs. 15.0% (1,400/9,316) in non-MTH (p<0.001), and 58.2% (1,074/1,864) in P-ROSC vs. 7.9% (725/9,161) in ED-ROSC (p<0.001). MTH was performed in 15.4% of total patients, 16.1% in P-ROSC (n=1,846), and 13.2% in ED-ROSC (n=9,161), respectively. There was a significant association between MTH and good neurological recovery (AOR=1.32, 95% CI=1.11-1.57). In the interaction model, AOR of MTH and interaction effect with P-ROSC and ED-ROSC was 0.78 (0.58-2.70) and 1.68 (1.34-1.98), respectively.

Conclusions: MTH was significantly associated with good neurological recovery among OHCA survivors, but the effect was different in P-ROSC and ED-ROSC. Prehospital ROSC group showed substantially higher good neurological recovery. However, MTH showed significant benefits in patient group with ROSC at ED, not in P-ROSC group, in a nationwide observational study.

Keywords: Cardiac Arrest, Hypothermia, Return of Spontaneous Circulation, Outcomes

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INTRODUCTION

Out of hospital cardiac arrest (OHCA) is recognized as a worldwide, serious public health problem. The incidence of emergency medical services (EMS) treated OHCA was reported to be between 50-130 cases per 100,000 (1). In the US, only 9.8% of EMS-treated adult OHCAs survived to discharge from hospital (2). In Korea, we have also reported that the incidence of EMS-assessed OHCA was approximately 45 per 100,000, and 3.5% of those patients survived to discharge from hospital (3).

Previous studies have reported that factors such as witnessed arrest, initial shockable rhythm, bystander CPR, shorter EMS response time, use of public access defibrillator (PAD) program play a key role in survival to hospital discharge after OHCA (4-6). Hospital interventions (i.e., post cardiac arrest care) comprised of targeted temperature management, optimal ventilation/oxygenation, optimizing hemodynamic parameter, seizure control, and electrolyte/glucose control have been developed to improve neurological outcome and survival of patients after cardiac arrest (7).

Over the past decades, researchers have found that hypothermia can decrease cerebral oxygen demand (8) and block chemical cascade leading to further cerebral injury (9, 10). Mild therapeutic hypothermia (MTH) is the core treatment that has demonstrated neurological benefits in comatose survivors with shockable cardiac arrest (7, 11-13). In 2002, two randomized trials have shown that hypothermia therapy in patients with initial shockable rhythm increased the rates of favorable neurological outcome One study enrolled adults OHCA patients who had ventricular fibrillation or ventricular tachycardia as initial rhythm and achieved ROSC within 60 minutes after cardiac arrest and reported MTH was significantly associated with more favorable neurological outcome at 6 month (12). The other one also revealed that MTH gave OHCA patients with ventricular fibrillation as initial rhythm more chances to have good neurological outcome at discharge (11). Moreover, even with the controversial debate over the effectiveness of hypothermia therapy, MTH still has possible neurological benefits in comatose adult OHCA patients with non-shockable rhythm (14-17). As a result, MTH is incorporated as a part of standard post-cardiac arrest care (7). Furthermore, in recent years, some researchers have verified that targeted temperature management (36℃) without significant variation had similar effect on good neurological outcome compared with MTH (18).

On the other hand, previous studies reported that prehospital ROSC (P-ROSC) is associated with more favorable neurological outcomes than ROSC at emergency department (ED-ROSC) (19-21). However, these studies did not account for the interaction effect between MTH and location of ROSC on favorable neurological outcome. We assumed that ischemic brain damage of OHCA patients resuscitated at ED is much greater than that of patients who achieved ROSC at prehospital stage. Therefore, we hypothesized that the effect of MTH on neurological outcome could be different in patients depending on the location of ROSC. The purpose of this study was to investigate the effect of MTH on favorable neurological outcome in comatose adult patients after an out-of-hospital cardiac arrest according to the location of ROSC.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the Seoul National University Hospital in 2013 (No. 1206-007-412).

Data source

The Cardiovascular Disease Surveillance (CAVAS) database is a nationwide, population-based, EMS-assessed OHCA cohort database in Korea (20). The primary data were accumulated from the electronic ambulance run sheet database of the National Emergency Management Agency (NEMA). Ambulance run sheets include chief complaints, sociological data, place of cardiac arrest, bystander cardiopulmonary resuscitation (CPR), time variables of resuscitation efforts, prehospital cares and the destination hospital information. Cases were coded as OHCA if the chief complaint was cardiac or respiratory arrest or if the patient received CPR during transport. Designated medical record reviewers of the Korean Centers for Disease Control and Prevention collected secondary data for hospital outcomes and related information using customized Utstein style. The Data Quality Management Control (QMC) team composed of study co-investigators, statistics experts, medical record review experts, fire department managers and an epidemiologist conducted quality control activities (3).

Study setting

Korea has a single-tier, basic life support (BLS) ambulance system operated by 16 provincial headquarters of the national fire department. Ambulance crews can give pre-hospital cares comparable to that of intermediate emergency medical technician (EMT-I) level in the US. However, advanced life support is only available in hospitals. The EMTs cannot declare death or stop CPR in the field or during transport unless ROSC occurs. Therefore, all patients with OHCA should be transported to the nearest ED. Public access defibrillator program was not available until 2008, so most defibrillation procedures in prehospital stage were given by ambulance crews. Every ambulance has an automatic external defibrillator. A withdrawal guideline for use in unsalvageable cases such as evidence of rigor mortis was included in the EMS act, but validity of such decision-making was not studied. Levels of hospital EDs are designated by the government based on capacity and resource availability such as facility, staffing, and devices. Level 1 EDs (n=20) and level 2 EDs (n=110) provide the highest level of emergency services by emergency medicine physicians for 24 hours and 7 days. Level 3 EDs (n=310) provide basic emergency care by general physicians. All EDs are subject to mandatory performance evaluation every year by Ministry of Health and Welfare (3). Hospital EDs generally accept international guidelines on acute cardiac care and resuscitation. However, no standard protocols for post-resuscitation care at hospitals care have been implemented.

Study subjects

We included all EMS-assessed OHCA patients who are 15 years of age or older with presumed cardiac cause and survived to hospital admission from January 1, 2008 to December 31, 2013 (6 years total). All cases were confirmed by medical record review. Patients who died prior to hospital admission as well as patients who had non-cardiac etiology (i.e., trauma, drowning, asphyxia, hanging or other obvious non-cardiac causes) were excluded. Furthermore, patients with unknown neurological status due to incomplete medical record were also excluded.

Study variables

We collected all potential confounders: sex, age, place of arrest, witnessed status, bystander CPR, residence in metropolitan (defined as population over 1 million), response time interval, scene time interval, transport time interval, initial electrocardiogram (ECG), pre-hospital defibrillation, level of ED, reperfusion therapy, and location of any ROSC (i.e., P-ROSC or ED-ROSC). Level of ED was divided into 3 groups according to the Korean Emergency Medical Service Act as regional emergency medical center, local emergency medical center, and local emergency medical facility. Reperfusion therapy included emergency coronary intervention, thrombolysis, and coronary artery bypass grafting (CABG).

Main exposure

MTH was defined as a case receiving mild therapeutic hypothermia using methods such as external cooling (water, fanning, ice padding, cool gel packs, Artic Sun®), internal cooling (gastric lavage, bladder cooling, or intravascular cooling using a catheter) or mixed cooling. In standard, the target temperature should be between 32 and 34 °C and the minimum duration of hypothermia should be at least 12 hours, but we regarded the case as part of the hypothermia-treated group if the hospital attempted the procedure regardless of the actual duration or early withdrawal of the procedure due to death during induced hypothermia. During the study period, hospitals had generally accepted 32 to 34 °C as the targeted temperature range in Korea.

Study Outcome

The primary outcome was survival with favorable neurological outcome at discharge after cardiac arrest, defined as having a Cerebral Performance Category(CPC) score of 1 (good performance, no neurological disability) or 2 (moderate disability, can work) on a five point scale; the remaining categories were 3 (severe disability, dependent), 4 (a vegetative state), and 5 (dead) (21). The CPC score was determined by the medical recorder reviewers based on the discharge summary abstracts or documentations in medical records. Discharge summary abstracts or documentations were drafted by inpatient care doctors, and the summaries were usually reviewed and revised for greater validity by the hospital medical record review team because the summaries were utilized for national health insurance claim data after discharge. However, there was no standard recording frame for the CPC score among the participating hospitals. Therefore, the scores were determined and coded by the medical record reviewers of the Korean CDC who were supervised by the project QMC via on- and off-line consultation for ambiguous cases.

Analysis

Study patients were divided into 2 groups based on the application of MTH (MTH group and non-MTH group) and location of ROSC (P-ROSC group and ED-ROSC group). These two types of baseline characteristics were compared using the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. Multiple logistic regression analyses for the primary outcome with (interaction model) or without (simple model) the interaction term between MTH and location of ROSC were performed to adjust for potential confounders. Statistical analyses were performed with SAS software version 9.3 (SAS Institute Inc, Cary, NC). A 2-sided value of $P < 0.05$ was regarded as statistically significant.

RESULTS

From 138,410 eligible OHCA patients, we excluded patients who were younger than 15 years old at the time of arrest (N=2,814), had non-cardiac causes of arrest (N=38,675), had been dead prior to admission (N=85,763), had incomplete medical record (N=78), and had unknown neurological status at discharge (N=73). The remaining 11,007 patients who survived to admission were included in the analysis (Figure 1). Among those, 1,691(15.4%) were induced MTH. In MTH(+) and MTH(-) group, 298 (17.6%) and 1,548(16.6%) were resuscitated from arrest at pre-hospital stage, respectively (Table 1).

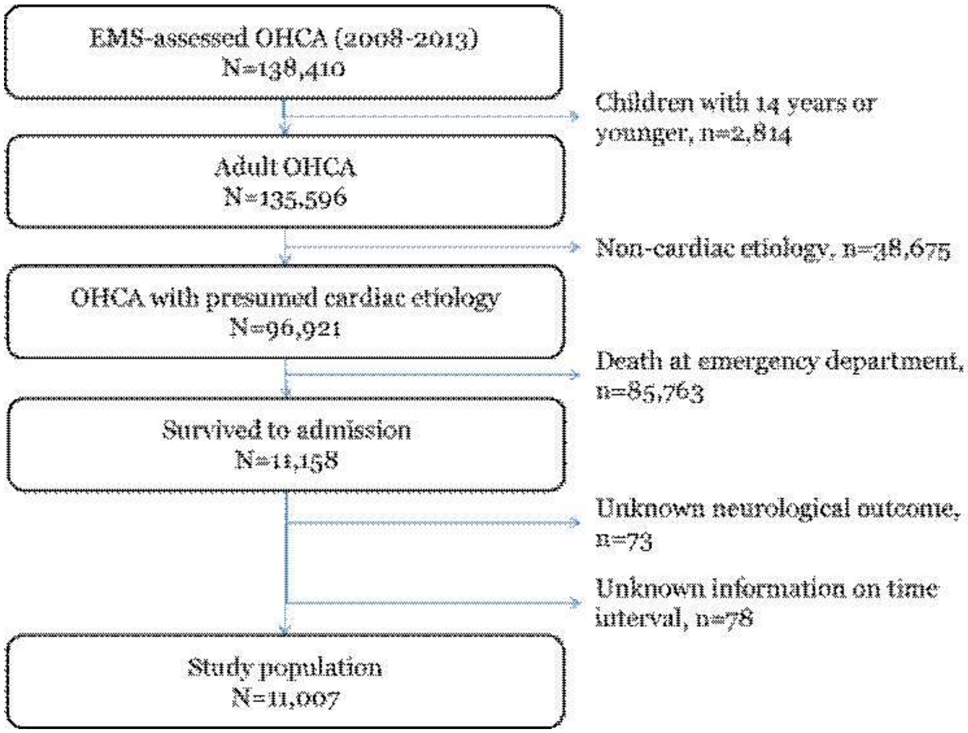

Figure 1. Study population

Generally, the two groups divided by the application of MTH had significantly different baseline characteristics except the location of ROSC. Patients treated with MTH were more likely to be younger male, have a witness, receive bystander CPR, reperfusion therapy and survival to discharge compared with non-MTH group (Table 1). Compared with P-ROSC group, Patients resuscitated in ED stage were more likely to be older female, less likely to be witnessed, were less likely to receive bystander CPR and reperfusion therapy. No significant difference was there on MTH between P-ROSC and ED-ROSC group (Table 2).

Table 1. Demographic findings of study population between mild therapeutic hypothermia and non-mild therapeutic hypothermia group

Variables	All		Non-MTH		MTH		p-value
	N	%	N	%	N	%	
All, Total	11007	100.0	9316	100.0	1691	100.0	
Gender							<0.001
Female	3612	32.8	3184	34.2	428	25.3	
Male	7395	67.2	6132	65.8	1263	74.7	
Age group							<0.001
15-29	379	3.4	275	3.0	104	6.2	
30-39	580	5.3	451	4.8	129	7.6	
40-49	1664	15.1	1401	15.0	263	15.6	
50-59	2523	22.9	2100	22.5	423	25.0	
60-69	2280	20.7	1946	20.9	334	19.8	
70-79	2336	21.2	2005	21.5	331	19.6	
80-	1245	11.3	1138	12.2	107	6.3	
Median (Q1-Q3)	61.5	(50.4-72.9)	62.1	(50.9-73.4)	58.0	(47.6-70.1)	

Response time interval							0.015
0～4	1115	10.1	957	10.3	158	9.3	
5～8	6728	61.1	5662	60.8	1066	63.0	
9～12	2346	21.3	1981	21.3	365	21.6	
13～16	551	5.0	472	5.1	79	4.7	
16～	267	2.4	244	2.6	23	1.4	
Median (Q1-Q3)	6	(5-8)	6	(5-8)	6	(5-8)	
Scene time interval							0.011
0～4	2363	21.5	2024	21.7	339	20.0	
5～8	4631	42.1	3959	42.5	672	39.7	
9～12	2650	24.1	2209	23.7	441	26.1	
13～16	935	8.5	768	8.2	167	9.9	
16～	428	3.9	356	3.8	72	4.3	
Median (Q1-Q3)	6	(4-9)	6	(4-9)	6	(4-10)	
Transport time interval							<0.001
0～4	1691	15.4	1500	16.1	191	11.3	
5～8	5307	48.2	4449	47.8	858	50.7	
9～12	2219	20.2	1818	19.5	401	23.7	
13～16	818	7.4	703	7.5	115	6.8	
16～	972	8.8	846	9.1	126	7.5	
Median (Q1-Q3)	6	(4-9)	6	(6-9)	6	(5-9)	
Metropolitan							<0.001
Non-metropolitan	4934	44.8	4339	46.6	595	35.2	
Metropolitan	6073	55.2	4977	53.4	1096	64.8	
Place							<0.001
Public	2433	22.1	1934	20.8	499	29.5	
Private	7375	67.0	6338	68.0	1037	61.3	
Unknown	1199	10.9	1044	11.2	155	9.2	

Witness							<0.001
Unwitnessed	3447	31.3	3023	32.4	424	25.1	
Witnessed	7560	68.7	6293	67.6	1267	74.9	
Bystander CPR							<0.001
No	9532	86.6	8277	88.8	1255	74.2	
Yes	1475	13.4	1039	11.2	436	25.8	
Primary ECG							<0.001
VF/ VT	2170	19.7	1698	18.2	472	27.9	
PEA	1186	10.8	935	10.0	251	14.8	
Asystole	7651	69.5	6683	71.7	968	57.2	
Defibrillation at EMS							<0.001
No	8533	77.5	7485	80.3	1048	62.0	
Yes	2474	22.5	1831	19.7	643	38.0	
Level of ED							<0.001
Level 1	1957	17.8	1364	14.6	593	35.1	
Level 2	7241	65.8	6171	66.2	1070	63.3	
Level 3	1809	16.4	1781	19.1	28	1.7	
Reperfusion							<0.001
No	9741	88.5	8298	89.1	1443	85.3	
Yes	1266	11.5	1018	10.9	248	14.7	
CPB circulation							<0.001
No	10704	97.2	9111	97.8	1593	94.2	
Yes	303	2.8	205	2.2	98	5.8	
Prehospital ROSC							0.308
No	9161	83.2	7768	83.4	1393	82.4	
Yes	1846	16.8	1548	16.6	298	17.6	

Survival to discharge							<0.001
No	6728	61.1	5971	64.1	757	44.8	
Yes	4279	38.9	3345	35.9	934	55.2	
CPC 1 or 2 at discharge							<0.001
No	9208	83.7	7916	85.0	1292	76.4	
Yes	1799	16.3	1400	15.0	399	23.6	

MTH: mild therapeutic hypothermia, CPR: cardiopulmonary resuscitation, VF/VT: ventricular fibrillation/ ventricular tachycardia, PEA: pulseless electrical activity, EMS: emergency medical services, ED: emergency department, CPB: cardiopulmonary bypass, ROSC: return of spontaneous circulation, CPC: cerebral performance category

Table 2. Comparison of characteristics between prehospital return of spontaneous circulation (ROSC) and emergency department ROSC groups

Variables	All		P-ROSC		ED-ROSC		p-value
	N	%	N	%	N	%	
All, Total	11007	100.0	1846	100.0	9161	100.0	
Gender							<0.001
Female	3612	32.8	483	26.2	3129	34.2	
Male	7395	67.2	1363	73.8	6032	65.8	
Age group							<0.001
15-29	379	3.4	91	4.9	288	3.1	
30-39	580	5.3	120	6.5	460	5.0	
40-49	1664	15.1	343	18.6	1321	14.4	
50-59	2523	22.9	510	27.6	2013	22.0	
60-69	2280	20.7	366	19.8	1914	20.9	
70-79	2336	21.2	282	15.3	2054	22.4	
80-	1245	11.3	134	7.3	1111	12.1	
Median (Q1-Q3)	61.5	(50.4-72.9)	56.6	(47.9-68.6)	62.7	(51.0-73.6)	

Response time interval							<0.001
0~4	1115	10.1	219	11.9	896	9.8	
5~8	6728	61.1	1073	58.1	5655	61.7	
9~12	2346	21.3	395	21.4	1951	21.3	
13~16	551	5.0	88	4.8	463	5.1	
16~	267	2.4	71	3.8	196	2.1	
Median (Q1-Q3)	6	(5-8)	6	(4-8)	6	(5-8)	
Scene time interval							<0.001
0~4	2363	21.5	302	16.4	2061	22.5	
5~8	4631	42.1	702	38.0	3929	42.9	
9~12	2650	24.1	503	27.2	2147	23.4	
13~16	935	8.5	216	11.7	719	7.8	
16~	428	3.9	123	6.7	305	3.3	
Median (Q1-Q3)	6	(4-9)	7	(4-10)	6	(4-9)	
Transport time interval							<0.001
0~4	1691	15.4	228	12.4	1463	16.0	
5~8	5307	48.2	678	36.7	4629	50.5	
9~12	2219	20.2	363	19.7	1856	20.3	
13~16	818	7.4	175	9.5	643	7.0	
16~	972	8.8	402	21.8	570	6.2	
Median (Q1-Q3)	6	(4-9)	8	(5-14)	6	(4-9)	
Metropolitan							0.008
Non-metropolitan	4934	44.8	879	47.6	4055	44.3	
Metropolitan	6073	55.2	967	52.4	5106	55.7	
Place							<0.001
Public	2433	22.1	473	25.6	1960	21.4	
Private	7375	67.0	1078	58.4	6297	68.7	
Unknown	1199	10.9	295	16.0	904	9.9	
Witness							<0.001
Unwitnessed	3447	31.3	428	23.2	3019	33.0	
Witnessed	7560	68.7	1418	76.8	6142	67.0	
Bystander CPR							<0.001
No	9532	86.6	1400	75.8	8132	88.8	
Yes	1475	13.4	446	24.2	1029	11.2	

Primary ECG							<0.001
VF/ VT	1957	17.8	593	35.1	1364	14.6	
PEA	7241	65.8	1070	63.3	6171	66.2	
Asystole	1809	16.4	28	1.7	1781	19.1	
Defibrillation at EMS							<0.001
No	8533	77.5	821	44.5	7712	84.2	
Yes	2474	22.5	1025	55.5	1449	15.8	
Level of ED							<0.001
Level 1	1957	17.8	446	24.2	1511	16.5	
Level 2	7241	65.8	1211	65.6	6030	65.8	
Level 3	1809	16.4	189	10.2	1620	17.7	
Reperfusion							<0.001
No	9741	88.5	1388	75.2	8353	91.2	
Yes	1266	11.5	458	24.8	808	8.8	
CPB circulation							<0.001
No	10704	97.2	1819	98.5	8885	97.0	
Yes	303	2.8	27	1.5	276	3.0	
Hypothermia							0.308
No	9316	84.6	1548	83.9	7768	84.8	
Yes	1691	15.4	298	16.1	1393	15.2	
Survival to discharge							<0.001
No	6728	61.1	389	21.1	6339	69.2	
Yes	4279	38.9	1457	78.9	2822	30.8	
CPC 1 or 2 at discharge							<0.001
No	9208	83.7	772	41.8	8436	92.1	
Yes	1799	16.3	1074	58.2	725	7.9	

MTH: mild therapeutic hypothermia, CPR: cardiopulmonary resuscitation, VF/VT: ventricular fibrillation/ ventricular tachycardia, PEA: pulseless electrical activity, EMS: emergency medical services, ED: emergency department, CPB: cardiopulmonary bypass, ROSC: return of spontaneous circulation, CPC: cerebral performance category

In the simple model without the interaction term, MTH had an association with good neurological outcome (adjusted odds ratio=1.32, 95% confidence interval=1.11-1.57) (Table 3). In the interaction model, the effect of MTH on favorable neurological outcome differed by the location of ROSC. If patients were resuscitated from arrest at prehospital stage, the beneficial effect of MTH on neurological outcome could not be identified (adjusted odds ratio=0.78, 95% confidence interval =0.58-2.70). If patients, however, were resuscitated at emergency department, MTH was significantly associated with good neurological outcome (adjusted odds ratio=1.68, 95%, confidence interval =1.34-1.98) (Table 4)

Table 3. Logistic regression analysis on outcomes by mild therapeutic hypothermia and location of return of spontaneous circulation

Outcomes	Exposure Group	Total	Positive		Unadjusted			Adjusted		
		N	N	%	OR	95% CI		OR	95% CI	
Survival to discharge, Total		11,007	4,279	38.9						
	MTH†									
	Non-MTH	9,316	3,345	35.9	1.00					
	MTH	1,691	934	55.2	2.20	1.98	2.45	1.87	1.65	2.21
	ROSC§									
	ED	9161	2822	30.8	1.00					
	Prehospital	1846	1457	78.9	8.41	7.46	9.49	6.47	5.63	7.43
CPC 1 or 2 at discharge, Total		11,007	1,799	16.3						
	MTH†									
	Non-MTH	9,316	1,400	15.0	1.00					
	MTH	1,691	399	23.6	1.75	1.54	1.98	1.32	1.11	1.57
	ROSC§									
	ED	9,161	725	7.9	1.00					
	Prehospital	1,846	1074	58.2	8.41	7.46	9.49	11.78	10.14	13.69

† Adjusted for gender, age group, ECG group, metropolitan, place of event, witness, bystander cardiopulmonary resuscitation, defibrillation at prehopsital period, level of emergency department, response time interval, scene time interval, transport time interval, reperfusion therapy, cardiopulmonary bypass, and prehospital return of spontaneous circulation

§ Adjusted for gender, age group, ECG group, metropolitan, place of event, witness, bystander cardiopulmonary resuscitation, defibrillation at prehopsital period, level of emergency department, response time interval, scene time interval, transport time interval, reperfusion therapy, cardiopulmonary bypass, and mild therapeutic hypothermia

MTH: mild therapeutic hypothermia, ROSC: return of spontaneous circulation, ED: emergency department ,CPC: cerebral performance category, OR: odds ratio, 95% CI: 95% confidence interval

Table 4. Logistic regression analysis on outcomes by mild therapeutic hypothermia across the location of return of spontaneous circulation

Outcomes	Location of ROSC	MTH versus non-MTH		
		Adjusted OR*	95% CI	
Survival to discharge				
	Prehospital	2.04	1.79	2.32
	ED	0.84	0.59	1.19
CPC 1 or 2 at discharge				
	Prehospital	0.78	0.58	2.70
	ED	1.68	1.34	1.98

* Adjusted for gender, age group, ECG group, metropolitan, place of event, witness, bystander cardiopulmonary resuscitation, defibrillation at prehopsital period, level of emergency department, response time interval, scene time interval, transport time interval, reperfusion therapy, cardiopulmonary bypass, prehospital return of spontaneous circulation (ROSC), and interaction term between mild therapeutic hypothermia and location of ROSC

MTH: mild therapeutic hypothermia, ROSC: return of spontaneous circulation, ED: emergency department, CPC: cerebral performance category, OR: odds ratio, 95% CI: 95% confidence interval

DISCUSSION

Regardless of location of ROSC, the current guideline for post-resuscitation care strongly recommends application of MTH to comatose adult patients resuscitated from OHCA of ventricular fibrillation, and weakly recommends to those with non-shockable initial rhythm (7, 17). The primary purpose of this study was to determine the association between MTH and neurological outcome after OHCA according to the location of ROSC. We found a significant association between MTH and good neurological outcome; however, MTH did not have positive effects on good neurological outcome in prehospital ROSC group as opposed to significant benefit in ED-ROSC group.

One possible explanation for this result is that P-ROSC can be related to early ROSC. Early ROSC may be associated with less ischemic brain injury, so patients resuscitated in prehospital stage may benefit less from MTH. Animal studies have shown that ischemic brain damage after cardiac arrest increased when time interval from arrest to ROSC was beyond 8 minutes (24, 25). Additionally, Christoph Testori et al. reported that when the duration of complete circulatory standstill increased, the positive effects of MTH in OHCA patients increased (26). These findings implicate early ROSC as the lacking factor for patients who display diminished effect of MTH.

Two case series studies revealed the shorter time interval from collapse to ROSC as an important prognostic factor for good neurological outcome after cardiac arrest (27, 28). In our data, time from call to departure from scene was 13 minutes (median) in P-ROSC and 12 minutes (median) in ED-ROSC group. When considering that many patients in P-ROSC group were resuscitated before leaving the scene in our EMS practice, it is possible to predict that time from arrest to ROSC in P-ROSC group was much shorter than that of ED-ROSC group. This assumption is supported by other studies (21). The study setting on EMS system follows “scoop and run” model. The model encourage EMS providers to deliver shorter CPR at the field by providing less than 3 to 4 cycles of CPR with rhythm analysis and to transport the patient to ED while providing ambulance CPR unless the patient is not resuscitated. Most cases in P-ROSC group might have very short time interval (several minutes) from collapse to ROSC than ED-ROSC (longer than 20 minutes) when assuming the time from time interval variables including response time interval, scene time interval, and transport time interval. We could not compare the exact time from collapse to ROSC due to lack of information on time at ROSC.

We found that prehospital ROSC was an important predictor of good neurological outcome after OHCA (adjusted odds ratio=11.78). This result is consistent with previous studies. Koichi Hayakawa et al. (19) and Youichi Yanagawa et al. (20) analyzed and reported that P-ROSC was associated with good neurological function at discharge regardless of initial rhythm. However, these studies did not consider MTH as a confounder, so they could not demonstrate the interaction between MTH and location of ROSC. Takuro Shinada et al. (21) reported that P-ROSC was a powerful prognostic factor on favorable neurological outcome in OHCA patients who had MTH. However, this study faces several limitations for the findings to be generalized as the study included a small number of patients and was conducted in a single hospital.

Current guideline also recommends MTH to be induced as soon as possible after ROSC based on previous animal model studies of cardiac arrest (29-31). James H. Walters et al. reported that earlier cooling might not have important impact on good neurological outcome (17). Furthermore, no clinical studies have been reported to define who benefits more or less from MTH in terms of time to ROSC or location of ROSC. Based on our results, the shorter the time to ROSC, the greater benefit MTH may disappear on cerebral resuscitation.

To date, optimal hypothermia protocol remains unclear. Many researcher and practitioner considered 32-24℃ as optimal target temperature (17). Recently, Niklas Nielsen et al. (18) performed randomized controlled trial and revealed that hypothermia protocol could be considered targeted temperature management. Our study can add one evidence on ‘who’ will be the target of MTH to current practice.

There are several limitations to this study. We did not adjust all potential confounders such as quality of CPR or specific type of MTH procedure.

Hospital EDs do not have the same protocol for post resuscitation care and hypothermia interventions. We could not measure the exact time for ROSC, which could have potentially biased our analysis. We measured the clinical neurological outcomes obtained by medical record reviewers from discharge abstract or medical record, not by specialties of physician who performed clinical neurological examination were not specified. We also didn't collect data concerning the important variables such as seizure status, administrating sedative drugs or anticonvulsant drugs which might influence neurological status on discharge. In addition, though, we provided strict data quality assurance program during data collection, an inter-rater agreement issue could be raised. The most important limitation is the EMS system characteristics. The study setting accepts "scoop and run model," which is far different from the Western EMS programs. The difference should be considered when the study results are generalized to be interpreted.

In conclusion, MTH was significantly associated with good neurological recovery in OHCA survivors, but the effect was different by location of ROSC. MTH was significantly beneficial for ED-ROSC patients, but not for P-ROSC patients in this EMS system.

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국문 초록

서론: 치료적 저체온요법(mild therapeutic hypothermia)은 병원 밖 심정지(out-of hospital cardiac arrest, OHCA) 환자의 양호한 신경학적 호전(good neurological outcome)과 관련이 있다고 알려져 있다. 또한 병원 전단계 자발순환회복(return of spontaneous circulation)은 응급실 자발순환회복의 경우보다 더 좋은 병원결과와 관련이 있다고도 알려져 있다. 그러나 심정지환자의 양호한 신경학적 호전에 있어서 치료적 저체온요법과 자발순환회복 위치(병원 전단계 vs. 응급실)사이에 교호작용이 있는지는 잘 알려져 있지 않다. 본 연구의 목적은 이러한 교호작용을 평가하는 것이다.

방법: 2008년부터 2013년까지의 전국적 심질환 등록자료(nationwide cardiac registry)를 자료원으로 하여 심장성으로 추정되는 원인으로 병원 밖에서 심정지가 발생한 성인 환자 중 살아서 병원에 입원한 환자만을 추출하였다. 본 연구에서 주요하게 다룬 변수는 나이, 성별, 심정지 발생장소, 심정지 목격여부, 발견자 심폐소생술 여부, 대도시 여부, 구급대 반응시간, 병원 전단계 제세동 여부, 응급실 수준, 재관류 치료 유무, 초기 심전도 그리고 자발순환회복 위치(병원 전단계 vs. 응급실)였다. 방법과 상관없이 저체온 유도를 받았을 경우 치료적 저체온요법을 받은 것으로 하였다. 의무기록 조사를 통해 확인된 신경학적 수행능력 평가지표(cerebral performance categories scale, CPC) 중에서 1점 또는 2점을

양호한 신경학적 회복의 기준으로 보았고, 이것을 본 연구의 일차결과로 하였다. 다변량 로지스틱 회귀분석을 통하여 잠재적인 혼란변수들뿐만 아니라 치료적 저체온요법과 자발순환회복 위치 사이의 교호작용항(interaction term)을 보정하였다. 그 결과는 보정된 오즈비(adjusted odds ratio)와 95% 신뢰구간(confidence interval)으로 제시하였다.

결과: 총 138,410명의 성인 심정지 환자 중에서 11,158명(8.1%)의 환자가 살아서 병원에 입원하였다. 그 중 병원 전단계 자발순환회복을 보인 환자 중에서 양호한 신경학적 회복을 보인 환자는 1,074명(58.2%)였고, 응급실에서 자발순환회복을 보인 환자 중에서 그 숫자는 725명(7.9%)였다($p<0.001$). 치료적 저체온요법을 받은 환자와 그렇지 않은 환자에서 양호한 신경학적 회복을 보인 비율은 각각 399명(23.6%)과 1,400명(15.0%)이었다($p<0.001$). 치료적 저체온요법은 총 15.4%의 환자에게 적용되었는데, 병원 전단계 자발순환회복을 보인 환자의 경우 15.8%에게, 응급실에서 자발순환회복을 보인 환자의 경우 13.2%에게 적용되었다. 교호작용항을 보정하지 않은 다변량 로지스틱 회귀분석에서 치료적 저체온요법과 양호한 신경학적 회복 사이에 통계적으로 유의한 관련성이 있었다(보정된 오즈비=1.32, 95% 신뢰구간=1.11−1.57). 더욱이 병원 전단계에서 자발순환이 회복된 환자는 응급실에서 회복된 환자에 비해 신경학적 회복이 양호할 가능성이 11.8배 높았다 (보정된 오즈비=11.78, 95% 신뢰구간=10.14−13.69). 하지만, 교호작용항을 보정하였을 때 치료적 저체온요법이 양호한 신경학적 회복에 미치는 영향은 병원 전단계에서 자발순환이 회복된 환자의 경우 0.78 (0.58−2.70), 응급실에서 자발순환이 회복된 환자의 경우 1.68 (1.34−1.98)이었다.

결론: 치료적 저체온요법은 병원 밖 심정지환자의 신경학적 회복과 유의한 관련이 있었다. 하지만 그 효과는 자발순환이 회복된 위치가 병원 전단계인지 응급실인지에 따라 달랐다. 병원 전단계에서 자발순환이 회복된 환자는 응급실에서 자발순환이 회복된 환자에 비해 양호한 신경학적 회복을 보일 가능성이 매우 높았지만, 치료적 저체온요법의 신경학적 회복에 대한 효과는 오히려 응급실에서 자발순환이 회복된 환자에게서만 확인되었다.

주요어 : 심정지, 저체온, 자발순환회복, 결과
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