Outcomes in Cardiac Arrest Patients due to Toxic Exposure Treated with Therapeutic Hypothermia

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Abstract The incidence and outcome of patients who undergo therapeutic hypothermia (TH) after toxin-induced cardiac arrest (TICA) is not previously described. Our study aimed to describe the incidence, epidemiologic characteristics, and outcomes of patients who experience TICA in a dedicated clinical pathway for post-cardiac arrest care between November 2007 and February 2013. All patients were treated in an evidence-based clinical pathway that included TH. Database and medical records were independently reviewed by investigators to

ascertain TICA. TICA was defined as cardiac arrest (CA) directly and immediately caused by a xenobiotic exposure. All patients were enrolled at Carolinas Medical Center, an urban 874-bed teaching hospital that serves as a regional cardiac resuscitation center. All patients were adult victims of cardiac arrest who had obtained return of spontaneous circulation and were enrolled in a clinical pathway for post-cardiac arrest care that included TH. Three hundred eighty-nine patients underwent treatment following CA during the study period and 48 (12 %) were deemed TICA. Patients who suffered TICA were slightly younger, less likely to have an initial shockable rhythm, and less likely to receive bystander CPR as compared to non-toxic cases. TICA accounted for a significant proportion of patients in this study. Additional, larger studies are needed to fully elucidate the optimal role for TH in TICA.

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Keywords Cardiac arrest · Toxic ingestion · Therapeutic hypothermia

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Introduction

During the 1950s, varying degrees of hypothermia were first used in patients undergoing prolonged cardiac surgery to help decrease the likelihood of anoxic brain injury. In the decades since, this cerebroprotective treatment has been expanded to cardiac arrest (CA) victims and termed therapeutic hypothermia (TH). In 2002, the Advanced Life Support (ALS) Task Force of the International Liaison Committee on Resuscitation (ILCOR) recommended that adult patients with spontaneous circulation after out-of-hospital cardiac arrest due to ventricular fibrillation (VF) who remain unconscious should be cooled to 32 to 34 °C for 12 to 24 h. ILCOR added that patients suffering an in-hospital CA or initial rhythm other than

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VF may benefit from the same cooling practice [1]. Many institutions have since incorporated TH into their resuscitation efforts.

Multi-center studies have investigated the mortality and neurologic outcomes of patients treated with TH after CA with promising results [2]. However, organic heart disease is the focus of these reports and there is limited published experience regarding the epidemiology of toxin-induced cardiac arrest (TICA) and resuscitation outcomes. Six prior database studies in the last 11 years from Austria [3], the USA [4–7], and Australia [8] found a prevalence of drug-induced cardiac arrest from 3–10 %. Overall survival ranged widely from 1–34 % in five of these reports and none of these studies included TH as a therapeutic modality. The outcome benefit of hypothermia for TICA remains to be determined. In theory, the same neuroprotective benefits that hypothermia confers for primary organic CA may also apply for TICA.

Katz et al. was the first to specifically include therapeutic cooling as a part of resuscitation from TICA [4]. Patients that were cooled had an overall survival rate of 16 % and survival rate with good neurologic outcome of 13 %. With these limited data in mind, we sought to compare the clinical characteristics and outcomes of adult TICA and non-TICA patients enrolled in our institutional structured resuscitation pathway that included TH. We hypothesized that clinical characteristics of TICA patients were different from non-TICA patients and that TICA patients experienced lower rates of favorable neurologic outcome.

Methods

We performed a retrospective review of all patients enrolled and treated in our post-CA clinical pathway consisting of collected data between November 2007 and February 2013. Patients were enrolled in this clinical pathway prospectively. Our study examined patients in this registry retrospectively and a database was constructed to include not only information entered in the registry, but also additional information pertinent to our research question found in the patient's medical record. This study was approved by the Institutional Review Board (IRB) of the Carolinas HealthCare System. Waiver of informed consent and waiver of authorization were granted. The IRB additionally determined the study posed minimal risk to subjects and met criteria for expedited review.

Setting

All patients were enrolled following admission to Carolinas Medical Center, an urban 874-bed teaching hospital that serves as a regional cardiac resuscitation center. All study subjects were identified at admission in the emergency department (ED) or upon arrival to the intensive care unit in the case

of an in-hospital cardiac arrest based on enrollment into a dedicated post-CA clinical pathway that includes structured resuscitation and TH. Our institution's TH protocol, along with inclusion and exclusion criteria, has been previously described [9]. The protocol includes a rapid intravenous (IV) infusion of 30 mL/kg of 4 °C normal saline, application of ice packs to the groin and axilla, long-acting neuromuscular blockade to prevent shivering, and use of a surface cooling device with a target temperature of 33 °C. In 2009, patients started receiving intra-arrest infusion of 2 l of 4 °C normal saline prior to ED arrival. Additionally, our protocol includes resuscitative hemodynamic and ventilatory goals per American Heart Association guidelines.

Subjects

Resuscitated victims of in-hospital or out-of-hospital, non-traumatic CA, with persistent coma defined as Glasgow Coma Scale (GCS) ≤ 8 or inability to follow verbal commands 15 min following return of spontaneous circulation (ROSC) were eligible for the pathway regardless of presenting rhythm. The only strict exclusion criterion was pre-existing terminal illness.

Data Collection

Clinical data including arrest and treatment variables and outcome data were collected on consecutively enrolled patients with the use of a preformatted standard electronic data collection tool utilizing Utstein criteria and outcomes measured via the Cerebral Performance Categories (CPC) Scale. Utstein definitions and templates were developed to assist in the standardization of CA research and clearly describe terms such as witnessed versus unwitnessed arrest, presence or absence of bystander CPR, and ROSC so that these definitions are standard across international registries [10]. The CPC Scale is a standard neurologic outcome measure used in resuscitation research. By convention, a CPC score of 1 or 2 represents a good neurologic outcome and a score of 3, 4, or 5 represents a poor neurologic outcome. A score of 1 is assigned to patients with very minimal neurologic impairment and a score of 5 is assigned to patients with brain death. Scores of 2, 3, and 4 represent a spectrum between these two clinical situations [11]. For our study's purposes, we defined a poor outcome as a CPC score of 3, 4, or 5 at the time of hospital discharge and a good neurologic outcome as a CPC score of 1 or 2 at the time of discharge.

Registry database information and medical records were independently reviewed by two investigators who assigned causality based on a structured a priori definition of TICA. TICA was defined as cardiac arrest that resulted directly and immediately from an ingestion or exposure to a toxin (including medication, substance of abuse, chemical, or natural

compound such as venom) without a non-toxic more likely alternative cause of death. Patients that were merely exposed to a toxin (i.e., had a positive urine drug screen) were not defined as TICA unless the exposure was determined by investigators to be the direct and immediate cause of death. The chart and database review included, but was not limited to, pre-hospital EMS reports, emergency physician documentation, the admitting physician's history and physical exam, physician consultation notes, all lab results, vital signs, EKGs, radiographic imaging and reports, heart catheterization reports, and autopsy results. In cases where information was not available or missing it was not recorded. Among the first 20 % ($n=80$) kappa agreement between two investigators was less than our pre-determined goal of 90 % and therefore the remainder of the database continued to be reviewed by two investigators (one of whom was a board certified medical toxicologist and both who were emergency medicine physicians). Disagreement was arbitrated via a third independent reviewer. A third reviewer was required in 4 % ($n=17$) of the 389 total cases to reach a consensus. The overall kappa agreement for the entire study was >90 %. It is unclear why over half of disagreements occurred between the first 80 cases, but perhaps there was a learning curve among investigators.

Among patients determined to have suffered TICA, data was extracted and organized into a Microsoft Excel spreadsheet and included the following: patient demographics, pre-existing comorbidities including prior substance abuse, prior suicide attempts, suspected or confirmed toxic agent (s), assignment of a "primary" agent if more than one was ingested, intent of the ingestion or exposure (accidental, adverse drug reaction, envenomation, environmental, homicide, iatrogenic overdose, recreational, suicide, or unknown), location of arrest (in-hospital or out-of-hospital), prehospital CPR (bystander, trained provider, or both), prehospital cardioversion or defibrillation (bystander or trained provider), prehospital medications, cardiac rhythm on EMS arrival, cardiac rhythm on hospital arrival, best GCS prior to initiation of TH, time to ROSC, location of initiation of TH (pre-hospital or in-hospital), method of TH, lowest body temperature recorded, duration of TH, complications during hospitalization, hospital length of stay, outcome (survival or death), airway status at discharge or death (extubated recovered, extubated to comfort care, intubated, or tracheostomy), discharge destination (home, rehabilitation, long-term acute care, skilled nursing facility, left against medical advice), cause of death, discharge CPC score, and autopsy findings if performed.

Analysis

Patients and toxins were characterized using descriptive statistics. These characteristics and outcome variables were compared using two-tailed Fisher's exact test if categorical, unpaired t tests if continuous, and multiple logistic regression. A

p value of <0.05 was determined to be significant. Statistical tests and logistic regression model build was performed using SAS Enterprise Guide v6.1 software (Copyright 2013 by SAS Institute Inc., Cary, NC). Given the high number of predictive variables relative to our patient population of study, independent logistic regression model variables were selected as those variables shown were significant based on chi-square or t test for significance. From here, a backward elimination stepwise model selection process was used for the final logistic regression build.

Results

Patient Characteristics

A total of 389 patients underwent pathway registration and TH during the study period. Forty-eight (12 %) of the total database patients were deemed to suffer TICA. Confirmatory laboratory testing for toxins in the form of urine drug screens, serum alcohol levels, or gas chromatography was available in 77 % of our cases. Autopsy reports were available for four (10 %) TICA patients. In all four reports, the medical examiner's cause of death and the causality assigned by investigators agreed.

All patients in the study reached goal temperature of 33 °C during the study period. Our median time to goal temperature from arrival to the hospital was 223 min with a mean of 245 min. From the time of ROSC, median time to goal temperature was 271 min with a mean of 306 min. During this study period, we do not have data on how many patients received the entire pathway (i.e., a full 24 h of cooling); however, it was a vast majority of patients. The only patients who did not complete 24 h of cooling were those who developed complications of cooling such as active serious bleeding or hemodynamic compromise at which time either normothermia was targeted or simply a higher target temperature.

TICA patients were younger, less likely to have an initial shockable rhythm, and less likely to receive bystander CPR than non-toxic cases (see Table 1). There was no survival difference between the toxin-induced and non-toxic CA group (42 vs 45 %; NS). Good neurologic outcome was also similar between the two groups (35 vs 41 %; NS).

Causative Toxins

Within the TICA group, the most common causative toxins included cocaine ($n=16$), benzodiazepines ($n=13$), and opioids ($n=9$) (see Table 2). The arrests could further be classified as sympathomimetic or arrhythmogenic in 49 % of cases and a CNS depressant in 49 % of cases. The categorization of toxins was assigned by one of the emergency medicine physician investigators and agreed upon by one of the board

Table 1 Subject characteristics and outcomes

	Toxic arrests (<i>n</i> = 48)	Non-toxic Arrests (<i>n</i> = 341)	<i>p</i> value	Totals
Mean age ± SD (years)	47 ± 13.6	59 ± 19.1	0.0001	NA
Age range (years)	18–77	19–94		NA
Male	29 (60 %)	217 (64 %)	0.75	246 (63 %)
Out-of-hospital arrest	43 (90 %)	328 (96 %)	1.00	371 (95 %)
Initial shockable rhythm	18 (38 %)	215 (63 %) ^a	0.0001	231 (59 %)
Survival	20 (42 %)	152 (45 %)	0.76	172 (44 %)
High functioning survivors ^b	17 (35 %)	139 (41 %)	0.53	156 (40 %)
Bystander CPR	21 (44 %) ^c	212 (62 %) ^d	0.03	233 (60 %)

NA not applicable

^a Four (4) unknown presenting rhythms for non-toxic out of hospital cardiac arrests

^b High functioning survivors are those with CPC scores 3, 4, or 5 on hospital discharge

^c Eight (8) unknown if CPR was received pre-hospital

^d Thirty-eight (38) unknown if CPR was received pre-hospital

certified medical toxicologist investigators. One case of insect envenomation accounted for the remaining TICA (see Fig. 1). Although cocaine was the most prevalent sympathomimetic/arrhythmogenic agent, other arrhythmogenics as a cause of primary arrest included fluoroquinolone antibiotics (*n* = 2), potassium supplements (*n* = 1), furosemide (*n* = 1), caffeine (*n* = 1), amphetamine (*n* = 1), and bupivacaine (*n* = 1). The death attributed to furosemide involved a patient taking supratherapeutic furosemide doses and presented with refractory arrhythmias and critically low potassium. The death attributed to bupivacaine resulted from inadvertent intravascular administration and took place in-hospital. Other central nervous system (CNS) depressants leading to CA included carbon monoxide (*n* = 1) and ethanol (*n* = 1). Benzodiazepines in this group included alprazolam, clonazepam, diazepam, and “unknown benzodiazepines” that were mentioned in the medical records, but not further defined. Opioids ingested included transdermal fentanyl, hydrocodone, methadone, and unknown opioids that were mentioned in the medical records, but not further defined. The only barbiturate that was a primary agent in a TICA was methohexital. In 67 % (*n* = 32) of toxic arrests, multiple agents were involved (Table 3).

Predictive Analysis

Within the TICA subset, we sought to identify characteristics that might be associated with outcome. Patient demographics, pre-existing comorbidities including prior substance abuse, suspected or confirmed toxic agent (s) and number of agents, “primary” agent if more than one was ingested, the intent of the ingestion or exposure, location of arrest (in-hospital or out-of-hospital), prehospital CPR, prehospital airway, prehospital cardioversion or defibrillation, prehospital medications, cardiac rhythm on EMS arrival (shockable or non-shockable), cardiac rhythm on hospital arrival (shockable or non-shockable), best GCS prior to initiation of TH, location of initiation of TH

(pre-hospital or in hospital), lowest body temperature recorded were evaluated using chi-square test of proportions for categorical variables and *t* test for continuous variables as possible factors associated with outcome. Variables included in the database were only analyzed if available for at least 30 patients.

Significant differences in outcome were detected for patients receiving certain pre-hospital medications. In particular, administration of bicarbonate (11/48) and naloxone (22/48) correlated with a significantly higher mortality. Patients who received bicarbonate had a survival rate of 9.1 vs 48.7 %

Table 2 Causative agents of toxic deaths

	<i>n</i> (%)
Cocaine	16 (33)
Benzodiazepine	13 (27)
Opiate	9 (19)
Antibiotic	2 (4 %)
Potassium supplement	1 (2 %)
Furosemide	1 (2 %)
Caffeine	1 (2 %)
Amphetamine	1 (2 %)
Carbon monoxide	1 (2 %)
Insect envenomation	1 (2 %)
Alcohol	1 (2 %)
Bupivacaine	1 (2 %)
Multiple agents involved (overlaps with above identified as primary)	32 (67 %)

Benzodiazepine = alprazolam, clonazepam, diazepam, unknown benzodiazepine

Opiate = brexital, oxycodone, hydrocodone, fentanyl transdermal, methadone, unknown opiates

Antibiotic = levofloxacin, ciprofloxacin

Table 3 Survival based on toxic agent

	Overall survival
CNS depressants (BZD, opiate, CO, alcohol)	29 % (7)
Arrhythmogenic agents (cocaine, abx, K, furosemide, caffeine, amphetamine, bupivacaine)	56 % (13)
Other (insect envenomation)	0 % (1)

Two-tailed *p* value between CNS depressants and arrhythmogenic agents for survival 0.0798

survival rate for those patients who did not receive bicarbonate ($p=0.02$). In the case of naloxone, mortality was 22.7 % for those who received naloxone vs 53.9 % for those who did not ($p=0.03$).

A statistically significant higher proportion of patients with an initial shockable rhythm survived (11/18) compared to those with a non-shockable rhythm (7/30) ($p=0.01$; Fisher's exact test). Our subset analysis also compared patients exposed to an arrhythmogenic agent vs CNS depressant. Overall survival was not statistically significantly different in the arrhythmogenic group (13/23) than the CNS depressant group (7/17) (NS). Analysis also failed to detect any difference in good neurologic outcomes between arrhythmogenic and CNS depressant toxins (10/23) vs the CNS depressant group (7/24) (NS; Fisher's exact test). Survival was associated with a significantly higher mean GCS upon hospital arrival (mean GCS 4.2 vs 3.1; $p=0.01$; 95 % CI [0.3–1.9]).

A logistic regression model was built using backward elimination selection method with a required significance threshold $p=0.05$. Initial model variables included those four variables found to have a significant association with survival outcome based on our initial statistical tests: initial rhythm (shockable/non-shockable), best GCS prior to initiation of TH (a discrete variable with unit change of 1/2), bicarbonate administration, and naloxone administration. Two patients were removed from the model build due to lack of GCS and initial rhythm data. Bicarbonate and naloxone were not part of the final model as they did not meet the significance threshold for model entrance ($p=0.17$ and $p=0.49$ respectively). The final model AUC for the ROC curve was 0.79. GCS prior to initiation of TH was included as part of the final model with $p=0.03$, where for each half point increase in a patient's GCS, the probability of survival increased 2.6 times (95 % CI [1.3–7.4]). The initial rhythm was also part of the final model ($p=0.04$) with a shockable rhythm being associated with a 4.8 times greater likelihood for survival (95 % CI [1.1–21.8]).

Discussion

Unfortunately, use of illicit substances such as cocaine remains prevalent and abuse of prescription drugs is on the rise. Between 2009 and 2011, the rate of ED visits involving illicit substances rose 68 %. The misuse and abuse of prescription opioids was responsible for more than 475,000 ED visits in

2009, a number that almost doubled in 5 years [12]. The total lifetime costs associated with unintentional drug overdose resulting in death was estimated to be \$23 billion in the USA in 2000 [13]. Deaths from drug overdose have risen consistently since 1970. In 2011, drug overdose was the leading cause of injury death among adults 25 to 64 years old, causing more deaths than motor vehicle collisions [14]. These data are reflected in our study that found a significant proportion of CA at our regional cardiac resuscitation center were attributable to a toxin. This is most likely due to the increased trends in abuse of cocaine, benzodiazepines, and opioids. Our data also has important clinical implications. Clinicians involved in CA resuscitation need to be cognizant that TICA is common and increasing. Use of specific antidotes was suggested by one prior TICA resuscitation study as well [5].

Our study found that 12 % of patients in a CA registry who underwent TH had presumed TICA. This is in contrast to a 10-year retrospective review of deaths in Melbourne, Australia which found a 6.43 % rate of overdose as a cause of death and in contrast to Katz et al. who found a rate of 2.5 % of CA attributable to drug overdose [4, 8]. Several explanations may account for our increased prevalence of TICA. First, both the Melbourne study and Katz study were chart reviews that relied on coding or physician documentation as cause of death rather than an investigator review of the medical chart as was the case in our study. This reliance on coding and Emergency Medicine physician diagnoses may have underdiagnosed TICA. Also, both of these studies looked at drug overdose rather than all toxins and may have missed some TICA by excluding iatrogenic exposures, envenomation, or other environmental exposure leading to CA which are not traditionally thought of as drug overdoses but are poisonings nonetheless.

Regarding outcome, this study found an overall survival rate and survival with good neurological outcome rate of 42 % and 35 %, respectively, for TICA patient that underwent TH. Survival was similar to non-TICA patients. This was surprisingly higher than we anticipated and compared to previous data (1–19 %) [4–7]. Only one prior study reported similar rates of survival with good neurological outcome of 34 % [3]. The survival data of 8.5 % in the Melbourne study and 16 % in Katz's study is significantly lower than our finding of 42 % survival. This is most likely because not all patients in the Melbourne nor Katz studies underwent TH. All of the patients in our database underwent a TH clinical pathway,

which excluded patients with severe terminal illness prior to CA and refractory shock. This may have selected for patients with higher likelihood of survival. Also, patients who died in the ED or were pronounced dead in the field were not included in our study, unlike the Melbourne study which included all out of hospital CA. Our study was also a single-center and tertiary care center very comfortable with TH which may lead to our increased survival rates.

In our review, patients with a TICA were younger and less likely to receive bystander CPR. Mortality rates and neurologic outcomes were similar among deaths that were toxic versus non-toxic. Higher rates of survival and good neurologic outcome were associated with shockable rhythms. Within our toxin-specific subgroup analysis, overall survival was not statistically significantly different in the arrhythmogenic group than the CNS depressant group. Analysis also failed to detect any difference in good neurologic outcomes between arrhythmogenic and CNS depressant toxins versus the CNS depressant group. This lack of difference between groups may be due to the small number of patients in these subgroups, but is more likely due to the fact that most patients who suffered TICA had an initial rhythm of PEA or asystole rather than a shockable rhythm despite what their presumed ingestion was.

Identification of a TICA may provide the opportunity for additional resuscitation options beyond those typically present in post-CA pathways such as serum or urinary alkalization, lipid rescue, high-dose insulin therapy, hemodialysis, or extracorporeal membrane oxygenation (ECMO) when clinically appropriate. In some cases, consideration of a toxic exposure might modify typical resuscitation measures. For example, lidocaine may be a better antidysrhythmic for sodium channel antagonist-induced ventricular dysrhythmia than amiodarone [15]. Vasopressor doses may be considerably higher for drug-induced shock than ischemic shock [16].

There are several limitations to our study. Although our academic teaching hospital cares for a diverse patient population from a relatively large geographic catchment area, our results may not represent the experience of a different geographic population based on practice variation in post-CA care as well as resource availability. Toxin exposure will also vary geographically. For example, one patient suffered an insect envenomation which would not be expected to occur where venomous insects are not endemic. We also found that cocaine was the most common toxin in our toxic subset, but found no cases of phencyclidine and only one case of amphetamine use. Emerging toxins may also affect post-resuscitation care. Synthetic marijuana (“spice”) and synthetic cathinones (“bath salts”) are both associated with deaths due to hyperthermia, seizures, and direct cardiovascular toxicity [17, 18]. There is no published experience with TH and these more novel toxins.

Patients that truly experienced TICA may have been under or overestimated in this report for several reasons. First,

because of the relatively wide variety of toxin exposures in the database, we could not construct specific “gold standard” inclusion criteria for assigning causality and we experienced difficulty in assigning causality in some cases. However, our methodology employing three independent investigators attempted to control for differential case interpretation. Secondly, confirmatory diagnostic testing was not performed or possible in some cases. Urine drug screening used by the hospital laboratory is an immunoassay technique and limited to six classes of substances: amphetamines, barbiturates, benzodiazepines, cocaine, opioids, and marijuana. The particular assay is not sensitive for all amphetamines, benzodiazepines, and opioids so some toxins may have gone undetected. Some toxins are not amenable to routine confirmatory testing, synthetic cannabinoids, bath salts, common antibiotics, or diuretics. However, 77 % of our patients had some type of laboratory testing via urine drug screen, serum testing, or gas chromatography that constructively contributed to the consensus determination. Also, our data abstractors were not blinded to the study hypotheses which may have influenced causality assignment.

Our study also did not look specifically at complications of TH and while we have little suspicion that complications of TH would be higher in TICA patients than in general post-CA patients, this is another limitation of our study.

Lastly, we were unable to control for, confirm, or perform analysis of comorbid conditions in our patients. The accuracy of the comorbid conditions in our patients is also questionable as patients were unable to provide their own medical history. Additionally, in cases where the patient had not previously visited our hospital for a comprehensive history and physical we relied on chart review of what had been relayed by friends and family of any pre-existing conditions. Comorbidities certainly could contribute to our patients’ outcomes, but would probably do so equally between toxic and non-toxic CA.

Conclusions

A significant proportion of out-of-hospital CA is toxin induced. Mortality and neurologic outcomes are similar among patients with toxin induced and non-toxic CA following treatment in our post-CA clinical pathway which included TH. Our findings may encourage physicians to consider a possible toxic exposure or to test for toxins in undifferentiated CA. Identification of a TICA may provide the opportunity for additional resuscitation options or modify typical resuscitation measures.

While there is ongoing debate on the role of TH in CA patients, our study does not suggest a difference in benefit conferred by TH in patients suffering a toxic versus non-toxin induced CA [19]. While we did not evaluate study

subjects for complications from TH such as bleeding or immunosuppression, these aspects were originally tracked in the post-cardiac arrest care database, but the prevalence was similar and indistinguishable from critical illness in general, so these were dropped from prospective database entry. Complications related to TH are well reported in the former randomized trials of this treatment. In the absence of suspicion for higher TH complications in TICA patients, we explored survival with good neurologic outcome as the primary outcome measure in our comparison groups.

While some past studies looking at treatment of post-CA patients in coma with TH have excluded patients with TICA, our results showing similar rates of survival with good neurologic outcome in both TICA and non-toxic induced CA would suggest that future studies looking at TH or TTM after CA include patients with TICA [20]. Larger studies with subjects from varied geography are needed to fully elucidate the optimal role and value of TH in TICA. Studies at outside institutions will also serve to clarify our results with separate investigators assigning toxic causality in a post-CA database and validate our findings of the incidence of TICA in a larger population.

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