Variability of Post-Cardiac Arrest Care Practices Among Cardiac Arrest Centers: United States and South Korean Dual Network Survey of Emergency Physician Research Principal Investigators

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There is little consensus regarding many post-cardiac arrest care parameters. Variability in such practices could confound the results and generalizability of post-arrest care research. We sought to characterize the variability in post-cardiac arrest care practice in Korea and the United States. A 54-question survey was sent to investigators participating in one of two research groups in South Korea (Korean Hypothermia Network [KORHN]) and the United States (National Post-Arrest Research Consortium [NPARC]). Single investigators from each site were surveyed ($N=40$). Participants answered questions based on local institutional protocols and practice. We calculated descriptive statistics for all variables. Forty surveys were completed during the study period with 30 having greater than 50% of questions completed (75% response rate; 24 KORHN and 6 NPARC). Most centers target either 33°C ($N=16$) or vary the target based on patient characteristics ($N=13$). Both bolus and continuous infusion dosing of sedation are employed. No single indication was unanimous for cardiac catheterization. Only six investigators reported having an institutional protocol for withdrawal of life-sustaining therapy (WLST). US patients with poor neurological prognosis tended to have WLST with subsequent expiration ($N=5$), whereas Korean patients are transferred to a secondary care facility ($N=19$). Both electroencephalography modality and duration vary between institutions. Serum biomarkers are commonly employed by Korean, but not US centers. We found significant variability in post-cardiac arrest care practices among US and Korean medical centers. These practice variations must be taken into account in future studies of post-arrest care.

Keywords: cardiac arrest, targeted temperature management, therapeutic hypothermia, critical care neuro-prognostication, withdrawal of life-sustaining therapies

Introduction

THE APPROACH TO MANAGING temperature after cardiac arrest has evolved significantly over the last 15 years, leaving considerable room for practice variation (Camp-Rogers *et al.*, 2013; Kotini-Shah *et al.*, 2016). Preclinical

animal work almost uniformly supports lowering body temperature after cardiac arrest (Busto *et al.*, 1987, 1989; Sterz *et al.*, 1991; Yamashita *et al.*, 1991; Kuboyama *et al.*, 1993; Nozari *et al.*, 2004). Whereas two initial trials demonstrated improved outcomes in comatose survivors of out of hospital cardiac arrest (OHCA) with therapeutic hypothermia (TH)

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targeted at 32–34°C (Bernard *et al.*, 2002; Hypothermia after Cardiac Arrest Study, 2002), a subsequent trial was neutral for short-term and long-term survival in patients treated with either TH at 33°C or targeted temperature management (TTM) strategy at 36°C (Nielsen *et al.*, 2013; Cronberg *et al.*, 2015; Lilja *et al.*, 2015). A pediatric trial of OHCA found the same neutral results for either 33°C or 36.8°C (Moler *et al.*, 2015; Slomine *et al.*, 2016), but has been criticized as being underpowered to detect subpopulations that may benefit from deeper cooling (Vincent and Taccone, 2015). In the wake of these trials, institutions target to either 33°C or 36°C and the optimal target temperature remains a topic of debate (Bernard, 2014; Kim *et al.*, 2015a; Polderman and Varon, 2015a, 2015b). A 2015 international consensus statement actually supports variability in practice, broadening the recommended temperature range to 32–36 degrees centigrade, and emphasizing the avoidance of hyperthermia (Callaway *et al.*, 2015).

By comparison, there is even less evidence to make specific recommendations about other aspects of temperature management (duration, cooling and rewarming rates, and induction and maintenance methods), let alone cardiac catheterization, neurological prognostication, and withdrawal of life-sustaining therapy (WLST). Unknown variability in any of these practices could potentially influence outcomes in observational studies and represent site-level confounders in multicenter prospective trials (Geocadin *et al.*, 2012; Perman *et al.*, 2012; Geri *et al.*, 2015; Elmer *et al.*, 2016).

The objective of the current study is to describe post-cardiac arrest care practices among an international group of medical centers in the TTM (post-Nielsen) era. We hypothesize there will be a degree of practice variability in aspects of post-arrest care, including target temperature, duration at target temperature, neuromonitoring devices utilized during temperature management, indications and contraindications for cardiac catheterization, neurological prognostication, and disposition of patients with poor neurological prognosis.

Methods

The University of Pittsburgh Institutional Review Board granted IRB exemption for this voluntary survey study. The survey was constructed initially during a meeting of study investigators. Multiple iterations and revisions were composed through email communication until a consensus was reached. A 54-question survey concerning post-cardiac arrest care practices was sent to investigators participating in one of two research groups in South Korea (Korean Hypothermia Network [KORHN]) and the United States (National Post-Arrest Research Consortium [NPARC]) through Qualtrics survey software (Provo, UT). The survey was available in both English and Korean. The KORHN was founded in 2011 and consists of 35 medical centers in South Korea (Kim *et al.*, 2015b). Participating centers populate a shared registry with common data elements for OHCA patients. NPARC consists of seven tertiary care medical centers in the United States and was established to investigate treatment strategies for OHCA and perform clinical trials (Donnino *et al.*, 2011, 2014). Participating investigators from both KORHN and NPARC sites are involved in the care of OHCA patients from admission to hospital discharge.

We sent the survey to a single principle investigator from each KORHN and NPARC site ($N=40$) (Appendix). Investigators were instructed to answer survey questions based

on local institutional protocols and practice of OHCA patients that achieve return of spontaneous circulation (ROSC). OHCA was defined as a patient that received chest compressions outside of a hospital from a healthcare provider, regardless of initial rhythm. ROSC was defined as sustained return of spontaneous circulation for greater than 20 minutes. The survey was sent in December 2015 and final data collection was completed in January 2016. Survey responses were included in the analysis if greater than 50% of questions were answered. We calculated descriptive statistics for all variables using STATA 13.1 (College Station, TX). We compared practices between high- and low-volume Korean (≤ 50 OHCA per year) and US centers. Data presented below compares only Korean and US centers as practice did not significantly differ between low- and high-volume Korean centers (data not shown).

Results

The survey (Fig. 1) was sent to a total of 33 South Korean and 7 US investigators. Forty surveys were completed during the study period for a 100% overall response rate with 30/40 (75%; 24 KORHN and 6 NPARC), having greater than 50% of questions completed, and characteristics of surveyed institutions and investigators being listed in Table 1 and Supplementary Table S1 (Supplementary Data are available online at www.liebertpub.com/ther).

Targeted temperature management

Most centers target either 33°C ($N=16$) or vary the target based on patient characteristics ($N=13$) (Table 2). Variables used to determine target temperature included degree of brain injury, bleeding, and degree of hemodynamic instability. One center targets only 36°C. Single methods of cooling are used at most institutions (Surface cooling blankets=4; Endovascular=8; Surface hydrogel=13). Patients are kept at target for either 24 hours after ROSC ($N=12$) or 24 hours after goal temperature was reached ($N=16$). One center prolongs TTM to 48 hours in severely brain-injured patients. Rewarming rates range from 0.2 to 0.5°C/hr with most centers rewarming at a rate of 0.25°C/hr ($N=12$). After the initial TTM period, fever is actively prevented with continued use of cooling devices ($N=24$) (Table 2).

Many different combinations of both bolus and continuous infusion dosing of sedation are employed, including midazolam, propofol, fentanyl, remifentanyl, and dexmedetomidine (Supplementary Table S2). A bolus dose of midazolam is most

FIG. 1. Consort diagram of study population.

TABLE 1. DEMOGRAPHICS OF SURVEYED INVESTIGATORS AND HOSPITALS

<i>Number of arrests treated at hospital per year</i>	<i>USA (N=6), n (%)</i>	<i>Korea (N=24), n (%)</i>
<10	0 (0)	0 (0)
10–24	0 (0)	2 (8)
25–49	0 (0)	4 (17)
50–74	1 (16)	2 (8)
75–99	1 (16)	3 (13)
100–124	2 (34)	2 (8)
>125	2 (34)	11 (46)
<i>Number of arrests treated with TTM per year</i>	N=5	
<10	0 (0)	4 (17)
10–24	0 (0)	8 (33)
25–49	2 (40)	7 (29)
50–74	1 (20)	5 (21)
75–99	1 (20)	0 (0)
100–124	0 (0)	0 (0)
>125	1 (20)	0 (0)
<i>Number of post-arrest cardiac catheterizations per year</i>	N=5	
<10	1 (16)	6 (25)
10–19	2 (34)	8 (32)
20–29	1 (16)	6 (25)
30–39	0 (0)	3 (13)
40–49	0 (0)	0 (0)
50–59	1 (16)	1 (5)
60–70	0 (0)	0 (0)

TTM, targeted temperature management.

often used for sedation ($N=21$). Additionally, a wide range of neuromuscular blocking agents are utilized for a variety of indications and durations ranging from standardized periods to PRN bolus dosing for shivering.

Cardiac catheterization

Indications for cardiac catheterization are listed in Table 3. No single indication was unanimous among all surveyed investigators. The only absolute contraindications to cardiac catheterization reported were impending brain death, irreversible cause of cardiac arrest, including intracerebral hemorrhage, and refusal by surrogate decision maker.

Neurological prognostication

Only six (20%) of the surveyed investigators reported having an institutional protocol for WLST (Table 4). Facilitation of WLST conversations with families is most often done by the unit attending on duty ($N=13$; 43%). The most common disposition of patients with poor neurological prognosis in the United States was WLST with subsequent expiration ($N=5$; 84%), whereas the Korean patients with poor neurological prognosis tended to be transferred to a secondary care facility ($N=19$; 80%). Both electroencephalography (EEG) modality and duration vary between institutions (Table 4). Serum biomarkers are commonly employed in Korea, but not in the United States. Timing of serum biomarkers

TABLE 2. TTM PRACTICE CHARACTERISTICS

	<i>USA (N=6), n (%)</i>	<i>Korea (N=24), n (%)</i>
TTM goal temperature		
33°C	2 (34)	14 (58)
36°C	0 (0)	1 (4)
Admission temperature	0 (0)	0 (0)
Variable (33°C or 36°C)	4 (66)	9 (38)
Method of cooling		
Surface cooling blankets	1 (16)	3 (13)
Endovascular	2 (34)	6 (25)
Surface Hydrogel	2 (34)	11 (45)
Both blankets and endovascular	0 (0)	1 (4)
Both hydrogel and endovascular	1 (16)	3 (13)
Goal temp duration		
12 hours after ROSC	0 (0)	0 (0)
24 hours after ROSC	2 (34)	10 (42)
12 hours after goal temp reached	0 (0)	1 (4)
24 hours after goal temp reached	4 (66)	12 (50)
Other duration ^a	0 (0)	1 (4)
Post TTM fever prophylaxis		N=22
Anti-pyretic medications	2 (34)	2 (9)
Cooling blanket or wrap	2 (34)	12 (55)
Endovascular catheter	1 (16)	7 (32)
Other ^b	1 (16)	1 (4)
None	0 (0)	0 (0)
Contraindication to TTM		N=24
Nonshockable rhythm	0 (0)	0 (0)
Unwitnessed arrest	0 (0)	0 (0)
IHCA	0 (0)	3 (13)
>30 minutes of BLS w/o ROSC	0 (0)	1 (4)
Total ischemic time >60 minutes	1 (16)	1 (4)
Total ischemic time >30 minutes	0 (0)	0 (0)
Hypothermia on admission	0 (0)	5 (21)
GCS ≥ 8	1 (16)	8 (33)
>85 years old	0 (0)	3 (12)
Pregnant	0 (0)	8 (33)
Existing DNR/DNI	4 (66)	24 (100)
Terminal illness before arrest	2 (34)	18 (75)
Poor baseline neurological status	4 (66)	16 (67)
Increased INR/DIC/active bleeding	0 (0)	12 (50)
Noncardiac etiology	1 (16)	0 (0)
Recent trauma	0 (0)	3 (13)
Recent surgery	0 (0)	4 (17)
Other medical comorbidities	0 (0)	3 (13)
No contraindications	1 (16)	0 (0)

^aOther duration of cooling included extension of TTM to 48 hours in severely brain-injured patients.

^bOther post-TTM fever prophylaxis included continued use of employed device.

BLS, basic life support; DIC, disseminated intravascular coagulation; DNI, do not intubate; DNR, do not resuscitate; INR, international normalized ratio; ROSC, return of spontaneous circulation.

varied with some institutions drawing biomarkers at emergency department admission only while others complete multiple analyses during hospitalization (Supplementary Table S2).

Discussion

We found significant variability in temperature management strategies, cardiac catheterization indications, determination of neurological prognostication, and disposition of patients with

TABLE 3. POST-ARREST CARDIAC CATHETERIZATION INDICATIONS

	USA (N=6), n (%)	Korea (N=24), n (%)
Indications for cardiac catheterization		
STEMI	6 (100)	22 (92)
History of CAD	1 (16)	8 (33)
Focal wall motion abnormality	3 (50)	11 (46)
History of VF/VT	4 (66)	7 (29)
Elevated troponin	1 (16)	4 (17)
Cardiogenic shock	1 (16)	6 (25)
Other ^a	0 (0)	3 (13)

^aOther indications for cardiac catheterization included high suspicion for acute coronary occlusion and no other identifiable etiology of arrest.

CAD, coronary artery disease; STEMI, ST-segment elevation myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

poor neurological prognosis among an international cohort of surveyed investigators. WLST practices and cardiac catheterization indications varied between US and Korean centers. Individual clinician practice, belief in therapies, and prognostic tools, as well as hospital availability of interventions, specifically cardiac catheterization, EEG, and biomarkers may influence indications and use. The variability of these clinical practices must be taken into account when comparing registry data across institutions and countries. For example, different durations and depths of temperature management could affect

TABLE 4. CHARACTERISTICS OF NEUROLOGICAL CARE AND PROGNOSTICATION

	USA (N=6), n (%)	Korea (N=24), n (%)
WLST institutional protocol		
Yes	3 (50)	3 (12)
No	3 (50)	21 (88)
WLST clinical facilitator		
Attending on duty	1 (16)	12 (50)
Critical care team on duty	2 (34)	0 (0)
Post-arrest team	3 (50)	2 (8)
Ethics committee	0 (0)	3 (13)
Palliative care	0 (0)	1 (4)
Cannot withdraw	0 (0)	6 (25)
Disposition of patients with poor neurological prognosis		
Continued active ICU care	0 (0)	2 (8)
No escalation of ICU care	0 (0)	2 (8)
Withdrawal	5 (84)	0 (0)
Transfer to secondary care facility	0 (0)	19 (80)
Surrogate decides destination	1 (16)	1 (4)
EEG use		
Yes	6 (100)	20 (83)
No	0 (0)	4 (17)
Serum biomarker use	N=5	
Yes	1 (20)	22 (92)
No	4 (80)	2 (8)

EEG, electroencephalography; GFAP, glial fibrillary acidic protein; ICU, intensive care unit; NSE, neuron-specific enolase; WLST, withdrawal of life-sustaining therapy.

the pharmacokinetics of many sedation and antiepileptic agents (Tortorici *et al.*, 2007; Hostler *et al.*, 2010; Zhou and Poloyac, 2011; Zhou *et al.*, 2011; Empey *et al.*, 2013). If left unaccounted for in future trials, subgroups may be exposed to adverse drug events or unexpectedly prolonged sedation, confounding neurological examination. Additionally, the variability in these practices by definition supports clinical equipoise for sequent clinical trials surrounding these post-cardiac arrest care practices.

These reported variations represent potential confounders of retrospective studies. These may explain some of the heterogeneity seen when comparing survival and good neurological outcome between studies. Future multicenter studies and meta-analyses may be unable to combine patients treated with various protocols for TTM. These results accentuate the need for standardized care and prognostic workup in future trials (Nielsen *et al.*, 2013). Similarly, extended fever treatment and prophylaxis may influence TTM results. Fever, both during and post TTM, has been associated with poor outcomes, an additional layer of variability and potential confounder (Gebhardt *et al.*, 2013; Picetti *et al.*, 2016). Thus, neuronal susceptibility to fever may change over time. There is room to understand future TTM adoption and deadoption practices among institutions. Given the variability in care delivery, one way to standardize comparisons between groups is with post-cardiac arrest illness severity scores. These risk stratification tools could be used in future studies to ensure consistent comparisons between groups (Rittenberger *et al.*, 2011; Coppler *et al.*, 2015).

Few formalized WLST protocols were reported by the respondents. Encouraging a standardized approach may limit early withdrawal (Elmer *et al.*, 2016). Given social norms preventing withdrawal of support, the KORHN appears well poised to study which patients have delayed awakening without the confounder of a self-fulfilling prophecy (Geocadin *et al.*, 2012).

Limitations

Our work has several limitations. We present a survey study of single principal investigators for which participants answered questions based on local protocols and usual clinical care. The survey may not reflect the entire range or actual clinical care across individual practitioners at each site. Reported variation may be greater at the provider level than the site level (Leary *et al.*, 2015; Deye *et al.*, 2016; Kotini-Shah *et al.*, 2016). Additionally, comparing a smaller US cohort to a larger Korean cohort may not reflect all variability between these countries. Finally, the surveyed institutions may not be representative of “typical” care delivered at most hospitals. Most investigators represent a high-volume cardiac arrest center, which may provide more aggressive care as compared to lower volume noncardiac arrest centers.

Conclusions

We found significant variability in post-cardiac arrest care practices among US and Korean medical centers. These practice variations must be taken into account in future prospective as well as retrospective multicenter studies of post-arrest care.

Author Disclosure Statement

No competing financial interests exist.

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