Practice guideline: Reducing brain injury after cardiopulmonary resuscitation

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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Dr. Armstrong serves on the Level of Evidence editorial board for *Neurology*® (but is not compensated financially) and is an evidence-based medicine methodologist for the AAN.

Dr. Damian is a member of the editorial board and receives editorial fees for *Neuromuscular Disorder* (Elsevier) and co-chair of the Neurocritical Care Specialist Panel, European Academy of Neurology.

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Dr. Ornato has served as the American editor of *Resuscitation* and has received research funding support from the NIH.

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Dr. Torbey has served on a speakers bureau for Genentech and has received research funding support from the NIH.

Dr. Dubinsky serves on a scientific advisory board of Allergan Pharmaceuticals; has received funding for travel from Allergan Pharmaceuticals, the Huntington Study Group, and the AAN; has served as a Level of Evidence associate editor for the *Neurology* journal; received honoraria from and served on a speakers bureau for Allergan Pharmaceuticals; and received research funding support from Allergan Pharmaceuticals, the NIH, and the Agency for Healthcare Research and Quality. Dr. Dubinsky's spouse owns stock in Abbott Laboratories.

Dr. Lazarou serves on the Level of Evidence Review Team for the *Neurology* journal.

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Dr. Geocadin**:** study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

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ABBREVIATIONS

AEs: adverse events

BRCTI: Brain Resuscitation Clinical Trial I Study Group

CPC: Cerebral Performance Category

CPR: cardiopulmonary resuscitation

GSC: Glasgow Coma Scale

HACA: Hypothermia After Cardiac Arrest

HR: hazard ratio

ICU: intensive care unit

IHCA: in-hospital cardiac arrest

OHCA: out-of-hospital cardiac arrest

OR: odds ratio

PEA: pulseless electrical activity

RD: risk difference

ROSC: return of spontaneous circulation

TH: therapeutic hypothermia

TTM: targeted temperature management

VF: ventricular fibrillation

VT: ventricular tachycardia

ABSTRACT

Objective: To assess the evidence for the acute therapeutic interventions that are provided to reduce brain injury in adult patients who are comatose after successful cardiopulmonary resuscitation and to make evidence-based recommendations.

Methods: A review of the published literature from 1966 to August 29, 2016, was performed, with evidence-based classification of relevant articles.

Results and recommendations: For patients who are comatose in whom the initial cardiac rhythm is either pulseless ventricular tachycardia (VT) or ventricular fibrillation (VF) after out-of-hospital cardiac arrest (OHCA), therapeutic hypothermia (TH; 32°C–34°C for 24 hours) is highly likely to be effective in improving functional neurologic outcome and survival compared with normothermia (2 Class I studies) and should be offered (Level A). For patients who are comatose in whom the initial cardiac rhythm is either VT/VF or asystole/pulseless electrical activity (PEA) after OHCA, targeted temperature management (36°C for 28 hours, normothermia 37.5°C for 72 hours) is likely as effective as TH (1 Class I study) and is an acceptable alternative to TH (Level B). For patients who are comatose in whom the initial cardiac rhythm is either PEA or asystole after cardiac arrest, TH possibly improves survival and functional neurologic outcome at discharge (3 positive Class III studies and meta-analysis of 5 Class III studies) and functional neurologic outcome at discharge (2 positive Class III studies and meta-analysis of 7 Class III studies) and may be offered (Level C). Prehospital cooling as an adjunct to TH is highly likely to be ineffective in further improving neurologic outcome and survival (multiple Class I studies) and should not be offered (Level A). In patients who are comatose with cardiac arrest, a single loading dose of thiopental is likely to be ineffective in improving survival or neurologic outcome (1 Class I study) and should not be offered (Level B).

In patients who are comatose, coenzyme Q_{10} in addition to TH possibly improves survival but not neurologic status after cardiac arrest (1 Class II study) and may be offered (Level C). In patients with OHCA, there is insufficient evidence to support or refute the use of a single 2 g loading dose of magnesium sulfate for improving survival or awakening (1 Class I study; Level U), and a single 10 mg loading dose of diazepam or the calcium channel blocker lidoflazine is likely to be ineffective in improving survival or awakening (1 Class I study; Level B). In patients who are comatose with cardiac arrest, there is insufficient evidence to support or refute the use of epoetin alfa and selenium (single Class III studies; Level U). In patients with OHCA, there is insufficient evidence to support or refute the use of corticosteroids for improving survival or neurologic outcome (1 Class II study and 1 Class III study with insufficient statistical precision to exclude a moderate or large benefit; Level U). In patients with witnessed OHCA and VT/VF, there is insufficient evidence to support or refute the routine clinical use of xenon gas in addition to TH, as it probably results in less white matter damage as measured by fractional anisotropy, but the clinical importance of this is unknown and it probably does not improve 6-month neurologic outcome as measured by the Cerebral Performance Category (1 Class I study with mixed outcomes; Level U). In patients with cardiac arrest, there is insufficient evidence to support or refute the use of nimodipine, the administration of 100% oxygen, or the use of isovolumic high-volume hemofiltration (single Class I studies with insufficient statistical precision to exclude a potentially important clinical effect; Level U).

INTRODUCTION

Outcomes for patients after nontraumatic cardiac arrest is dismal. Only 6–9.6% of all patients with out-of-hospital cardiac arrest (OHCA) survive to hospital discharge[e1,e2]; and an estimated 22.3% of patients with in-hospital cardiac arrest (IHCA) survive to hospital discharge.[e3] It is recognized that brain injury related to cardiac arrest is a major determinant of mortality and disability.[e3] Until recently, the postresuscitation acute management of survivors of cardiac arrest was directed mainly toward the systemic injury, and acute neurologic care focused mainly on prognostication, with some supportive care of neurologic complications. Recently, there has been resurgence of interest in providing acute neuroprotective interventions directed primarily at the brain injury to improve survival and independence of survivors.[e4]

This practice guideline reviews the available evidence regarding neuroprotective interventions in adult patients who are comatose after successful cardiopulmonary resuscitation (CPR). Because of the hererogeneity among the studies, the terms *coma* and *comatose* as used in this guideline include patients who, after return of spontaneous circulation (ROSC), were encephalopathic (not following commands, unresponsive, unconscious, Glasgow Coma Scale [GCS] score <9). Depending on the study, the terms *normothermia* and *non-hypothermia* are both used in this guideline in an attempt to stay true to the original papers if the terminology was defined. Study-specific descriptions are in the evidence table. (See table e-1.) The guideline authors assessed the impact of medical and neurologic critical care on the following outcomes: good neurologic recovery, disability, vegetative state, and death. This guideline seeks to answer the following clinical questions:

1. In patients with nontraumatic cardiac arrest, does induced mild therapeutic hypothermia (TH) or targeted temperature management (TTM) improve outcome after CPR in adults who are initally comatose?
2. In patients with nontraumatic cardiac arrest, do putative neuroprotective drugs improve outcome after CPR in adults who are initally comatose?
3. In patients with nontraumatic cardiac arrest, do other medical interventions or combinations of interventions improve outcome after CPR in adults who are initally comatose?

DESCRIPTION OF THE ANALYTIC PROCESS

The Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology (AAN) convened a panel of experts to develop this practice guideline (appendices e-1 and e-2) according to the process outlined in the 2004 AAN guideline development process manual.[e5] A literature search of MEDLINE and Embase was performed for relevant articles published from 1966 to March 2014, with a pragmatic literature search update performed for studies published between March 2014 and August 30, 2016 (see appendix e-3 for the original complete search strategy). A secondary search of review articles was performed August 29, 2016, to find any missed citations. All abstracts were reviewed by 2 committee members working independently of each other; the full text of potentially relevant articles was subsequently reviewed by at least 2 committee members working independently of each other. The guideline panel excluded review articles and case reports. At least 2 committee members independently rated each article using the AAN classification scheme for therapeutic articles (appendix e-4). Differences between reviewers were resolved through discussion with a third

reviewer. Recommendations were formulated and linked to the strength of the evidence using the scheme described in appendix e-5.

The guideline panel's recommendations are based on the Class I, II, and III studies. The Class IV studies are not discussed further.

ANALYSIS OF EVIDENCE

A total of 447 abstracts was reviewed, of which 73 were deemed potentially relevant and underwent full-text review. The guideline panel included 36 relevant articles, of which 14 are Class I, 3 are Class II, and 26 are Class III (table e-1). Because studies with the lowest risk of bias (i.e., studies of higher class) drive recommendations, where high-quality evidence exists, studies with lower ratings are not discussed.

In patients with nontraumatic cardiac arrest, does induced mild TH or TTM improve outcome after CPR in adults who are initially comatose?

TH is defined as cooling to a core body temperature of 32°C to 34°C and is achieved in patients via various methods, such as external (e.g., skin pads, ice packs), endovascular, and regional cooling (e.g., intranasal cooling). As discussed subsequently, comparative studies of different surface vs invasive cooling methods have not found one method to be more effective, so for this question all global (as opposed to regional) cooling methods were regarded as equivalent.

Studies on TH can be distinguished by the type of initial cardiac rhythm upon ROSC in the included patients. Ventricular tachycardia (VT) or ventricular fibrillation (VF) is an indication for immediate cardiac defibrillation (shockable rhythm), whereas asystole and pulseless electrical activity (PEA) do not require any kind of electrical intervention (nonshockable

rhythm). Because these groups differ significantly with respect to causation of arrest (PEA/asystole has numerous noncardiac causes), outcomes (mortality rates are far higher in patients presenting with PEA/asystole),[e4] and potential response to TH, the guideline panel chose to report the impact of TH on outcomes in patients presenting with VT/VF and PEA/asystole separately when possible. Several studies combined patients with VT/VF and patients with asystole/PEA.

Initial cardiac rhythm: VT/VF

The guideline panel found 4 Class I studies that provided TH (32°C–34°C) to patients who were comatose with VT/VF as the initial cardiac rhythm after ROSC. The first Class I study, from the Hypothermia After Cardiac Arrest (HACA) group,[e6] is a randomized controlled trial that enrolled 273 patients who were unresponsive to verbal command after resuscitation from witnessed OHCA with VF or pulseless VT and who achieved ROSC within 60 minutes. The study randomized patients to receive TH (32°C–34°C for 24 hours followed by passive rewarming over 8 hours) or normothermia. The primary outcome was favorable neurologic outcome (Cerebral Performance Category [CPC][e7] 1 or 2 on a 5-point scale, wherein 1 = good recovery, 2 = moderate disability, 3 = severe disability, 4 = vegetative state, and 5 = death), and the secondary outcome was survival at 6 months. A favorable outcome occurred in 55% (75/136) of patients in the TH group vs in 39% (54/137) of patients in the normothermia group (risk difference [RD] 16% favoring TH, 95% CI 4%–27%, $p = 0.009$). The study also found that 41% (56/137) of patients in the hypothermia group died compared with 55% (76/138) in the normothermia group (RD 14% favoring TH, 95% CI 3%–26%). There was no difference in adverse events (AEs) between groups.

A Class I study by Bernard et al[e8] included 77 adult patients who were comatose and had ROSC after out-of-hospital VF arrest. The patients were randomized within 2 hours of ROSC to receive TH (33°C for 12 hours followed by active rewarming over 6 hours) or normothermia (target core temperature was 37°C). The primary outcome was the proportion of patients discharged to home or to a rehabilitation facility, which was considered a good outcome, vs discharged to a long-term facility or death, which was considered an unfavorable outcome. A good outcome occurred in 49% (21/43) of patients in the hypothermia group vs 26% (9/34) of patients in the normothermia group (RD 22% favoring TH, 95% CI 1%–43%). A multivariate logistic regression adjusting for baseline differences in age and in time from collapse to ROSC found an odds ratio (OR) of 5.25 (95% CI 1.47–18.76) in favor of hypothermia ($p = 0.011$). There was no difference in AEs between the 2 groups.

A Class I study by Nielsen et al[e9] randomized comatose (GCS <9) patients with any initial rhythm after ROSC after OHCA to receive either TH (33°C for 24 hours) or TTM (core temperature target 36°C for 24 hours). In both groups the intervention was followed by 8 hours of rewarming to 37°C, and then core body temperature was maintained below 37.5°C until 72 hours after the cardiac arrest. The primary outcome was death at the end of the trial. Secondary outcomes included unfavorable neurologic outcome and death at 180 days. The study provided prespecified clinical parameters and a set observation period after the end of active intervention before withdrawal of treatment could be considered. In patients whose initial rhythm was shockable, 97% of whom had VT/VF, 153/375 (41%) patients in the TH group died at the end of the trial compared with 150/377 (40%) patients in the TTM group (hazard ratio [HR] 1.06, 95%

CI 0.84–1.34). Neurologic outcome at 180 days was not provided separately for patients whose initial rhythm was VT/VF. Nevertheless, 80% of patients did have VT/VF, and there was no difference in neurologic outcome between the 2 groups of combined patients who were shockable and patients who were nonshockable.

A Class I study[e10] randomized patients who were comatose after OHCA and ROSC to receive 24 hours of TH at either 34°C or 32°C through use of an intravascular cooling technique. The study failed to reach significance in the primary outcome (survival "free from dependence" at 6 months) in the combined population of shockable and nonshockable rhythms. A prespecified subgroup analysis of the patients who presented with VF as the initial rhythm found that 62% in the 32°C group survived to 6 months vs 15% in the 34°C group (RD 46% favoring 32°C, 95% CI 13%–79%). After correction for multiple comparisons, this result also did not reach significance (threshold $p > 0.025$). All patients who survived were "free of severe dependence" at 6 months (Barthel Index > 60).

Six Class III studies were identified that included patients with OHCA or IHCA and initial rhythm of VT/VF who were treated with TH vs normothermia.[e11–e16] Because these lower-class studies would not change the recommendations, they are not discussed further.

Conclusions

For patients who are comatose and in whom the initial cardiac rhythm is either VT or VF after cardiac arrest, TH (32°C–34°C for 24 hours) is highly likely to be effective in improving neurologic outcome and survival compared with normothermia (2 Class I studies).

For patients who are comatose and in whom the initial cardiac rhythm is either VT/VF or PEA/asystole after cardiac arrest, TTM (36°C for 24 hours followed by 8 hours of rewarming to 37°C and temperature maintenance below 37.5°C until 72 hours) is likely as effective as TH in improving neurologic outcome and survival (1 Class I study).

For patients who are comatose and in whom the initial rhythm is VF after cardiac arrest, there is insufficient evidence to support or refute the use of 32°C vs 34°C TH because of lack of statistical precision (6 Class III studies).

Clinical context

In the study by Nielsen et al[e9] investigating TTM in patients who are comatose after cardiac arrest, patients in both groups were treated with cooling (ice packs, ice-cold fluids, intravascular or surface temperature management devices) to achieve a target temperature of either 33°C or 36°C. This study compared 2 levels of cooling and should not be mistakenly interpreted as comparing cooling with no cooling. Also notable is that 72 hours of TTM is longer than the TH periods in the original HACA study[e6] (24 hours TH + 8 hours rewarming) and in the Bernard et al study[e8] (12 hours TH + 6 hours rewarming). It is important to consider that, although the outcomes are considered equivalent, crucial differences in trial designs may have contributed importantly to the outcome observed. The previous studies (HACA[e6] and Bernard et al[e8]) focused on maintaining normothermia without controlling for fever, and they allowed the managing clinicians to decide the manner and timing of prognostication and withdrawal of life-sustaining therapies. In contrast, the Nielsen et al study[e9] focused on fever control and provided a defined prognostication protocol that resulted in a longer observation period after active intervention than

in previous studies. Although the studies have emphasized temperature and medical interventions, it is also important to focus on observing patients and to allow more time for the interventions to take effect before decisions regarding withdrawal of life-sustaining therapies are implemented. Despite the methodologic differences between the TH and TTM trials, the available data strongly support the use of temperature control.

Initial cardiac rhythm: PEA/asystole

The guideline panel found 1 Class I and 12 Class III studies that provided induced mild hypothermia (32°C–34°C) to patients who were comatose with asystole/PEA after ROSC.

A single Class I study[e9] randomized patients who were comatose and had any initial rhythm after ROSC after OHCA to receive either TH (33°C for 28 hours) or TTM (core temperature target 36°C). The primary outcome was death at the end of the trial. Secondary outcomes included unfavorable neurologic outcome and death at 180 days. For those whose initial rhythm was nonshockable, death occurred in 82/98 (84%) patients in the TH group and in 74/88 (84%) patients in the TTM group (HR 1.08, 95% CI 0.79–1.48). Secondary outcomes were not reported separately for patients with shockable and patients with nonshockable rhythms, but in the combined group there was no difference between the 2 treatment groups (HR 1.02, 95% CI 0.88–1.16).

Twelve Class III studies included patients with nonshockable rhythms, typically PEA or asystole, or a mixed population of patients with shockable and patients with nonshockable rhythms. A Class III study[e17] included 374 patients with OHCA and initial nonshockable rhythm who were

treated with TH vs non-hypothermia. A significant improvement was seen in the rate of good neurologic outcome (CPC 1–2) at 6 months in the group receiving TH (RD 12% favoring TH, 95% CI 2%–21%) and a reduction in mortality at 6 months (RD 15% favoring TH, 95% CI 5%–25%). Another Class III study[e18] included 100 patients with OHCA and initial PEA or asystole who were treated with TH vs non-hypothermia. There was a significant improvement in the rate of good neurologic outcome (CPC 1–2) at hospital discharge in the group receiving TH (RD 16% favoring TH, 95% CI 1%–32%) and in survival at hospital discharge (RD 20% favoring TH, 95% CI 3%–37%). Another Class III study[e11] included patients with OHCA and patients with IHCA, some with shockable and some with nonshockable rhythms, who were treated with TH vs non-hypothermia. In the 197 patients with nonshockable rhythms, 41% of patients receiving TH and 21% of patients receiving non-hypothermia treatment survived to hospital discharge (RD 17% favoring TH, 95% CI 5%–30%), although there was no benefit in reduction of unfavorable outcome, defined as CPC 3–5, at hospital discharge. A Class III population-based cohort study[e15] included patients with OHCA, some with shockable rhythms and some with nonshockable rhythms, who were treated with TH vs non-hypothermia. In the 223 patients with nonshockable rhythms, TH conferred no benefit on survival or good neurologic outcome compared with non-hypothermia. Twenty-seven percent of patients treated with TH survived to 1 year vs 19% of patients treated with non-hypothermia (RD 8% favoring TH, 95% CI -4% to 20%), and 19% of treated patients and 16% of controls had a good neurologic outcome at 1 year (RD 3% favoring treatment, 95% CI -8% to 14%). Another Class III study[e12] included 211 patients with either OHCA or IHCA, some with shockable and some with nonshockable rhythms, who were treated with TH vs non-hypothermia. No improvement was seen in 1-month survival in the subgroup of patients with nonshockable rhythms who received TH (proportion

surviving at 1 month: TH 30%, non-hypothermia 44%; RD 14%, 95% CI -5% to 33%). A Class III study of 367 patients with OHCA and IHCA and nonshockable rhythms by Storm et al[e19] found no benefit of TH vs non-hypothermia in improving the rate of good neurologic outcome (CPC 1–2) at the time of discharge from the intensive care unit (ICU) (risk of good outcome: TH 28%, non-hypothermia 18%; RD 9%, 95% CI -3% to 22%). Another Class III study[e13] included a mixed population of patients with OHCA and shockable and nonshockable rhythms who were treated with TH vs non-hypothermia. There was no difference in the proportion of patients with a good neurologic outcome (CPC 1–2) at the time of hospital discharge among the 437 patients with an initial nonshockable rhythm (risk of good outcome: TH 15%, non-hypothermia 17%; RD -3%, 95% CI -10% to 5%). A Class III study by Don et al[e14] included patients with OHCA, some with shockable and some with nonshockable rhythms, who were treated with TH vs non-hypothermia. The study found that in the subgroup of 313 patients with nonshockable rhythms, TH failed to improve the rate of good neurologic outcome, defined as having no evidence of impairments at discharge (risk in TH 12%, non-hypothermia 9%; RD 3%, 95% CI -4% to 10%) or survival to hospital discharge (risk in TH 21%, non-hypothermia 19%; RD 2%, 95% CI -7% to 11%).

In a Class III retrospective cohort study using a regional registry,[e20] over a 28-month period, 1,713 patients were resuscitated from an initial nonshockable OHCA, 1,423 of whom met inclusion criteria and had available data, with 596 (42%) receiving TH. Survival with good neurologic outcome (CPC 1–2) at hospital discharge occurred in 14% in the group receiving TH vs 5% in the nontreated group (RD 8%, 95% CI 5%–12%). Survival to hospital discharge was 30% in the TH group and 16% in the nontreated group (RD 14%, 95% CI 10%–19%).

A Class III retrospective cohort study[e16] included 8,316 patients who were comatose after IHCA and compared survival and neurologic outcome at hospital discharge between the group of 214 patients who received TH and the group of 8,102 who did not. Outcome was not reported separately for the nonshockable group, but 87% of patients were nonshockable and the outcome for the entire group showed no benefit of TH for either survival or good neurologic outcome (adjusted OR for survival 0.83, 95% CI 0.65–1.23; adjusted OR for good neurologic outcome 0.93, 95% CI 0.65–1.32). Another Class III study[e21] of 33 patients with IHCA examined the effect of TH on survival and neurologic outcome at hospital discharge. Three of the 33 patients had an initial shockable rhythm, and the other 30 had an initial nonshockable rhythm. There was no benefit of TH over non-hypothermia for either survival or good neurologic status, although this study lacked statistical precision.

One additional Class III study[e22] of patients with asystole/PEA was identified; this was a pilot study to test the feasibility and speed of a helmet device to achieve a target temperature of 34°C in patients who are comatose after OHCA. The helmet was removed when the bladder temperature reached 34°C or 4 hours passed. Sixteen patients were randomized to the helmet group and 14 to the control (no cooling) group. A core temperature of 34°C as measured by a bladder thermometer was achieved after a median time of 180 minutes (range 70–240 minutes); tympanic temperature was achieved after a median of 60 minutes (range 15–240 minutes). Only 3 patients in the treatment group (19%) and 1 patient in the control group (7%) survived to discharge (RD 12%, 95% CI -16% to 37%), but sufficient statistical precision was lacking. This study was not included in the subsequent meta-analysis because of both the use of a regional

cooling technique and the short duration of hypothermia (4 hours or less, compared to typical protocols using TH for at least 24 hours).

There were 7 additional Class III studies[e23–e29] examining patients with OHCA and any initial rhythm who were treated with TH vs non-hypothermia. These studies will not be discussed further because it was not possible to extract the results for the subgroup of patients with PEA/asystole, which limits conclusions.

Meta-analysis

The guideline panel performed 2 meta-analyses to investigate whether TH improves the outcome in patients who are comatose with an initial cardiac rhythm of PEA or asystole after cardiac arrest. Seven of the studies[e11,e13,e14,e18–e21] (described in more detail in the previous section) provided outcome data on good neurologic outcome, generally defined as CPC 1–2, and most had an endpoint of hospital discharge. The exceptions to this included the study by Don et al[e14] in which a chart review was conducted and a prespecified definition of good vs unfavorable outcome was used rather than CPC 1–2 and the study by Storm et al,[e19] which used an endpoint of ICU discharge rather than hospital discharge. When a random-effects model was used, there was a small benefit in the proportion of patients with good neurologic outcomes for patients treated with TH vs non-hypothermia (RD 6%, 95% CI 3%–9%, $I^2 = 41$). Five studies provided data on survival to hospital discharge,[e11,e14,e15,e18,e20] 3 of which showed a benefit of TH on survival.[e11,e18,e20] With use of a random-effects model, a significant benefit was seen in the proportion of patients who survived to hospital discharge for patients treated with TH vs non-hypothermia (RD 12%, 95% CI 8%–16%, $I^2 = 49$). Tests for heterogeneity were nonsignificant

in both analyses.

Conclusions and recommendations

For patients who are comatose and in whom the initial cardiac rhythm is either PEA or asystole after cardiac arrest, treatment with TH vs non-hypothermia possibly improves survival to hospital discharge (RD 12%, 95% CI 8%–16%, I^2 = 49; meta-analysis of 5 Class III studies) and good neurologic outcome at hospital discharge (RD 6%, 95% CI 3%–9%, I^2 = 41; meta-analysis of 7 Class III studies).

Although the frequency of survival and good neurologic outcome after nonshockable rhythms is small, for patients who are comatose and in whom the initial cardiac rhythm is either PEA or asystole after cardiac arrest, TH possibly improves survival and good neurologic recovery at discharge compared with standard care and may be offered (Level C).

Prehospital cooling

The progression of the neurologic injury after the initial brain insult is time-dependent. Laboratory studies suggest that neurologic injury is significantly decreased if cooling is initiated as soon as possible after resuscitation.[e30–e33] However, the optimal timing of induction of TH after resuscitation for cardiac arrest remains unclear. Induction of TH immediately after successful resuscitation has been undertaken. Five Class I studies and 1 Class II study investigated optimal timing of TH induction after resuscitation.

A Class I study[e34] included adult patients with any initial cardiac rhythm after ROSC following OHCA who were treated with prehospital administration of 2 L of 4°C normal saline or no prehospital cooling. Most patients (77%) in the VF group who survived to hospitalization received in-hospital cooling (with equal proportions receiving and not receiving field cooling), and a smaller percentage of patients in the non-VF group received in-hospital cooling at the discretion of the treating physician (57%). In the group of patients who received in-hospital cooling, prehospital cooling reduced the time to reach target temperature compared with patients who did not receive prehospital cooling. Prehospital cooling did not improve either survival to hospital discharge or neurologic status at hospital discharge in either the VF group or the non-VF group. For patients with VF as the initial rhythm, 63% of patients receiving prehospital cooling survived to hospital discharge vs 65% of patients in the control group (RD 2% favoring prehospital cooling, 95% CI -10% to 6%), and 58% receiving prehospital cooling fully recovered or were minimally impaired at discharge vs 62% in the control group (RD -4% favoring no prehospital cooling, 95% CI -12% to 4%). Similar results were reported for the non-VF cohort. Survival to discharge in the prehospital cooling group was 19% vs 16% in the control group (RD 3% favoring prehospital cooling, 95% CI -2% to 8%), and 14% of patients in the prehospital cooling group had a good neurologic outcome vs 13% of patients in the control group (RD 1% favoring prehospital cooling, 95% CI -4% to 6%). Significantly higher rates of rearrest were seen in the prehospital treatment group. The prehospital cooling group also had significantly higher rates of rearrest, lower oxygenation, increased pulmonary edema on first chest x-ray, and greater use of diuretics during the first 12 hours of hospitalization than the control group.

Another Class I study[e35] included 200 patients with no specified initial cardiac rhythm after witnessed OHCA, 75 of whom survived to hospital admission. The intervention was prehospital hypothermia using an intranasal cooling device provided during the time of arrest, followed by in-hospital cooling, vs in-hospital cooling alone. Although the primary outcome was the time to target core body temperature, the study also generated data on survival rates and favorable outcome at discharge (CPC 1–2). The study found no added benefit of prehospital treatment in patients presenting with VF or PEA and asystole. Of the 37 patients presenting with VF who survived to hospital admission, 63% of treated patients and 48% of controls survived to hospital discharge (RD 15% favoring prehospital cooling, 95% CI -17% to 47%), and 50% of treated patients and 29% of controls had a favorable outcome at discharge (RD 21% favoring prehospital cooling, 95% CI -10 to 53%). Of the 37 patients presenting with PEA and asystole surviving to hospital admission, 25% of treated patients and 14% of controls survived to hospital discharge (RD 11% favoring prehospital cooling, 95% CI -15% to 37%, not significant), and 19% of treated patients and 14% of controls had a favorable outcome at discharge (RD 5% favoring prehospital cooling, 95% CI -20% to 29%, not significant). Epistaxis (serious in 1 patient) and nasal whitening were reported AEs of the intranasal cooling device.

Another Class I study[e36] included 234 patients with initial cardiac rhythm of VF after OHCA who were treated with prehospital cooling using 2 L of ice-cold Ringer's lactate or no prehospital cooling. All patients surviving to hospital admission received in-hospital cooling. A concurrent study,[e37] published separately, used the same protocol of prehospital cooling in 163 patients with OHCA from any cause (45% had noncardiac causes) and initial rhythm of PEA or asystole. Both studies reported no benefit of prehospital cooling on the primary outcomes of

favorable outcome at hospital discharge (CPC 1–2) or survival to discharge. In patients with VF, 48% of treated patients and 53% of control patients had a favorable outcome at hospital discharge (RD -5%, 95% CI -18% to 8%), and 47% of treated patients and 53% of control patients survived to hospital discharge (RD 6%, 95% CI -19% to 7%). In patients with PEA or asystole, 12% of treated patients and 9% of control patients had a favorable outcome at hospital discharge (RD 4% favoring prehospital cooling, 95% CI -6% to 13%), and 13% of treated patients and 9% of control patients survived to hospital discharge (RD 5% favoring prehospital cooling, 95% CI -5% to 14%). Similar negative results were reported for the subgroup of patients with PEA and patients who were asystole with a cardiogenic cause for their cardiac arrest. No significant differences in the rate of pulmonary edema and recurrent cardiac arrest were found between the 2 groups in the VF study. AEs were not reported in the PEA/asystole study.

Another Class I study[e38] (for the primary endpoint of nasopharyngeal temperature at hospital admission) randomized 43 patients to a prehospital cooling group which received +4°C Ringer's solution with a target temperature of 33°C or conventional fluid therapy. Patients were enrolled if ROSC was greater than 9 minutes and GCS was less than or equal to 5, regardless of initial cardiac rhythm. The primary endpoint was nasopharyngeal temperature on arrival to the emergency department. During hospital admission, patients were treated according to the postresuscitation policies of the 5 participating hospitals, such that different patients received different hospital management strategies. It was unclear if treating physicians were blinded to the prehospital cooling assignment. Temperature decreased more in the cooling group than the control group during transport (-1.5 ± 0.8°C vs -0.1 ± 0.6°C, $p < 0.001$), resulting in a lower nasopharyngeal temperature at the time of admission in the cooling group (34.1 ± 0.9°C vs 35.2

± 0.8°C, $p < 0.001$). There was no benefit of prehospital cooling on survival to discharge or favorable outcome at discharge (all patients who survived had a favorable outcome; 42% in prehospital cooling group vs 44% of controls, RD 2.3%, 95% CI -27.0% to 31.3%), although wide CIs demonstrate insufficient precision to exclude an important effect.

The final Class I study[e39] included 245 patients with any rhythm after OHCA. Patients were randomized to receive either intra-arrest TH with external cooling and an infusion of cold saline or no prehospital cooling. All patients surviving to hospital admission (n = 77) received in-hospital TH. Initial rhythm was VF/VT in 36/123 (29.3%) of the intra-arrest TH group and 32/122 (26.2%) of the control group. There was no benefit of intra-arrest TH on survival to discharge (5.7% in intra-arrest TH group vs 4.1% of controls, RD 1.6%, 95% CI -4.3% to 7.7%) or favorable outcome at discharge (CPC 1–2) (5.7% vs 3.3%, RD 2.4%, 95% CI -3.2% to 8.4%). The RR for 1-month survival was not significant when patients were stratified by initial rhythm (VF/VT 1.78, 95% CI 0.48–6.53, asystole/PEA 0.52, 95% CI 0.05–5.6), but broad CIs with important risks in each direction show that this analysis had insufficient precision to confirm or refute an important difference within groups.

A Class II study[e40] in which 125 patients who were comatose after OHCA were treated with prehospital cooling using 2 L 4°C normal saline or no prehospital cooling found no impact on survival to hospital discharge in patients presenting with either VF or PEA/asystole as their initial rhythm. Only 60 of the 97 patients who survived to hospital admission were also treated with TH in the hospital. Exploratory analysis revealed no significant effect of prehospital cooling in those who received in-hospital TH vs those who did not.

Conclusion

For patients who are comatose and in whom the initial cardiac rhythm is VT/VF or PEA/asystole after cardiac arrest, prehospital cooling with 2 L 4°C IV solutions or intranasal cooling as an adjunct to in-hospital cooling is highly likely to be ineffective in further improving neurologic outcome and survival (multiple Class I studies).

Clinical context

Several clinical studies with varying methodologies showed that prehospital cooling, whether post-ROSC or intra-arrest, did not provide additional neurologic benefit when used to augment standard interventions that included in-hospital cooling. The absence of a clear understanding of the mechanisms by which hypothermia exerts its neuroprotective effects limits the ability to identify the most opportune time to initiate the intervention.

Studies comparing different cooling methods

Various strategies are used to achieve and maintain TH. They can be broadly divided into 2 categories: surface cooling and invasive cooling. Examples of surface cooling methods are ice packs and automated systems using cooling blankets. Examples of invasive cooling methods are manual and automated endovascular cooling, intravascular infusion of ice-cold saline, or peritoneal lavage with ice-cold saline. The studies discussed next directly compare 2 different cooling methods.

A Class III study[e41] included 78 patients with either OHCA or IHCA of presumed cardiac origin and either shockable or nonshockable initial rhythms. Patients were treated with either invasive cooling using an automated device via an endovascular catheter placed in the femoral vein or an automated surface cooling device using cooled distilled water. Although data were not reported separately for the shockable and nonshockable rhythms, the study data are included in the guideline analysis because all patients received TH. There was an equal proportion of patients with shockable and nonshockable rhythms in both treatment groups. No difference in either survival or good neurologic outcome at hospital discharge was seen between the 2 treatment groups (survival RD 8% favoring invasive cooling, 95% CI -14% to 30%; good neurologic outcome RD 0%, 95% CI -21% to 21%). Target temperature was maintained more accurately with less variability in the invasive cooling group, but this group also had more bleeding complications (43.6% vs 17.9%).

Another Class III study[e42] examined 115 patients, 16 of whom were comatose and admitted to the ICU with either shockable or nonshockable rhythms after cardiac arrest and treated with an automated system in which chilled Ringer's lactate is continuously infused into the peritoneal cavity. These 16 patients were compared with a historical control group of 99 patients who were comatose with cardiac arrest and were treated with surface cooling. Sixty-nine percent of the patients treated with peritoneal lavage survived to hospital discharge compared with 46% of the patients treated with surface cooling, which was not a significant difference (RD 22% favoring peritoneal lavage, 95% CI -3% to 47%). Peritoneal lavage shortens the time to reach target temperature and provides more stable temperature control than surface cooling. No serious complications were reported.

Conclusion

In patients who are comatose with cardiac arrest, there is insufficient evidence to support or refute the use of invasive cooling methods (including endovascular catheter or peritoneal lavage) instead of surface cooling (single Class III studies).

Standardized protocols

An additional Class III[e43] study included 150 patients, some with IHCA and some with OHCA, with either shockable or nonshockable rhythms, and compared rates of survival and good neurologic status at hospital discharge before and after the institution of a standardized treatment protocol termed *CODE ICE*, which included burst paging, uniform pathways of care, and dissemination of the protocol to all providers of care. There was no improvement in either survival rates (RD 4% favoring standard care CI -20% to 12%) or rates of good neurologic outcome (RD 8% favoring standard care CI -24% to 7%) in the CODE ICE group compared with the standard care group, but time to initiation of TH and time to target temperature were reduced in the CODE ICE group.

Conclusion

In patients who are comatose after cardiac arrest, there is insufficient evidence to support or refute the use of a standardized protocol of care for the provision of TH.

Induced mild hypothermia in combination with coenzyme Q_{10}

A Class II study[e44] randomized 49 adult patients with OHCA of presumed cardiac origin and a mixture of VT/VF and PEA/asystole as their initial cardiac rhythm to receive 24 hours of either hypothermia (35°C) plus liquid coenzyme Q_{10} 250 mg once, followed by 150 mg TID for 5 days, or hypothermia alone. Significantly more patients in the combination-therapy group survived to 3 months (68%, 17/25) compared with the hypothermia-alone group (29%, 7/24) (RD 39% favoring coenzyme Q_{10}, 95% CI 13%–65%). Survival to hospital discharge and good neurologic status at 3 months were not significantly different between the 2 groups. No significant AEs were reported.

Induced mild hypothermia in combination with high-dose erythropoietin

A Class III study[e45] in 58 adult patients who were comatose after cardiac arrest compared hypothermia plus epoetin alfa 40,000 U every 12 hours for 2 days with hypothermia alone. The study found that epoetin alfa was not associated with added benefit in survival (RD 8% favoring epoetin alfa, 95% CI -20% to 36%). The study authors noted a significant increase in thrombosis in patients treated with epoetin alfa compared with controls (15% vs 5%).

Conclusions

In patients who are comatose after OHCA, the addition of coenzyme Q_{10} to TH possibly improves survival but does not improve neurologic status at 3 months (1 Class II study). There is insufficient evidence to support or refute the use of epoetin alfa to improve outcome after induced mild hypothermia in patients who are comatose after cardiac arrest (1 Class III study).

Recommendations

For patients who are comatose and in whom the initial cardiac rhythm is either VT or VF after cardiac arrest, TH (32°C–34°C for 24 hours) is highly likely to be effective in improving neurologic outcome and survival compared with normothermia and should be offered (Level A).

For patients who are comatose and in whom the initial cardiac rhythm is either VT/VF or PEA/asystole after cardiac arrest, TTM (36°C for 24 hours followed by 8 hours of rewarming to 37°C and maintained below 37.5°C until 72 hours) is likely as effective as TH in improving neurologic outcome and survival and is an acceptable alternative to TH (Level B).

For patients who are comatose and in whom the initial cardiac rhythm is VT/VF or PEA/asystole after cardiac arrest, prehospital cooling with 2 L 4°C IV solutions or intranasal cooling as an adjunct to in-hospital cooling should not be offered (Level A).

In patients who are comatose after cardiac arrest, the addition of coenzyme Q_{10} to TH possibly improves survival but does not improve neurologic status at 3 months and may be offered (Level C).

No recommendations are made on the use of 32°C vs 34°C TH; use of TH in patients whose initial cardiac rhythm is PEA or asystole; use of invasive cooling instead of surface cooling; use of standardized protocols for TH; or use of epoetin alfa in addition to mild TH (Level U).

Clinical context

The success of TH in post–cardiac arrest brain injury is defined by improvement not only in survival but also in the neurologic status of survivors. This success has given rise to the possibility that other agents or combinations of agents will further enhance the neurologic outcome benefits. As an added agent to TH, coenzyme Q_{10} showed survival benefit but failed to show improvement in neurologic status at 3 months. Because the TH plus coenzyme Q_{10} study is a pilot study, more data are needed to define the role of coenzyme Q_{10} in patients post cardiac arrest.

In patients with nontraumatic cardiac arrest, do putative neuroprotective drugs improve outcome after CPR in adults who are initially comatose?

Xenon gas

A single-blind Class I study[e46] enrolled 110 comatose survivors of witnessed OHCA with VF/VT and ROSC within 45 minutes. Patients were randomized to inhaled xenon (to achieve an end-tidal xenon concentration of at least 40%) combined with TH (33°C) for 24 hours (n = 55) vs TH alone (n = 55), following an earlier Class III study.[e47] The primary endpoint was the degree of cerebral white matter damage as measured by fractional anisotropy from diffusion tensor MRI performed 36–52 hours after OHCA. The mean global fractional anisotropy value was 3.8% higher (95% CI 1.1%–6.4%) in the xenon group when adjusting for age, sex, and site. This suggests less white matter damage in the xenon group, but the clinical importance of this is unknown. The difference in 6-month mortality between the 2 groups was not statistically significant (27.3% in the xenon group and 34.5% in the control group; RD -7.3%, 95% CI -24.0% to 9.8%), but CIs included clinically important differences in both directions. Neurologic

outcome at 6 months as measured by the CPC was also not significantly different between the groups, with median scores of 1 (IQR 1–5) in both groups (median difference 0, 95% CI 0%–0%).

Calcium channel blockers

A Class I study[e48] used nimodipine after resuscitation from cardiac arrest. The study randomized 155 patients who were unresponsive with OHCA and ROSC to receive either nimodipine 10 μg/kg IV injection immediately upon ROSC followed by infusion of 0.5 μg/kg/min for 24 hours or placebo. There was no difference in survival (40% nimodipine vs 36% placebo, RD 4%, 95% CI -12% to 19%) or good neurologic outcome at 1 year (29% nimodipine vs 24% placebo, RD 6%, 95% CI -8% to 20%).

One Class I study[e49] of 516 patients demonstrated that 3 doses of the calcium channel blocker lidoflazine (given immediately after ROSC [1 mg/kg] and at 8 and 16 hours after resuscitation [0.25 mg/kg]) provided no beneficial effect. At 6 months, 18.5% of the patients treated with lidoflazine had survived vs 17% of the control patients (RD 1%, 95% CI -5% to 8%), and 24% of the patients treated with lidoflazine achieved a CPC of 1 or 2 at any time during the study vs 23% of the control patients (RD 1%, 95% CI -6% to 8%).

Selenium

One Class III study[e50] retrospectively followed a cohort of 227 patients who were comatose with any initial rhythm after OHCA or IHCA and who were treated with either selenium 1,000 μg for 5 days (124 patients) or no selenium. Sixty-seven percent of patients receiving selenium

experienced a favorable neurologic outcome within 6 months vs 48% of control patients (favorable outcome was defined in this study as CPC 1–3) (RD 19% favoring selenium, 95% CI 6%–32%). However, selenium treatment did not confer survival benefit at discharge or at 6 months.

Thiopental

One Class I study of 262 patients by the Brain Resuscitation Clinical Trial I Study Group (BRCTI)[e51] demonstrated that a loading dose of 30 mg/kg of thiopental after ROSC provided no beneficial effect. At 1 year, 23% of the patients treated with thiopental had survived vs 20% of the control patients (RD 3%, 95% CI -7% to 13%), and 20% of patients treated with thiopental had a favorable outcome (CPC 1–2) vs 15% of control patients (RD 5% favoring thiopental, 95% CI -5% to 14%).

Magnesium and diazepam

In one Class I study,[e52] 300 patients with nontraumatic OHCA were randomized to receive 2 g of magnesium sulfate, 10 mg of diazepam, both magnesium sulfate and diazepam, or placebo immediately after ROSC. Of the patients receiving magnesium sulfate, 38% awakened within 3 months vs 34% of patients not receiving magnesium sulfate (RD 4%, 95% CI -7% to 15%), and 30% survived to 3 months vs 28% (RD 2%, 95% CI -8% to 12%). Despite randomization, there were significant baseline differences in the diazepam treatment groups. After adjustment for these baseline differences, this study found no significant beneficial effect on survival in patients receiving diazepam vs those not receiving diazepam (RD -3%, 95% CI -13.5% to 7.4%).

Corticosteroids

One Class II study[e53] reanalyzed the data collected during the BRCTI trial, comparing outcomes between patients who received and patients who did not receive corticosteroids within 8 hours of ROSC. Corticosteroids were used at the discretion of the patient's attending physician. The corticosteroids prescribed were dexamethasone, methylprednisolone, betamethasone, and hydrocortisone. Patients were each assigned to 1 of 4 groups: low-, medium-, or high-dose corticosteroid treatment, or no corticosteroid treatment. There was no significant difference between patients who received and patients who did not receive corticosteroids in the proportion of patients achieving good neurologic outcome (RD 0%, 95% CI -13% to 13%) or survival (RD 10% favoring steroids, 95% CI -4% to 20%) at 1 year.

One Class III study[e54] of 389 patients who were comatose after OHCA found that steroids given at any time during hospitalization did not improve survival to hospital discharge or the likelihood of awakening before hospital discharge (OR 1.18, 95% CI 0.85–1.61).

Conclusions

In patients with witnessed OHCA, VT/VF, and ROSC, xenon (to achieve an end-tidal xenon concentration of at least 40%) and TH probably results in less white matter damage as measured by fractional anisotropy (1 Class I study), but the clinical importance of this is unknown. It probably does not improve 6-month neurologic outcome as measured by the CPC (1 Class I study). Impacts on 6-month mortality are uncertain (1 Class I study with insufficient precision). In patients with OHCA of presumed cardiac origin and ROSC, there is insufficient evidence to support or refute the use of nimodipine (1 Class I study with insufficient statistical precision;

Level U). In patients with cardiac arrest and ROSC, the calcium channel blocker lidoflazine is likely to be ineffective in improving survival and neurologic outcome (1 Class I study). In patients with cardiac arrest and ROSC, a single loading dose of thiopental is likely to be ineffective in improving survival or neurologic outcome (1 Class I study). There is insufficient evidence to support or refute the effectiveness of selenium in improving outcome (1 Class III study). In patients with OHCA, there is insufficient evidence to support or refute the use of a single 2 g loading dose of magnesium sulfate for improving survival or awakening (1 Class I study with insufficient statistical precision to exclude a meaningful benefit). On the basis of the same study, a single 10 mg loading dose of diazepam is likely to be ineffective in improving survival or awakening. In patients with OHCA, there is insufficient evidence to support or refute the use of corticosteroids for improving survival or neurologic outcome (1 Class II study and 1 Class III study with insufficient statistical precision to exclude a moderate or large benefit).

Recommendations

In patients with cardiac arrest and ROSC, the calcium channel blocker lidoflazine is likely to be ineffective in improving survival and neurologic outcome and should not be offered (Level B).

In patients with cardiac arrest and ROSC, a single loading dose of thiopental is likely to be ineffective in improving survival or neurologic outcome and should not be offered (Level B).

A single 10 mg loading dose of diazepam is likely to be ineffective in improving survival or awakening and should not be offered (Level B).

In patients with OHCA of presumed cardiac origin and ROSC, there is insufficient evidence to support of refute the use of nimodipine, selenium, a single 2 g loading dose of magnesium sulfate, or corticosteroids for improving survival or neurologic outcome (Level U).

In patients with witnessed OHCA, VT/VF, and ROSC, there is insufficient evidence to support or refute the routine clinical use of xenon gas in addition to TH, as it probably results in less white matter damage as measured by fractional anisotropy, but the clinical importance of this is unknown and it probably does not improve 6-month neurologic outcome as measured by the CPC. Further research into the clinical outcomes of this intervention is warranted.

Clinical context

To date, no putative neuroprotective drug has been shown to be effective in improving survival or neurologic outcome in patients who are comatose after cardiac arrest. Despite the lack of evidence to support or refute the use of agents such as nimodipine, xenon gas, selenium, and magnesium sulfate, currently none of these agents is routinely used in clinical practice to improve neurologic outcome or survival in this patient population. Furthermore, these agents may have serious AEs in this patient population, such as hypotension with calcium channel blockers and barbiturates, infections with corticosteroids, and sedation with benzodiazepines and barbiturates.

In patients with nontraumatic cardiac arrest, do other medical interventions or combinations of interventions improve outcome after CPR in adults who are initially comatose?

Oxygen therapy

One Class I study[e55] randomized 28 patients with ROSC after witnessed OHCA and VF as their initial rhythm to receive either 30% or 100% oxygen for 60 minutes followed by standard care, with some patients receiving TH and others not. There was no difference in survival (71% in each group) or good neurologic outcome (43% treatment vs 57% control) at hospital discharge, although the study lacked the statistical precision to exclude a potentially important effect (RD for survival 0%, 95% CI -34% to 34%; RD for good neurologic outcome -14%, 95% CI -51% to 22%). The study also failed to show any significant difference in the primary outcome of serum neuron-specific enolase and S100 levels at 24 and 48 hours after ROSC.

Conclusion

There is insufficient evidence to support or refute the use of 100% oxygen for 60 minutes immediately post resuscitation in patients with OHCA and ROSC (1 Class I study with insufficient statistical precision to exclude a potentially important clinical effect).

High-volume hemofiltration

One Class I study[e56]randomized 61 patients with OHCA of presumed cardiac etiology and an initial rhythm of either VF or asystole to 1 of 3 groups: isovolumic high-volume hemofiltration (HF) alone, HF combined with mild hypothermia (32°C for 24 hours by cooling the HF substitution fluid), or control with a primary endpoint of 6-month survival. There was no statistical difference in 6-month survival between groups (45% in the HF group, 32% in the HF-plus-hypothermia group, and 21% in the control group, $p = 0.28$; RD for HF vs controls 24.0%,

95% CI -5.5% to 48.2%, RD for HF plus hypothermia vs controls 10.8%, 95% CI -16.4% to 35.1%). After adjustment for baseline characteristics of the cardiac arrest, including initial rhythm, no-flow interval, and low-flow interval, the study reported a multivariate logistic regression model showed an improved odds of survival with HF (data pooled for both HF groups; OR for 6-month survival 4.4, 95% CI 1.1–16.6), although the CI included a lower bound of uncertain clinical relevance.

Conclusion

There is insufficient evidence to support or refute the use of isovolumic high-volume HF in patients with OHCA and ROSC (1 Class I study with insufficient statistical precision for the primary analysis of 6-month survival and with a secondary logistic regression model including a lower CI of uncertain clinical relevance).

Recommendations

There is insufficient evidence to support or refute the use of 100% oxygen for 60 minutes immediately post resuscitation in patients with OHCA and ROSC (Level U). There is insufficient evidence to support or refute the use of isovolumic high-volume HF (with or without TH) in patients with OHCA and ROSC (Level U).

CLINICAL CONTEXT FOR ALL EVIDENCE

Coma is a period of prolonged unconsciousness without response to external stimuli. The studies reviewed had heterogeneous definitions of coma, which limits prognostication based on initial presentation and clinical status upon rewarming. Patients who are comatose after successful

resuscitation from cardiac arrest require complex neurologic and medical care in the critical care unit. Induced mild hypothermia has emerged as an effective therapy to improve outcomes in patients with VT/VF as their initial cardiac rhythm, but its role in patients with PEA and asystole remains less certain, and the optimal therapeutic window for administering this therapy remains unclear. The 2 Class I studies provide support for induced hypothermia within 2 to 4 hours of ROSC, but the studies vary in the rate at which the target temperature range was reached. One of the studies showed that TTM followed by maintenance of normothermia seems to be equally effective in improving outcomes in patients resuscitated from cardiac arrest with shockable or nonshockable initial cardiac rhythms. It is important to note that neuroprotection was provided by adherence to TTM protocol, whether 36°C or 33°C for 24 hours. This should not be mistaken as normothermia only or no hypothermia at all. Although the 2 Class I studies used external cooling methods, other studies have used methods such as endovascular cooling with catheters, chilled IV solutions, and regional cooling (i.e., intranasal cooling). The Class I study on TTM used both external cooling and endovascular cooling with catheters. To date, no study has shown the optimal means by which to induce and maintain TH, and the rates of cooling to target temperature range need further clarification. We find no clear advantage of one method over another, but it is very important for clinicians to be aware of the existing methods and technologies so they are better informed when acquiring equipment and developing therapeutic protocols. The rewarming phase of the hypothermia therapy also varied in the studies available. Multiple brain-related complications such as seizures, status epilepticus, myoclonus, and cerebral edema have been noted in these patients. Although these conditions are believed to have a large impact on prognostication and quality of life of survivors, studies are too limited to support evidence-based treatment recommendations at this time. In the absence of adequate evidence to

provide a treatment recommendation, it is best to consider prevailing local standards in the management of these complications. The guideline panel also notes that most of the studies did not specifically address the impact of withdrawal of life-sustaining therapies in their analysis (see table e-1). The impact of this practice on the outcome of the trials needs careful study. Finally, there is a great need for further studies on methods of supplementing TH protocols, such as extracorporeal membrane oxygenation (ECMO) and pharmacologic agents (e.g., xenon gas, where the most recent study had mixed results).

RECOMMENDATIONS FOR FUTURE RESEARCH

Future research needs to carefully address the complexity of patient characteristics and the clinical course after from cardiac arrest. Precise definitions of coma, outcomes, and the decision for withdrawal of life-sustaining therapy are needed. Future research questions may include the following:

1. What are the best assessment methods and outcome measures to use? When is the best time to use these methods and measures?
2. What is the beneficial effect of TH and TTM on patients resuscitated from IHCA with all types of initial cardiac rhythm?
3. What are optimal temperature settings (time initiating and reaching target temperature, rate of rewarming, depth of target temperature [e.g., 32°C, 34°C, 36°C], duration of temperature management [e.g., 12 hours, 24 hours, 48 hours]) to provide the best outcome?
4. What is the treatment window (time lapse after ROSC) in which TTM will be most effective and ineffective?

5. What is the role of fever control over days after active TTM?
6. What strategies (e.g., ECMO, pharmacologic agents) may provide benefit in addition to hypothermia, and what is the impact of hypothermia on the action of other putative neuroprotective agents or interventions?
7. What are the best and safest methods of delivering hypothermia (external vs internal, global vs regional cooling)?
8. What is the impact of aggressive management of post–cardiac arrest neurologic complications (e.g., brain edema, seizures or seizure prophylaxis, intracranial pressure elevation, and ICU-related complications) on outcomes?
9. What is the impact of aggressive management of the etiology of cardiac arrest (e.g., myocardial infarction) and aggressive management of other systemic complications?
10. How does the use of TH affect the ability to prognosticate outcome in patients who are comatose after cardiac arrest?
11. What is the role of TTM induced and maintained by pharmacologic means in patients who are comatose after ROSC?
12. What is the role of biomarkers in the delivery and maintenance of TTM and the impact of biomarkers on prognostication?
13. What is the role of withdrawal of life-sustaining therapies in the outcomes of studies related to cardiac arrest resuscitation?

Appendix e-1: Mission Statement of GDDI

The mission of the GDDI is to develop, disseminate, implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The GDDI is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix e-2: 2014–2015 GDDI Subcommittee members

The AAN has structured its subcommittee overseeing guideline development in several ways in recent years. The GDDI was first formed in 2014; it existed under a previous name and structure when this guideline project was inaugurated. At the time this guideline was approved to advance beyond subcommittee development, the subcommittee was constituted as below.

Cynthia Harden, MD (Chair); Steven R. Messé, MD (Co-Vice-Chair); Sonja Potrebic, MD, PhD (Co-Vice-Chair); Eric J. Ashman, MD; Richard L. Barbano, MD, PhD; Brian Callaghan, MD; Jane Chan, MD; Diane Donley, MD; Richard M. Dubinsky, MD, MPH; Terry Fife, MD; Jeffrey Fletcher, MD; Michael Haboubi, DO; John J. Halperin, MD; Yolanda Holler, MD; Andres M. Kanner, MD; Annette M. Langer-Gould, MD, PhD; Jason Lazarou, MD; Nicole Licking, DO; David Michelson, MD; Pushpa Narayanaswami, MBBS, DM; Maryam Oskoui, MD; Richard Popwell, Jr., MD; Tamara Pringsheim, MD; Alejandro A. Rabinstein, MD; Alexander Rae-Grant, MD; Anant Shenoy, MD; Kevin Sheth, MD; Kelly Sullivan, PhD; Theresa A. Zesiewicz, MD; Jonathan P. Hosey, MD (Ex-Officio); Stephen Ashwal, MD (Ex-Officio); Deborah Hirtz, MD (Ex-Officio); Jacqueline French, MD (AAN Guideline Historian)

Appendix e-3: Complete search strategy

For complete search strategy, access the PDF "Appendix e-3: Complete search strategy," available as an online data supplement to the complete article on the *Neurology* journal website at Neurology.org.

Appendix e-4: Classification of evidence for therapeutic studies

Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

The following are also required:

a. concealed allocation

b. primary outcome(s) clearly defined

c. exclusion/inclusion criteria clearly defined

d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias

e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:

1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.

2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment.(e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective).

3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.

4. The interpretation of the results of the study is based upon a per-protocol analysis that takes into account dropouts or crossovers.

Class II: A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV: Studies not meeting Class I, II, or III criteria, including consensus or expert opinion.

*Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Appendix e-5: Classification of recommendations

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

DISCLAIMER

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The American Academy of Neurology is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms

were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2004 AAN process manual.[e5]

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