Original Article

Mild therapeutic hypothermia in patients resuscitated from out-of-hospital cardiac arrest: A meta-analysis of randomized controlled trials

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ABSTRACT

Aims: Guidelines recommend mild therapeutic hypothermia (MTH) for survivors of out-of-hospital cardiac arrest (OHCA). However, there is little literature demonstrating a survival benefit. We performed a meta-analysis of randomized controlled trials (RCTs) assessing the efficacy of MTH in patients successfully resuscitated from OHCA. **Materials and Methods:** Electronic databases were searched for RCT involving MTH in survivors of OHCA, and the results were put through a meta-analysis. The primary endpoint was all-cause mortality, and the secondary endpoint was favorable neurological function. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed using the Mantel–Haenszel method. A fixed-effect model was used and, if heterogeneity (I^2) was >40, effects were analyzed using a random model. **Results:** Six RCT (n = 1400 patients) were included. Overall survival was 50.7%, and favorable neurological recovery was 45.5%. Pooled data demonstrated no significant all-cause mortality (OR, 0.81; 95% CI 0.55–1.21) or neurological recovery (OR, 0.77; 95% CI 0.47–1.24). No evidence of publication bias was observed. **Conclusion:** This meta-analysis demonstrated that MTH did not confer benefit on overall survival rate and neurological recovery in patients resuscitated from OHCA.

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Key words: Cardiac arrest; Meta-analysis; Therapeutic hypothermia

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a significant problem worldwide, with an estimated rate of 36–128/100,000 patients and a mortality rate of approximately 65–95%.[1] In the United States alone, approximately, 424,000 people utilize emergency medical service assessment for OHCA each year.[2] Most of these patients are at high risk for death and poor neurological function.[3]

In 2002, two landmark randomized controlled trials (RCTs) were published that demonstrated the efficacy of mild therapeutic hypothermia (MTH) in comatose survivors after OHCA by decreasing mortality and improving neurologic outcomes.[4,5] Since then, numerous studies, mostly meta-analyses and retrospectives

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reviews,[6-9] supported MTH. The 2015 American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care and the International Liaison Committee on Resuscitation (ILCOR) recommend using MTH. They propose a core temperature goal of 32–34°C for unconscious adult patients with return of spontaneous circulation (ROSC) after witnessed out-of-hospital ventricular fibrillation arrest (strong recommendation, low-quality evidence) and nonventricular fibrillation and in-hospital cardiac arrest (CA) (weak recommendation, very low-quality evidence), for at least 24 h (strong recommendation, moderate-quality evidence).[10] Despite these recommendations, some investigators argue that the evidence of the early randomized trials has revealed conflicting results, have low power and limited methodology; moreover, a recent publication by Nielsen *et al*.[11] challenged the role of MTH in OHCA, demonstrating that normothermia (36°C) results in similar outcomes to MTH. With this new information and the potentially unfavorable side effects reported with hypothermia,[12-15] further analyses are warranted assessing the efficacy of MTH therapy on post-CA mortality and neurological outcome. With this in mind, we conducted a systematic review of literature and subsequent meta-analysis investigating the efficacy of MTH.

MATERIALS AND METHODS

Search strategy

A computerized literature search of all publications in PubMed, CENTRAL, EMBASE, The Cochrane Central Register of Controlled Trials, the ClinicalTrials.gov website, and Google Scholar databases was performed. We also utilized manual searches of the article reference lists and conference proceedings. This was last assessed as up-to-date: June 30, 2015.

Search terms keywords included: Hypothermia, therapeutic hypothermia, mild hypothermia protocol, CA, heart arrest, OHCA, anoxic brain injury, cardiopulmonary resuscitation, RCTs. No language restrictions were enforced. Only human trials were included.

Inclusion criteria

The PRISMA statement for reporting systematic reviews and meta-analyses of RCTs was applied to the methods for this study.[16] Only human studies were included for analysis.

Included studies met the following specifications: (1) RCT design, (2) evaluation of patients with OHCA defined as any nonperfusing cardiac rhythm, including shockable rhythms (ventricular fibrillation or ventricular tachycardia) and nonshockable rhythms (pulseless electrical activity and asystole) occurring in a patient not already in or admitted to a hospital with age more than 18 years old, (3) patient who successfully had ROSC but comatose after CA, (4) studies which provided data on patients who received MTH on neurological outcome and mortality, (5) MTH at a targeted temperature between 32°C and 34°C either prehospital or hospital initiation (any method of cooling was accepted), and (6) control group intervention treated with standard intensive unit care or maintained patients normothermic[17] at a target temperature ≥36°C.

Exclusion criteria were patients who are (1) pregnant, (2) did not meet the above-mentioned criteria, (3) age <18 years or patients who were hypotensive and did not achieve ROSC, and (4) control group cooled with MTH at a targeted temperature between 32°C and 34°C.

Two reviewers (PV and DB) independently extracted data from identified RCTs. Disagreements were resolved by consensus or, if necessary, by a third party (MM-EE).

Study endpoints

The primary outcome was all all-cause mortality. We considered mortality to hospital discharge or longest follow-up postarrest. The secondary outcome was a favorable neurological function. Neurological function was evaluated according to cerebral performance category (CPC) where CPC 1 and 2 was defined as a good neurological outcome.[18] We also considered a favorable neurological function to hospital discharge or longest postarrest follow-up. If one of these validated metrics were not reported, reasonably defined favorable neurologic outcome by the individual study authors was accepted. If outcomes were reported at more than one follow-up period, we used data from the longest follow-up for each trial.

Statistical analysis

Data were summarized across treatment arms using the Mantel–Haenszel odds ratio (OR) fixed-effects model. We evaluated heterogeneity of effects using the Higgins I^2 statistic.[19] In cases of heterogeneity (defined as $I^2 > 40\%$), random effects models were used.[20] To address publication bias, we used four methods: Funnel plots,[21] Begg–Mazumdar test,[22] Egger test,[23] and the

Duval and Tweedie's test.[24] Sensitivity analyses were performed using the one-study-out method, addressing the influence of each study by testing whether deleting each individual would significantly change the pooled results of the meta-analysis on the final effect and its precision. Finally, chronological cumulative analyses were used to test if the effect size and precision shifts based on the technical advancement of MHT seen over time.[19] The statistical analysis was performed by the Comprehensive Meta-Analysis version 2.0 software (Biostat, Inc., New Jersey, USA).

Individual study quality appraisal

Two authors (PV, MM) independently assessed the risk of bias of included trials using standard criteria defined in the Cochrane Handbook for Systematic Reviews of Interventions.[25] This validated instrument for appraising randomized trials measures risk of bias in seven categories: (1) Adequate random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other bias. Each trial is described as having a high, low, or unclear risk of bias in each of the seven domains. Discrepancies were resolved by discussion or adjudication by a third author (DB).

RESULTS

Study selection and characteristics

The flow diagram of study identification through the review is shown in Figure 1. The search strategy identified a total of 2352 potential articles. After removing duplicates and articles not meeting inclusion criteria, we screened 266 titles and abstracts. Of these, 14 were selected for further review of eligibility. Finally, 6 RCTs satisfied inclusion criteria, all of which were published in English.[4,5,11,26-28]

Baseline characteristics are presented in Table 1. Overall, the 6 RCTs enrolled a total of 1400 patients who were successfully resuscitated from OHCA. Numerous cooling methods were used in these included studies, including surface and invasive cooling. In all the studies, the target temperature of cooling range was between 32°C and 34°C, with a duration time of 12–24 h. Duration of follow-up ranged from hospital discharge up to 6 months.

Quantitative data synthesis

Endpoints

There were a total of 710 deaths reported in all patients

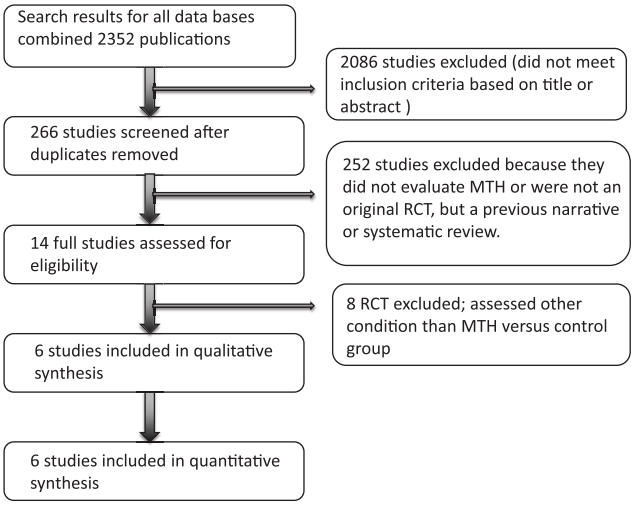

Figure 1: Search Strategy and Study Selection. RCT = Randomized Controlled Trial MTH = Mild therapeutic hypothermia

that suffered OHCA: 49.7% (352/710) in MTH group and 51.9% (358/690) in the control group. There was no significant difference in all-cause mortality between the two groups (OR, 0.81; 95% confidence interval (CI) 0.55–1.21) [Figure 2].

Among patients with OHCA, 633 had an overall favorable neurological outcome after OHCA. As indicated in Figure 3, using a random model, no significant difference was observed in favorable neurological outcome in patients who received MTH 46.9% (331/705 patients) versus control 44.1% (302/687 patients) (OR, 0.77; 95% CI 0.47–1.24).

Sensitivity analysis

Sensitivity analysis involving the removal of each of the RCT's one at a time did not demonstrate difference or any changes in the overall outcomes, even when the Nielsen *et al*.[11] trial was removed; all-cause mortality (OR, 0.68; 95% CI 0.41–1.14) and favorable neurological outcome (OR, 0.64; 95% CI 0.36–1.17) [Figure 1 in the Supplemental Material].

Cumulative analysis

Chronological cumulative analysis for each outcome did not find any significant change in the final effect outcomes; however, when the analysis was performed addressing all-cause mortality and favorable neurological outcomes, we observed transient changes in the final effect favoring the hypothermia group when the Bernard *et al*.[4] study was included. Subsequent accumulated analysis did not experience changes in the

Table 1: Baseline characteristics of trials

Study name	Total number of patients (*n*)	Event place	Intervention place	Rhythm	Intervention		Selection criteria		Follow up duration for primary and secondary endpoints	Outcomes			
					Experimental group	Control group	Inclusion criteria	Exclusion criteria		All Case Mortality *n*=t total number of deaths		Favorable Neurological outcomes	
										Intervention	Control	Intervention	Control
Hachimi-Idrissi *et al.*[26]	30	Out of hospital	In hospital	Asystole or PEA	Helmet device to achieve a target temperature of 34ºC. When temperature of 34°C achieved or 4ºh hours after initiation elapsed then passive rewarming for 8 hours	IV acetaminophen for temperature >38C, otherwise standard ICU care	>18 years, temp >30°C, GCS <7	Pregnancy, coagulopathy, other causes of coma (drugs, etc.), cardiogenic shock (MAP <60), GCS ≥7	14 days	13	13	2	0
Holzer *et al.*[5]	275	Out of hospital	In hospital	VF, VT	Air Cooling to a target temperature of 32°C to 34°C with the use of an external cooling device, and ice packs for 24 hours then passive rewarming for 8 hrs	No intervention for Temperature control, Standard ICU protocol care	Witnessed OHCA of cardiac origin, age 18-75 years, 5-15 minutes from collapse to CPR and, <60 minutes to ROSC	Temp <30°C, coma because of drugs before CA, pregnancy, response to verbal command, MAP <60 for >30 minutes, hypoxemia >15 minutes, terminal illness, factors making follow-up unlikely, coagulopathy, other study, CA after arrival of medical personnel	6 months	56	76	75	54
Bernard *et al.*[4]	77	Out of hospital	Pre hospital	VF	Ice packs, target temperature 33ºC for 12 hours then active rewarming for 6 hrs	No intervention for Temperature control, Standard ICU protocol care	Persistent coma after ROSC	Age <18 years for men <50 years for women, cardiogenic shock, other causes of coma than CA (drugs, etc.), no available ICU bed	Till hospital discharge	22	23	21	9

Contd...

Table 1: Contd...

Study name	Total number of patients (*n*)	Event place	Intervention place	Rhythm	Intervention		Selection criteria		Follow up duration for primary and secondary endpoints	Outcomes			
					Experimental group	Control group	Inclusion criteria	Exclusion criteria		All Case Mortality *n*=t total number of deaths		Favorable Neurological outcomes	
										Intervention	Control	Intervention	Control
Laurent *et al.*[28]	42	Out of hospital	In hospital	VF or asystole	CVVH for 8 h to target temp of 32-33C then external cooling to maintain temp for 16 hours then passive rewarming (rewarming duration not mentioned)	CVVH for 8 h to maintain temp of 37 thereafter no further temp control	Age 18-75 years, <10 min to start of CPR,<50 min to ROSC	Response to verbal command after ROSC, pregnancy, presence of terminal illness before CA	6 months	15	11	7	9
Kamarainen *et al.*[27]	37	Out of hospital	Pre hospital	VF, PEA, asystole	IV fluid (ringer lactate), to achieve a target temperature of 33ºC, then discontinuing, or at Physician disclosure, no mention on rewarming time	No intervention for Temperature control, Standard ICU protocol care	OHCA in >18 year old regardless of initial rhythm. GSC <=5 for >9 min after ROSC	Pregnancy, other causes of coma (drugs, etc.), cardiogenic shock SBP <100mmhg despite intervention	Till hospital discharge	11	10	8	8
Nielsen *et al.*[11]	939	Out of hospital	In hospital	VF, PEA, asystole	Ice packs, IV fluids, to target temperature of 33ºC for 28hrs then rewarming for 8 hours (hourly increment of 0.5 ºC)	Ice packs, IV fluids, to target temperature of 36C for 28hrs then rewarming for 1 hours (hourly increment of 0.5 C)	OHCA in >18 year old regardless of initial rhythm. GSC <8 for >20 min after ROSC	Temperature <30 C, Known or suspected acute stroke or intracranial hemorrhage, interval from ROSC to patient screening >240 min, and witnessed arrest with asystole as initial rhythm	6 months	235	225	218	222

CA: Cardiac arrest, C: Celsius, CCVH: Continuous veno venous filtration, CPR: Cardiopulmonary resuscitation, GSC: Glasgow comma scale, ICU: Intensive care unit, IV: Intra venous, MAP: Mean arterial pressure, OHCA: Out of hospital cardiac arrest, PEA: Pulseless electrical activity, ROSC: Return to spontaneous circulation, SBP: Systolic blood pressure, VF: Ventricular fibrillation, VT: Ventricular tachycardia

overall effect when the last two RCTs were added[11,27] [Figure 2 in the Supplemental Material].

Bias

Funnel plot did not show asymmetry suggesting bias for all-cause mortality outcomes except for favorable neurological outcomes [Figure 4]. However, after quantifying the observed bias with other methods (Begg–Mazumdar, Egger and Duval, and Tweedie's trim and fill test), no evidence of publication bias was observed [Figure 3 in the Supplemental Material]. The individual study quality appraisal and the risk of bias for the 6 included RCTs are summarized in Table 2.

DISCUSSION

This meta-analysis provides a comprehensive update of RCTs assessing the effect of mild MTH on patients successfully resuscitated post-OHCA. To our knowledge, this comprises the largest sample in the literature assessing the role of MTH in patients post-OHCA at the time of submission. This includes two trials not previously cited in meta-analysis,[29,30] including the latest trial published by Nielsen *et al*.[11] Our meta-analysis did not find a benefit of MTH on mortality or neurological outcome as reported in earlier analyses.[4-6,29,30] These results not only correlate with the finding in the strongest powered study to date,[11] but also correlate with "real world" observational studies[31,32] following OHCA showing similar poor outcomes,[33] and with multicenter trials in children were the evidence of MTH effect was not substantially different from adults,[34] regardless of the presenting rhythm.

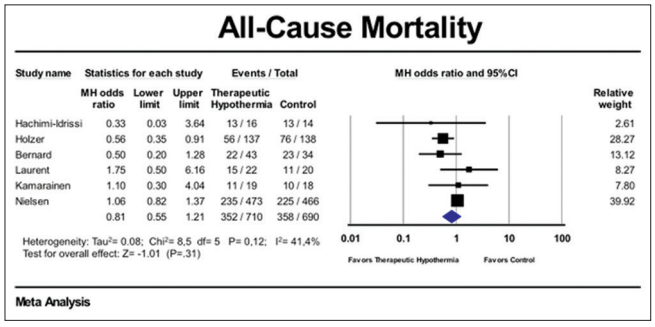

Figure 2: All-cause mortality. Comparison of all-cause mortality outcome between patients treated with MTH and the control group using a random model. Heterogeneity (I^2) = 41.4%. CI = Confidence interval; MH = Mantel-Haenszel; MTH = Mild therapeutic hypothermia

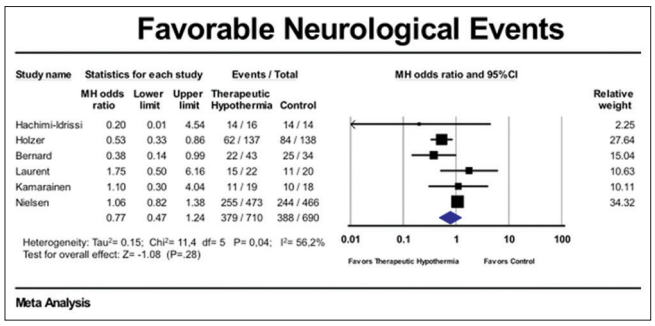

Figure 3: Favorable neurological outcomes. Comparison of favorable neurological outcome between patients treated with MTH and the control group using a random model. Heterogeneity (I^2) = 56.2%. CI = Confidence interval; MH = Mantel-Haenszel; MTH = Mild therapeutic hypothermia

We believe that the outcome differences in our analysis compared to some earlier trials by Holzer[5] and Bernard *et al*.[4] are a reflection not only of tight temperature control but also close monitoring and optimization of other parameters over the past 15 years. This includes, but is not limited to, improved patient monitoring of hemodynamics and metabolic control. In addition, advancements in circulatory support and early coronary interventions may have had an effect on the reported outcome, resulting in improved survival.[35] Early referral of postarrest patients to tertiary care centers was a vital contributor to improved outcomes, virtually doubling the likelihood that patient will survive to discharge.[36]

Along with the initial published RCTs and observational data,[37] current guidelines have influenced many centers to adopt a mandatory protocol utilizing MTH in patients presenting with OHCA.[37,38] MTH should be done with the awareness of all the physiological changes in the circulatory and metabolic systems causes by hypothermia.[39] Potential complications and side effects reported with MTH include but are not limited to coagulopathies, increased rates of infections, cardiovascular complications, hyperglycemia, and electrolyte disorders.[12-15,40-42] The financial burden of MTH is not to be overlooked. A cost-effectiveness analysis of MTH after OHCA showed that patients treated with MTH had an incremental cost of $31,254 compared to those treated conventionally.[43] While neurological recovery or survival cannot be predicted among survivors of CA, it is important to consider the additional cost of this intervention.

Many factors are tentative contributors to the potential improvement of CA patients, and the role for MTH should be further investigated. Review of the literature suggests a potential role for simply avoiding hyperthermia and specific means of cooling survivors of OHCA. As described by Zeiner *et al*.,[44] patients with hyperpyrexia after CA have worse neurologic outcomes that increase

for each degree Celsius higher, with an OR of 2.26. In this same study, patients with favorable neurologic recovery showed a higher lowest temperature and a lower highest temperature during the first 48 h after the restoration of spontaneous circulation. The majority of patients in the control groups included in our analysis were not treated actively for fever to keep them normothermic, allowing natural temperature course. This raises the possibility that the effect seen in early RCTs favoring MTH is due to an increased temperature in the control group. Nielsen *et al*.[11] attempted to answer this question comparing MTH with the control group temperature close to normothermia and found no significant differences between the two groups. These findings could be a key point to address future management of OHCA patients. Perhaps avoidance of fever, rather than hypothermia, is actually the most important element of temperature management after CA. Even Bernard *et al*., the author of one of the early trials that favored MHT,[4] has changed his own institution guidelines to a target temperature of 36°.[45] In addition to the limited therapeutic resources to mitigate the postanoxic injury in OHCA, arguments against changes on the target temperature set for MTH (32–34°C) are the lack of differences of adverse events seen with MTH compared to normothermia, and that there might be subgroups of patients, based on the severity of neurologic injury that may require more individualized degrees of hypothermia to achieve the best outcome. Two RCTs are currently recruiting patients to evaluated differences in target temperature; The Centre Hospitalier Departemental Vendee is randomizing patient with OHCA to a targeted temperature between 32.5°C and 33.5°C and the control group between 36.5°C and 37.5°C testing the potential improvement of neurological outcome with these two target temperatures. The other group from the University of Ottawa Heart Institute is being even more aggressive and is determining whether neurologic outcomes at 6 months are improved with moderate (31°C) versus mild (34°C) therapeutic hypothermia following ROSC in patients suffering OHCA.[46]

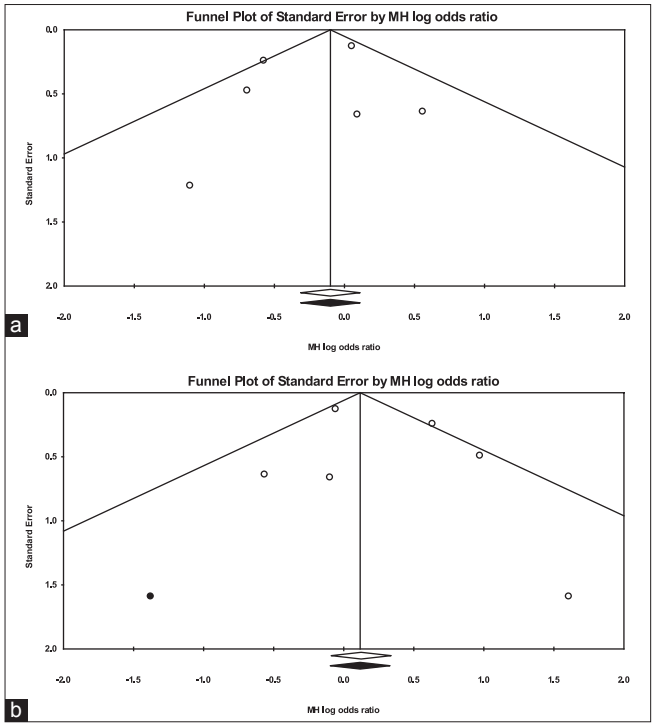

Figure 4: Funnel plots for each individual outcome: (a) All-cause mortality; table (b) favorable neurological outcomes. Randomized controlled trials are shown as open circles and the observed summary point estimate in log units is shown as an open diamond. The imputed studies are shown as a filled circle, and the imputed point estimate in log units is shown as a filled diamond, No imputed studies were seen for overall mortality. Two imputed studies were seen for favorable neurological outcomes. Under the random effect model the point estimate and 95% confidence interval for the combined studies is 0.78 (0.73, 0.83). Using trim and fill, the imputed point estimate is 0.77 (0.72, 0.82)

Other key point is the duration of MHT; the RCTs included in this meta-analysis utilized different durations of targeted temperature management after OHCA ranging from 12 to 28 h. There are no data that can be used to compare different durations of targeted temperature; however, we know that regardless of the target temperature chosen, temperature in postarrest patients should be tightly controlled and monitored. This important point was recognized in the new guidelines that updated the cooling time duration

Table 2: Risk of bias across individual randomized control trials

Study name	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Baseline	Source of funding bias	Academic bias
Holzer *et al*.[5]	Low	Low	Uncertain	Low	Low	High	Low	Low
Bernard *et al*.[4]	High	High	Low	High	Low	High	Low	Low
Hachimi-Idrissi *et al*.[26]	Uncertain	Uncertain	Uncertain	Low	Low	Uncertain	Low	Low
Kamarainen *et al*.[28]	Low	Low	Uncertain	Low	Low	Low	Low	Low
Nielsen *et al*.[12]	High	High	Low	High	Low	High	Low	Low
Laurent *et al*.[29]	Low	Low	Uncertain	Uncertain	Low	Uncertain	Low	Low

from 12 to 24 h to at least 24 h.[10] The TTH48 trial was recently completed and is examined prolonged MTH (32–34°C) in 24 versus 48 h with the primary outcome CPC after 6 months in OHCA patients.[47] Hopefully, we will have more answer on what is the optimal duration of MHT.

Though the new surface and endovascular (invasive) cooling methods are the most commonly used methods to both induce and maintain hypothermia. Optimal means of cooling have not yet been determined, but both randomized and observational studies suggest that endovascular cooling maintains target temperatures better than conventional surface cooling. Endovascular cooling also has less temperature fluctuation and has fewer complications associated with it than surface cooling.[48,49] Current guidelines do not specify which method to use but this may be a valuable consideration.

It has been discussed that a delay of several hours from resuscitation until the target temperature had been reached can impact neurologic outcomes. Some of the trials included in our meta-analysis started prehospital cooling as compared to hospital cooling, postulating earlier cooling results would improve neurologic recovery. This hypothesis was tested in the Hypothermia Network Registry[50] and some RCTs with adult patients after OHCA.[51,52] No differences in outcomes were observed. In fact, the intervention group was more likely to have re-arrest in the field.[52,53] The new hypothermia guidelines recommend against prehospital cooling with rapid infusion of large volumes of cold intravenous fluid (strong recommendation, moderate-quality evidence).[10]

We are not suggesting intensivists abandon temperature management after CA; however, the questions that remain are whether we should cool our postarrest patients to 36°C or continue with the old target temperatures. Regardless of the target temperature chosen, the temperature in postarrest patients should be tightly controlled and monitored. While 36°C may be a sufficient temperature goal, with no temperature control, many postarrest patients may become febrile with detrimental effects on mortality and neurologic function.

The benefit of MTH after in-patient CA has not been tested in RCTs. However, retrospective studies have shown no difference in neurological outcome at discharge among patients treated with MTH compared to control group.[54] The largest published cohort of patient included 8316 patients with complete data, of whom 214 (2.6%) had hypothermia induced, and 2521 (30%) survived to discharge. Only 40% were documented as achieving a temperature between 32°C and 34°C. Induced hypothermia was not associated with favorable neurological outcomes or improved survival. The lack of benefit in this population may reflect lack of effect, inefficient application of the intervention.[55] The new ILCOR and AHA, we suggest targeted temperature management as opposed to no targeted temperature management for adults with in-hospital CA (weak recommendation, very low-quality evidence) with any initial rhythm who remain unresponsive after ROSC.

In the perioperative setting, there are no specific guidelines to guide post-CA treatment. CA occurs in 0.7–2.9% of cardiac surgical patients.[56,57] The uncommon event of patient requiring MTH needing cardiac surgery can pose significant challenges to the perioperative physician. In terms of anesthetic management, the key goals relate to maintenance of normal hemodynamics (preservation of the myocardial oxygen demand/supply balance, judicious fluid management guided by appropriate intravascular monitoring and transesophageal echocardiographic and satisfactory pain management. Temperature management in the operating room and Intensive Care Unit can be difficult owing to the multiple factors that affect core body temperature in the perioperative period. To date, there is little specific data reporting safety or efficacy of TH in cardiac surgery patients who experience unintentional CA. Only a few published case series experience have been reported with a safe and successful use of MTH after unintentional perioperative CA in 3 cardiac surgery patients. The target temperature range between 32°C and 34°C and was maintained through the use of intermittent fanning for a period of 24 h, followed by passive rewarming.[54] High-quality controlled studies are required to better characterize the effect of induced hypothermia in this population.

LIMITATIONS

This systematic review and meta-analysis have several important limitations that should be acknowledged. First, this is a meta-analysis performed on study-level data. Second, the studies included in the meta-analysis enrolled heterogeneous populations and were characterized by different study protocols and defined endpoints differently. Third, none of the studies were

blinded for the intervention assignments, though some of the latest trials tried to decrease the bias by blinding statisticians. Fourth, there were differences in the target temperature for control groups; the results of our review come from mixed-up analyses that did not separate each hypothermic temperature level between 32°C and 34°C and for most studies included, it stated merely the body temperature level of hypothermia as 32–34°C. Finally, several of the trials we analyzed had premature patient withdrawal that may affect overall neurologic recovery. Most of the trials did not specify whether the decision on withdrawal of intensive care was made and if the assessor of the prognostication was blinded, except for the Nielsen *et al*.[11] trial that had a strict protocol for neurologic prognostication and withdrawal of life-sustaining therapies. Short-term follow-up may be troublesome since the neurological status for survivors can evolve over the first 6 months after the arrest.[58] All these limitations may explain some of the observed heterogeneity of the end points.

Interestingly, considering that none of the included studies were blinded for the intervention assignments, the open nature of the studies might, in theory, slightly favor the MTH intervention group.[59] This, and the consistency of the magnitude, direction, and the stability of summary effects after the sensitivity and cumulative analyses, further supports the results of this meta-analysis, but results should be interpreted cautiously.

CONCLUSIONS

The results of our meta-analysis did not confer benefit of MTH on overall survival rate or neurological recovery in survivors of OHCA. Overall survival rate and neurological recovery are very limited in these patients. Further studies are needed to determine the optimal temperature level of hypothermia therapy.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Smith TW, Cain ME. Sudden cardiac death: Epidemiologic and financial worldwide perspective. J Interv Card Electrophysiol 2006;17:199-203.
2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, *et al.* Heart disease and stroke statistics-2014 update: A report from the American Heart Association. Circulation 2014;129:e28-292.
3. Moulaert VR, Verbunt JA, van Heugten CM, Wade DT. Cognitive impairments in survivors of out-of-hospital cardiac arrest: A systematic review. Resuscitation 2009;80:297-305.
4. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, *et al.* Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557-63.
5. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549-56.
6. Arrich J, Holzer M, Havel C, Müllner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. Cochrane Database Syst Rev 2012;9:CD004128.
7. Busch M, Soreide E, Lossius HM, Lexow K, Dickstein K. Rapid implementation of therapeutic hypothermia in comatose out-of-hospital cardiac arrest survivors. Acta Anaesthesiol Scand 2006;50:1277-83.
8. Oddo M, Schaller MD, Feihl F, Ribordy V, Liaudet L. From evidence to clinical practice: Effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. Crit Care Med 2006;34:1865-73.
9. Soga T, Nagao K, Sawano H, Yokoyama H, Tahara Y, Hase M, *et al.* Neurological benefit of therapeutic hypothermia following return of spontaneous circulation for out-of-hospital non-shockable cardiac arrest. Circ J 2012;76:2579-85.
10. Donnino MW, Andersen LW, Berg KM, Reynolds JC, Nolan JP, Morley PT, *et al.* Temperature management after cardiac arrest: An advisory statement by the advanced life support task force of the international liaison committee on resuscitation and the american heart association emergency cardiovascular care committee and the council on cardiopulmonary, critical care, perioperative and resuscitation. Circulation 2015. pii: 10.1161/CIR.0000000000000313.
11. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, *et al.* Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013;369:2197-206.
12. Fischer UM, Cox CS Jr., Laine GA, Mehlhorn U, Allen SJ. Mild hypothermia impairs left ventricular diastolic but not systolic function. J Invest Surg 2005;18:291-6.
13. Geurts M, Macleod MR, Kollmar R, Kremer PH, van der Worp HB. Therapeutic hypothermia and the risk of infection: A systematic review and meta-analysis. Crit Care Med 2014;42:231-42.
14. Polderman KH, Peerdeman SM, Girbes AR. Hypophosphatemia and hypomagnesemia induced by cooling in patients with severe head injury. J Neurosurg 2001;94:697-705.
15. Watts DD, Trask A, Soeken K, Perdue P, Dols S, Kaufmann C. Hypothermic coagulopathy in trauma: Effect of varying levels of hypothermia on enzyme speed, platelet function, and fibrinolytic activity. J Trauma 1998;44:846-54.
16. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, *et al.* The PRISMA statement for reporting

systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. Ann Intern Med 2009;151:W65-94.
17. Mackowiak PA, Wasserman SS, Levine MM. A critical appraisal of 98.6 degrees F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich. JAMA 1992;268:1578-80.
18. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1:480-4.
19. Kapadia SR, Leon MB, Makkar RR, Tuzcu EM, Svensson LG, Kodali S, *et al*. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): A randomised controlled trial. Lancet 2015;385:2485-91.
20. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: An update. Contemp Clin Trials 2007;28:105-14.
21. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, *et al*. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.
22. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088-101.
23. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
24. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455-63.
25. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
26. Hachimi-Idrissi S, Corne L, Ebinger G, Michotte Y, Huyghens L. Mild hypothermia induced by a helmet device: A clinical feasibility study. Resuscitation 2001;51:275-81.
27. Kämäräinen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Prehospital therapeutic hypothermia for comatose survivors of cardiac arrest: A randomized controlled trial. Acta Anaesthesiol Scand 2009;53:900-7.
28. Laurent I, Adrie C, Vinsonneau C, Cariou A, Chiche JD, Ohanessian A, *et al*. High-volume hemofiltration after out-of-hospital cardiac arrest: A randomized study. J Am Coll Cardiol 2005;46:432-7.
29. Cheung KW, Green RS, Magee KD. Systematic review of randomized controlled trials of therapeutic hypothermia as a neuroprotectant in post cardiac arrest patients. CJEM 2006;8:329-37.
30. Wang XP, Lin QM, Zhao S, Lin SR, Chen F. Therapeutic benefits of mild hypothermia in patients successfully resuscitated from cardiac arrest: A meta-analysis. World J Emerg Med 2013;4:260-5.
31. Herlitz J, Engdahl J, Svensson L, Young M, Angquist KA, Holmberg S. Can we define patients with no chance of survival after out-of-hospital cardiac arrest? Heart 2004;90:1114-8.
32. Kuisma M, Jaara K. Unwitnessed out-of-hospital cardiac arrest: Is resuscitation worthwhile? Ann Emerg Med 1997;30:69-75.
33. Hunter BR, O'Donnell DP, Allgood KL, Seupaul RA. No benefit to prehospital initiation of therapeutic hypothermia in out-of-hospital cardiac arrest: A systematic review and meta-analysis. Acad Emerg Med 2014;21:355-64.
34. Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, *et al*. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. N Engl J Med 2015;372:1898-908.
35. Sunde K, Pytte M, Jacobsen D, Mangschau A, Jensen LP, Smedsrud C, *et al*. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation 2007;73:29-39.
36. Søholm H, Kjaergaard J, Bro-Jeppesen J, Hartvig-Thomsen J, Lippert F, Køber L, *et al*. Prognostic implications of level-of-care at tertiary heart centers compared with other hospitals after resuscitation from out-of-hospital cardiac arrest. Circ Cardiovasc Qual Outcomes 2015;8:268-76.
37. Jena AB, Romley JA, Newton-Cheh C, Noseworthy P. Therapeutic hypothermia for cardiac arrest: Real-world utilization trends and hospital mortality. J Hosp Med 2012;7:684-9.
38. Wolfrum S, Radke PW, Pischon T, Willich SN, Schunkert H, Kurowski V. Mild therapeutic hypothermia after cardiac arrest – A nationwide survey on the implementation of the ILCOR guidelines in German intensive care units. Resuscitation 2007;72:207-13.
39. MacLaren R, Gallagher J, Shin J, Varnado S, Nguyen L. Assessment of adverse events and predictors of neurological recovery after therapeutic hypothermia. Ann Pharmacother 2014;48:17-25.
40. Mirzoyev SA, McLeod CJ, Bunch TJ, Bell MR, White RD. Hypokalemia during the cooling phase of therapeutic hypothermia and its impact on arrhythmogenesis. Resuscitation 2010;81:1632-6.
41. Rohrer MJ, Natale AM. Effect of hypothermia on the coagulation cascade. Crit Care Med 1992;20:1402-5.
42. Shiozaki T, Hayakata T, Taneda M, Nakajima Y, Hashiguchi N, Fujimi S, *et al*. A multicenter prospective randomized controlled trial of the efficacy of mild hypothermia for severely head injured patients with low intracranial pressure. Mild Hypothermia Study Group in Japan. J Neurosurg 2001;94:50-4.
43. Merchant RM, Becker LB, Abella BS, Asch DA, Groeneveld PW. Cost-effectiveness of therapeutic hypothermia after cardiac arrest. Circ Cardiovasc Qual Outcomes 2009;2:421-8.
44. Zeiner A, Holzer M, Sterz F, Schörkhuber W, Eisenburger P, Havel C, *et al*. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Arch Intern Med 2001;161:2007-12.
45. Bernard S. Inducing hypothermia after out of hospital cardiac arrest. BMJ 2014;348:g2735.
46. Corporation OHIR. Mild Versus Moderate Therapeutic Hypothermia in Out-of-hospital Cardiac Arrest Patients (CAPITALCHILL). In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US); 2000. Available from: http://www.clinicaltrials.gov/show/NCT02011568NLMIdentifier: NCT02011568. [Last cited on 2015 Nov 25].
47. Aarhus Uo. The Cardiac Effects of Prolonged Hypothermia After Cardiac Arrest. In: ClinicalTrials.gov. Bethesda

(MD): National Library of Medicine (US); 2000. Available from: http://www.clinicaltrials.gov/show/NCT02066753NLMIdentifier: NCT02066753. [Last cited on 2015 Nov 25].
48. Deye N, Cariou A, Girardie P, Pichon N, Megarbane B, Midez P, *et al.* Endovascular versus external targeted temperature management for patients with out-of-hospital cardiac arrest: A randomized, controlled study. Circulation 2015;132:182-93.
49. Gillies MA, Pratt R, Whiteley C, Borg J, Beale RJ, Tibby SM. Therapeutic hypothermia after cardiac arrest: A retrospective comparison of surface and endovascular cooling techniques. Resuscitation 2010;81:1117-22.
50. Nielsen N, Hovdenes J, Nilsson F, Rubertsson S, Stammet P, Sunde K, *et al.* Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. Acta Anaesthesiol Scand 2009;53:926-34.
51. Bernard SA, Smith K, Cameron P, Masci K, Taylor DM, Cooper DJ, *et al.* Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: A randomized controlled trial. Circulation 2010;122:737-42.
52. Kim F, Nichol G, Maynard C, Hallstrom A, Kudenchuk PJ, Rea T, *et al.* Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: A randomized clinical trial. JAMA 2014;311:45-52.
53. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, *et al.* Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359-67.
54. Kory P, Fukunaga M, Mathew JP, Singh B, Szainwald L, Mosak J, *et al.* Outcomes of mild therapeutic hypothermia after in-hospital cardiac arrest. Neurocrit Care 2012;16:406-12.
55. Nichol G, Huszti E, Kim F, Fly D, Parnia S, Donnino M, *et al.* Does induction of hypothermia improve outcomes after in-hospital cardiac arrest? Resuscitation 2013;84:620-5.
56. Anthi A, Tzelepis GE, Alivizatos P, Michalis A, Palatianos GM, Geroulanos S. Unexpected cardiac arrest after cardiac surgery: Incidence, predisposing causes, and outcome of open chest cardiopulmonary resuscitation. Chest 1998;113:15-9.
57. el-Banayosy A, Brehm C, Kizner L, Hartmann D, Körtke H, Körner MM, *et al.* Cardiopulmonary resuscitation after cardiac surgery: A two-year study. J Cardiothorac Vasc Anesth 1998;12:390-2.
58. Arrich J, Zeiner A, Sterz F, Janata A, Uray T, Richling N, *et al.* Factors associated with a change in functional outcome between one month and six months after cardiac arrest: A retrospective cohort study. Resuscitation 2009;80:876-80.
59. Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, *et al.* Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: Meta-epidemiological study. BMJ 2008;336:601-5.