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Effects of Prehospital vs. In Hospital Therapeutic Hypothermia on Neurological Status after Cardiac Arrest

James Madison University Physician Assistant Program

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November 30, 2018

Abstract

Objective: To conduct an analysis of literature that examined whether the use of prehospital therapeutic hypothermia (TH) results in neurologic outcomes that are significantly increased or decreased in adults that experienced out-of-hospital cardiac arrest (OHCA). **Methods:** Systematic searches were conducted through PubMed at the James Madison University Library. The inclusion criteria included human adults who experienced out-of-hospital cardiac arrest and were treated by Emergency Medical Services (EMS) with and/or without prehospital TH by means of intravenous cold fluids and surface cooling. **Results:** Three studies involving 2180 cases were included. This review indicated that prehospital TH after cardiac arrest had similar effects on neurological outcome when compared to in-hospital therapeutic hypothermia. The only effect noted was that prehospital cooling decreased the amount of time to reach a targeted temperature while in hospital. **Conclusion:** A statistically significant difference was not found between the use of prehospital TH versus in-hospital TH.

Abbreviations used: Out of hospital cardiac arrest (OHCA); Emergency medical services (EMS); Therapeutic hypothermia (TH); American Heart Association (AHA); Return of spontaneous circulation (ROSC); Ventricular fibrillation (VF); Randomized control trial (RCT); Targeted Temperature Management (TTM)

INTRODUCTION

Neurologic injury is the most common cause of death in patients with out-of-hospital cardiac arrest (OHCA) and contributes to the mortality of in-patients with cardiac arrests.¹ Cardiac arrest causes significant neuronal damage due to the sudden termination of cerebral blood flow, which reduces cerebral oxygen and depresses cerebral function. In addition, the inflammatory cascade is activated during this process and can lead to cerebral edema, increased intracranial pressure, and brainstem herniation, which can cause remarkable damage in the central nervous system. Patients who experience cardiac arrest with resultant neurologic damage are often left in a vegetative state and cannot return to their previous level of functioning.²

Therapeutic hypothermia (TH) has been associated with slowing down of this cellular cascade and restricting the area of anoxia.² In fact, mild TH has proven to be an important therapy for cardiac arrest survivors, and the only therapy consistently shown to reduce mortality and improve neurological outcomes in these patients.³ Because of this research, American Heart Association (AHA) guidelines for post-cardiac arrest therapy were changed in 2015 to reflect this research. AHA now strongly recommends target temperature management for comatose (ie, lack of meaningful response to verbal commands) adult patients with return of spontaneous circulation (ROSC) after cardiac arrest for 12-24 hours.⁴

Despite these recommendations, there are still some factors that have yet to be determined regarding the way the TH is carried out. There is still research being conducted to determine the best methods to cool, the ideal duration of target temperature management, and optimal timing of induction of TH. This analysis focuses particularly on the timing of TH and assesses three randomized control trials that compared the effects of prehospital TH versus standard in-hospital TH on neurological outcomes of patients with OHCA.

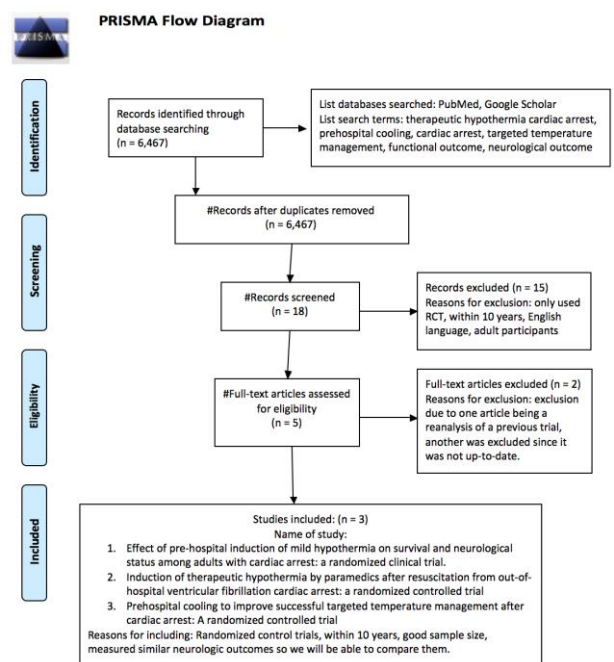
METHODS

Search methods and databases

The three articles were finalized using electronic search methods. Databases that were utilized include PubMed and Google Scholar. PubMed allowed for more specific criteria to search the articles, including human subjects older than 18, studies that were no older than 10 years, English language, and randomized control trials (RCT). The search terms that were used included the following: therapeutic hypothermia cardiac arrest, prehospital cooling, cardiac arrest, targeted temperature management, functional outcome, neurological outcome.

Inclusion and exclusion criteria for selection of studies:

The inclusion criteria for the chosen articles were the following:



1. Randomized control trials
2. Cardiac arrest occurring out of the hospital in order to administer prehospital cooling.
3. Patients had to be considered an adult, ie greater than or equal to 18 years old.
4. A comparison of administering pre-hospital cooling to in-hospital cooling based on the already established standard protocol.
5. Neurologic outcomes were measured

The exclusion criteria were as follows:

1. Meta-analysis
2. Review articles
3. Cohort studies
4. Age younger than 18 years old
5. Animal subjects
6. Study not in English
7. Older 10 years.

RESULTS

Search Results:

The literature search initially identified 6467 citations, of which 6449 were eliminated due to reasons listed above in the methods section. After reviewing titles and abstracts of the 18 remaining articles, 5 articles were selected for full text review. Finally, 3 studies were included in this study based on inclusion and exclusion criteria.

Study 1:

Effect of Prehospital Induction of Mild Hypothermia on Survival and Neurological Status Among Adults with Cardiac Arrest: A Randomized Clinical Trial⁵

Objective: To determine whether prehospital cooling improves outcomes after resuscitation from cardiac arrest in patients with ventricular fibrillation (VF) and without VF.

Study Design: This study was a randomized clinical trial that assigned 1359 adult patients with OHCA to standard care with or without prehospital cooling by infusion of up to 2L of 4°C normal saline as soon as possible following ROSC. The study took place in Seattle and King County, Washington. Patients were randomized between December 15, 2007, and December 7, 2012 with follow up completed by May 1, 2013.

Inclusion criteria included ROSC, tracheal intubation, intravenous access, successful placement of esophageal temperature probe, and unconsciousness. Exclusion criteria included traumatic cardiac arrest, age younger than 18 years, being awake, following commands, and having a temperature less than 34°C. Both VF and those without VF were eligible. Eligible patients were assigned to receive standard care alone (control) or standard care plus induction of mild hypothermia (intervention).

The intervention group received 2L of 4°C normal saline intravenously with pressure bag inflated to 300 mmHg, 7-10mg of pancuronium, and 1-2 mg of diazepam. Goal temperature was less than 34°C otherwise the intervention and control groups were treated the same. Once at the hospital, serial temperatures (measured by esophageal or tympanic thermometers) and the decision for a patient to received hospital cooling was determined by the ED provider.

Primary outcomes were survival and neurological status at hospital discharge. Neurological status was assessed by reviewing daily progress records and nursing notes and was assigned as full, recovery, mildly to moderate impaired, severely impaired, comatose, or dead.

Study Results: The intervention decreased mean core temperature by 1.20°C (95% CI, -1.33°C to -1.7°C) in patients with VF and by 1.30°C (95% CI, -1.40°C to -1.20°C) in patients without VF by hospital arrival and reduced the time to achieve a temperature of less than 34°C by 1 hour compared to the control group. Only 50% of patients received the full 2L of fluid. Reasons for not completing the 2L included recurrent arrest, death in the field, and lack of time before hospital arrival to complete the infusion. The average time to reach a goal temperature of less than 34°C was calculated. Patients who received prehospital cooling group reached the goal temperature by a mean of 4.2 hours compared to 5.5 hours for patients who received only in hospital cooling. This suggests that prehospital cooling reduced the time to goal temperature by more than 1 hour. Effects were similar for both patients with and without VF.

Survival to discharge outcomes among patients in the control group were 64.3% for those with VF and 16.3% without VF. For patients in the intervention group the outcome was 62.7% for those with VF and 19.2% without VF.

As far as neurological status at time of discharges there was not a significant difference found between the intervention and control group. In addition, the prehospital cool was not associated with improved neurological status of full recovery or mild impairment at discharge compare to the in hospital cooling group. These results are shown in Table 1.

Table 1. Status at Time of Discharge

	With Ventricular Fibrillation (n = 583)		P Value	Without Ventricular Fibrillation (n = 776)		P Value
	No. (%) [95% CI]			No. (%) [95% CI]		
	Intervention (n = 292)	Control (n = 291)		Intervention (n = 396)	Control (n = 380)	
Vital status						
Dead	109 (37.3) [32.0-43.0]	104 (35.7) [30.5-41.4]	.69	320 (80.8) [76.6-84.4]	318 (83.7) [79.6-87.1]	.30
Alive	183 (62.7) [57.0-68.0]	187 (64.3) [58.6-69.5]		76 (19.2) [15.6-23.4]	62 (16.3) [12.9-20.4]	
Neurological status at discharge						
Full recovery	125 (42.8) [37.3-48.5]	145 (49.8) [40.7-52.1]	.59	36 (9.1) [6.6-12.3]	34 (8.9) [6.5-12.2]	.74
Mildly impaired	43 (14.7) [11.1-19.2]	35 (12.0) [8.8-16.3]		21 (5.3) [3.5-8.0]	17 (4.5) [2.8-7.0]	
Severely impaired	6 (2.1) [0.9-4.4]	8 (2.7) [1.4-5.3]		5 (1.3) [0.5-2.9]	2 (0.5) [0.1-1.9]	
Disabled (severity unknown)	2 (0.7) [0.2-2.5]	0		0	0	
Comatose	4 (1.4) [0.5-3.5]	7 (2.4) [1.2-4.9]		12 (3.0) [1.7-5.2]	7 (1.8) [0.9-3.8]	
Alive (status unknown)	3 (1.0) [0.4-3.0]	2 (0.7) [0.2-2.5]		2 (0.5) [0.1-1.8]	2 (0.5) [0.1-1.9]	

Criticism: Strengths include randomization and adequate power to detect clinical significant differences as well as utilization

of a low-cost intervention for a condition, that accounts for substantial public health mortality. Patients with or without VF were both included in the study. In addition, baseline outcomes by the participating EMS agencies were high so it was unlikely that prehospital hypothermia was modified or confounded by the quality of prehospital care.

There were many limitations to the study. The dose and method of hypothermia could have been suboptimal since there is limited data regarding these factors. A target temperature of 34°C was used, despite lack of information regarding ideal temperature for TH. Patients who rearrested could be affected by a worsened brain ischemia and yet were still included in the study. Lastly, endpoints were measured only at the time of hospital discharge when functional status can improve for at least 6 months after resuscitation from cardiac arrest.

Study 2:

Induction of Therapeutic Hypothermia by Paramedics After Resuscitation From Out-of-Hospital Ventricular Fibrillation Cardiac Arrest: A randomized controlled trial.⁶

Objective: To determine if prehospital cooling has a better effect on neurologic injury (ie, decreased neurological injury) after ventricular fibrillation cardiac arrest that occurs out of hospital.

Study design: This was a prospective, RCT taken place in Melbourne, Australia between October 2005 until November 2007. A total of 234 patients were randomly assigned to paramedic cooling (118 patients) or hospital cooling (116 patients). The patients who received cooling were given an infusion of up to 2000 mL of ice-cold lactate Ringer's solution at a rate of 100 mL/minute during transport to the hospital using standard infusion set and a pressure bag that was inflated to 300 mmHg. This fluid was carried in an insulated container with a thermometer to ensure that the fluid temperature was less than 8°C. In addition, these patients received IV midazolam 0.1 mg/kg and pancuronium 12 mg to suppress shivering. The control patients received standard in-hospital cooling, which included a rapid infusion of 40 mL/kg of ice-cold lactated Ringer's solution, sedation, and a neuromuscular blocking agent. Midazolam was administered to facilitate assisted ventilation and pancuronium was only used if midazolam was ineffective.

Upon arrival to the hospital, cooling with 10-20 mL/kg was continued in the emergency department with a target temperature of 33 degrees C maintained for 24 hours. Core temperature was measured using a bladder temperature probe. After the 24 hours of cooling was complete, the patients were rewarmed 0.25°C per hour. In all of the subjects, ventilation with 100% oxygen was continued with a target end-tidal CO₂ of 35-40 mmHg. Epinephrine infusion was used if the systolic blood pressure was less than 90 mmHg. Temperature was measured with a tympanic temperature probe. Before hospital discharge, a rehabilitation physician who was blinded to the study evaluated patients and determined whether to discharge patients home or to a rehabilitation facility. Discharge to a rehabilitation facility was considered as a favorable outcome.

Patients were included in this study if they had OHCA with ventricular fibrillation as their rhythm, systolic blood pressure greater than 90 mmHg, ROSC, cardiac arrest time greater than 10 minutes, age greater than or equal to 15, and IV access available. Patients were excluded from the study if they were not intubated, were dependent on others for activities of daily living before the cardiac arrest event, were already hypothermic (temperature less than 34°C), or pregnant.

Study results: The patients who were allocated to pre-cooling had a decreased core body temperature upon arrival to the hospital (34.4°C, 95% CI 34.1 to 34.6) compared to the control group (35.2°C, 95% CI 34.9 to 35.4). However, this difference in temperature did not last long. The temperatures became similar within 1 hour of emergency department arrival. Also, there were no differences in functional outcome upon hospital discharge between the two groups. The favorable outcome (either discharge home or to a rehabilitation center) was 47.5% in the pre-cooled subjects and was 52.6% in the hospital cooled subjects. This difference was not significant (risk ratio 0.90, 95% CI 0.70 to 1.17, P=0.43). In the paramedic cooling group, 24 out of the 118 patients were discharged home, 32 were discharged to rehabilitation, and 62 died. In the hospital cooling, control group, 34 patients out of 116 were discharged home, 27 were discharged to rehabilitation, 1 was discharged to a nursing home comatose, and 54 died.

Study critique: The strengths of this study include the following: a physician who was blinded to the study that evaluated patients upon discharge, consistent prehospital cooling techniques of IV infusions, treatment was prospective, blinded, and computer randomized. There was also a high rate of paramedic compliance with the protocol of the study.

The limitations to this study include a relatively small sample size of only 234 patients, the paramedics were not blinded to the study, only half of the patients received the full amount of precooling due to short transport time to the hospital, there was not in depth neuropsychiatric assessment following the event due to limited resources, and 41% of patients (164) of 198 eligible patients were not enrolled in the study, which may have altered the outcomes. Also, there was no neurological functional assessment in this study, instead, the favorable outcome was discharge home or to a rehabilitation facility.

Study 3: Prehospital cooling to improve successful targeted temperature successful target temperature management after cardiac arrest: A randomized controlled trial⁷

Objective: To determine if prehospital cooling by paramedics leads to higher rates of 'successful TTM', defined as achieving a target temperature of 32–34°C within 6 h of hospital arrival. Primary outcome was successful TTM and secondary outcome was survival to hospital discharge with good neurological outcome, defined as score on the Modified Rankin Scale.⁸

Study Design: This study was a randomized control trial conducted by 4 EMS systems in the Greater Toronto Area from July 3, 2012 to January 8, 2016. The trial consisted of 582 patients who were randomized at a 1:1 ratio by sealed envelopes with variable (4-6) block sizes into two groups.

The intervention group received ice packs to their neck, axillae, and groin as well as 2L cold saline infusion at approximately 4°C as oppose to the control group who received conventional post-resuscitative supportive care

without prehospital cooling. This intervention was initiated 5 min after successful ROSC. In both groups, all in-hospital procedures were left to the discretion of the treating clinical team, but did implement protocols and order sets for delivering TTM, typically using surface cooling measures.

Patients were eligible if they had an EMS-treated OHCA and were ≥ 18 years, sustained ROSC of ≥ 5 minutes, had systolic blood pressure ≥ 100 mmHg, and were unresponsive to verbal stimuli or required endotracheal intubation. Patients were ineligible if etiology of cardiac arrest was trauma, burn, or exposure to hypothermia; or if they had clinical evidence of active severe bleeding, severe sepsis, known coagulopathy, known do-not-resuscitate (DNR) order, known pregnancy, or prisoner status.

Primary outcome was ‘successful TTM’ however there were multiple secondary outcomes. This analysis focused primarily on the secondary outcome of survival to hospital discharge with good neurological outcome. This outcome was measured using Modified Rankin Scale, defined as a score of either a 0, 1, or 2 (Table 2).⁸ These measurements were compared using Fisher’s exact test. In addition, adjustments were made for age, sex, EMS system, and shockable rhythm.

Study Results: Intention-to-treat method was used by researchers to analyze data. Rates of survival to hospital discharge and survival with good neurological outcomes were similar in both the intervention and control groups. Survival to hospital discharge had a relative risk of 1.01 (95% CI 0.81-1.23) and $p = 0.93$. Survival with good neurological outcomes had a relative risk of 1.11 (95% CI 0.88-1.39) and $p = .38$. See Table 3. In addition, patient temperatures on arrival to the hospital between the two groups were very similar (35.1°C in patients receiving prehospital cooling vs 35.2°C in control patients, $p=0.53$). Overall the trial showed no difference in the primary outcomes of survival and neurological status at hospital discharge when comparing both groups.

Table 2:
Modified Rankin Scale

0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability, unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Table 3
Outcomes.

	Prehospital Cooling (n=279)	Control (n=303)	RR (95% CI)	p-value
TTM reaching 32–34 °C within 6 hours, No. (%)	85 (30%)	77 (25%)	1.17 (0.91–1.52)	0.22
TTM applied in hospital (ever), No. (%)	190 (68%)	170 (56%)	1.21 (1.07–1.37)	0.003
Survival to hospital discharge, No. (%) ^a	92 (33%)	98 (32%)	1.02 (0.81–1.29)	0.88
Survival to 6 hours after ED admission, No. (%)	223 (80%)	233 (77%)	1.15 (0.84–1.56)	0.39
Survival to hospital discharge – patients presenting with VT/VF, No. (%)	79 (64%)	74 (55%)	1.16 (0.95–1.41)	0.16
Good neurological outcome ^a at hospital discharge, No. (%) ^b	82 (29%)	76 (26%)	1.13 (0.87–1.47)	0.37
Neurological status at discharge ^{b,c}				0.77
No symptoms (mRS 0), No. (%)	46 (16%)	45 (15%)		
No significant disability (mRS 1), No. (%)	26 (9.3%)	23 (7.8%)		
Slight disability (mRS 2), No. (%)	10 (3.6%)	8 (2.7%)		
Moderate disability (mRS 3), No. (%)	4 (1.4%)	4 (1.4%)		
Moderately severe disability (mRS 4), No. (%)	1 (0.4%)	5 (1.7%)		
Severe disability (mRS 5), No. (%)	5 (1.8%)	5 (1.7%)		
Dead (mRS 6), No. (%)	187 (67%)	205 (69%)		

Footnotes:

Abbreviations: RR=Relative Risk; CI=confidence interval; TTM=Targeted Temperature Management; ROSC=return of spontaneous circulation; VT/VF=pulseless ventricular tachycardia/ventricular fibrillation; mRS=Modified Rankin Scale

^a Good neurological outcome defined as a score of 0, 1, or 2 on the Modified Rankin Scale.

^b Neurological status at hospital discharge could not be obtained for 8 (2.6%) of patients in the control group and vital status at hospital discharge could not be obtained for 1 patient (0.3%) in the control group.

^c p-value based on Fisher’s exact test of scores on the Modified Rankin Scale by treatment assignment.

Study Critique: This study focused on a larger sample size as well as a multi-centered RTC. It took place in a metropolitan area and is the most recently completed trial regarding prehospital cooling for cardiac arrest patients. Though data was collected over 4 years, anticipated sample size was not achieved due to slower than expected enrollment. Researchers believe this could have resulted in inadequate power to detect small but clinically important differences in primary and secondary outcomes. One reason for this was that 16% of the eligible patients were not enrolled by participating paramedics due to individual paramedics declining to participate in the research. Otherwise there was no evidence of sampling bias.

One major limitation to the study was the target temperature that was used since it was a range of 32-34°C versus one specific temperature. This is due to the fact that optimal endpoint for prehospital cooling remains a topic of debate. In addition, researchers reported that there was incomplete delivery of the intervention for patients randomized

to receive prehospital cooling. For example, only two-thirds of patients had cold ice packs applied and about three-quarters received infusions of cold saline. The article also mentions that transport times may not have been long enough to facilitate effective intravenous cooling and that saline was not uniformly maintained at 4°C while stored in the cooler. Lastly, neurological outcome using the Modified Rankin scale was only applied upon discharge; there was no follow-up with the patients after weeks, months, or years following their event of cardiac arrest.

DISCUSSION

It was hypothesized that prehospital cooling would improve a patient's neurologic outcome following cardiac arrest. However, the three randomized control trials assessed in this meta-analysis found there are similar neurological outcomes in prehospital cooling compared to standard cooling in the hospital following cardiac arrest. Studies 1 and 2 revealed that those who received therapeutic hypothermia en route to the hospital had a decrease in core body temperature upon arriving to the hospital compared to the control group, but this ultimately had no effect on survival or neurological outcome.

Limitations

Several limitations are found within the 3 studies. There were inconsistencies regarding cooling methods, travel times, and neurological outcome. Cooling methods for study 3 included external ice packs in the groin, axilla, and neck in addition to cold saline IV infusion, whereas studies 1 and 2 only used infusion of IV methods to cool the patient. Also, travel time to the hospital affected the amount of fluid a person received; often, the patient did not receive the full amount of cooling due to shorter travel time. Travel time was not consistent with each patient, but this could be a barrier to results and an aspect that is uncontrollable. Neurologic outcome was used extensively in these studies. The main devastating effect of cardiac arrest is neurological deficits that occur due to brain hypoxia, but patients were not followed up with in regards to their progress after discharge. In the future, it would be beneficial to follow patients who are alive at hospital discharge to really determine the extent of brain damage, or healing, that occurs after cardiac arrest.

Biases

During the review of these studies there was no evidence that biases existed. This was mostly due to the fact that all were randomized control trials where all parties were blinded as much as possible including the provider who assessed the patients at time of discharge. In addition, it helped that most of the data collected was objective regarding the patient's status.

Strengths/weakness

Between all studies there was a total of 2180 cases involved. This provides a very large sample size to review allowing for greater statistical power and increased validity. For the most part, all studies used similar patient populations, methods of cooling, and measured the same outcome which makes comparisons between the studies more reliable. In addition, all the trials come to the same conclusion that earlier intervention for therapeutic hypothermia after cardiac arrest does not have an improved effect on neurological outcome which shows a consistency between the 3 large trials.

Though all the studies chosen for this review focus specifically on neurological outcome of the patients, they do not all use the same method to assess this outcome. For example, study 1 used nursing notes to assign patients at different levels of neurological impairment. Study 2 used an evaluation by a rehabilitation physician to determine discharge location, and depending on the location, the patient was assigned either favorable or unfavorable neurological outcome. Study 3 used a scale to assess neurological outcome called the Modified Rankin Scale. This makes compiling an overall assessment difficult since results could be interpreted differently depending on how neurological outcome were measured. Also, the p-values used for neurological status at hospital discharge were above 0.05 for study 1 and 3 indicating weaker evidence to reject the null hypothesis.

Overall, this review found consistent results, but the studies could have better clinical relevance if cooling methods, neurologic status, and targeted temperature endpoints were consistent. Although AHA guidelines for post-cardiac arrest therapy changed in 2015 to reflect the evidence that TH/TTM improves a patient's neurologic outcome, there are very few recent randomized control trials that have been completed regarding the initiation of TH as well as the optimal target temperature.

CONCLUSION

It is established that therapeutic hypothermia in the setting of cardiac arrest has been shown to improve neurological outcome and is widely used as management upon arrival to the emergency department. This meta-analysis looked at whether initiating cooling before arrival to the hospital had an increased effect on neurological outcome in patients compared to those who were cooled in the hospital. The three studies demonstrated there was no difference in neurologic outcome if cooling was initiated sooner. However, what the articles revealed is that precooling patients before arriving to the hospital allowed for better compliance of hospital personnel to administer therapeutic hypothermia to patients once they were in the hospital following cardiac arrest.

There are some inconsistencies among the research on the best methods for cooling (ie, IV infusion, ice packs externally) and the optimal temperature that should be reached when cooling a patient. Additional research on these areas would be beneficial for a standardized protocol to achieve the best prognosis. Lastly, further studies would be needed to identify how precooling would be most beneficial, such as concomitant with CPR, to improve neurological outcome even further.

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