CLINICAL RESEARCH STUDY

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Use of Targeted Temperature Management After Out-of-hospital Cardiac Arrest: A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

BACKGROUND: Individual randomized trials have yielded variable results regarding the benefits of targeted temperature management in patients encountering out-of-hospital cardiac arrest. This study aimed to systemically determine if targeted temperature management initiated after an out-of-hospital cardiac arrest was associated with improved outcomes.

METHODS: Electronic databases were searched for published randomized trials that compared targeted temperature management (core body temperature 32-34°C) vs control (core body temperature ≥36°C) after an out-of-hospital cardiac arrest. The main outcomes assessed were all-cause mortality and poor neurological outcome.

RESULTS: Six trials with 1391 patients were included in the analysis. Compared with the control group, targeted temperature management was associated with a nonsignificant reduction in all-cause mortality (relative risk [RR] 0.90; 95% confidence interval [CI], 0.77-1.04; $P = .15$, $I^2 = 34\%$), which was similar among those with a shockable rhythm (RR 0.89; 95% CI, 0.74-1.08, $P = .25$, $I^2 = 46\%$). All-cause mortality was significantly reduced with targeted temperature management after exclusion of one trial that allowed for mild hypothermia in the control arm (RR 0.83; 95% CI, 0.71-0.96; $P = .01$, $I^2 = 0\%$). There was a nonsignificant reduction in poor neurological outcome with targeted temperature management compared with control (RR 0.87; 95% CI, 0.74-1.03, $P = .10$, $I^2 = 54\%$), which was similar among those with a shockable rhythm (RR 0.87; 95% CI, 0.70-1.07, $P = .19$, $I^2 = 63\%$). Poor neurological outcome was significantly reduced with targeted temperature management after exclusion of one trial that allowed for mild hypothermia in the control arm (RR 0.82; 95% CI, 0.70-0.95; $P = .01$, $I^2 = 19\%$).

CONCLUSION: Targeted temperature management initiated after successful resuscitation in patients who encountered an out-of-hospital cardiac arrest was associated with a nonsignificant reduction in mortality and poor neurological outcome. Lack of benefit was strongly influenced by inclusion of one study that used mild hypothermia in the control arm. These results indicate that only mild hypothermia may be needed to improve outcomes among patients presenting with an out-of-hospital cardiac arrest.

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KEYWORDS: Cardiac arrest; Cardiopulmonary resuscitation; Hypothermia; Meta-analysis; Mortality

Out-of-hospital cardiac arrest is a relevant cause of death worldwide.[1,2] According to the American Heart Disease and Stroke statistics, the survival to hospital discharge following cardiac arrest due to any cause is as low as 10%.[3] Furthermore, only a minority of these patients are discharged from the hospital with a good neurological outcome.[1,4] In animal models, targeted temperature management has been shown to improve myocardial and cerebral function as well as overall survival.[5]

Earlier randomized trials demonstrated that targeted temperature management (core body temperature of 32-34°C)

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improved survival and neurological outcomes.[6,7] The American Heart Association guidelines recommend targeted temperature management for patients resuscitated after cardiac arrest with impaired consciousness,[8] mainly based on the results of these 2 trials.[6,7] However, in one of these trials,[6] some of the patients in the control arm had developed relative hyperthermia, which is associated with worse prognosis.[9] More recently, a randomized trial comparing targeted core temperature of 33°C vs 36°C showed that there was no significant difference in outcomes between treatment strategies.[10] We aimed to conduct a comprehensive meta-analysis to evaluate the outcomes associated with targeted temperature management compared with control (core body temperature ≥36°C) in patients who were successfully resuscitated after encountering an out-of-hospital sudden cardiac arrest.

CLINICAL SIGNIFICANCE

- Society guidelines endorse targeted temperature management for the management of patients who survive out-of-hospital cardiac arrest.
- This meta-analysis demonstrated that targeted temperature management was associated with nonsignificant reduction in mortality and poor neurological outcome.
- The lack of benefit was strongly influenced by inclusion of one study that used mild hypothermia in the control arm. These results indicate that only mild hypothermia may be needed to improve outcomes among these patients.

METHODS

Data Sources

A computerized search of the Medline, Web of Science, and Cochrane databases was performed without language restriction from inception until June 2015 using the keywords and Medical Subject Heading shown in **Supplementary Figure 1**, available online. The reference lists of the retrieved articles and prior meta-analyses were reviewed.

Selection Criteria and Data Extraction

Eligible studies were published clinical trials reporting clinical outcomes and randomized adult patients (≥18 years) who encountered an out-of-hospital cardiac arrest and remained with impaired consciousness, to either targeted temperature management (core body temperature 32-34°C) or control. The control arm was defined as patients who did not receive targeted temperature management or received mild targeted temperature management (core temperature ≥36°C). Studies in which the control group received targeted temperature management <36°C were excluded.[11-14] Studies with duplicate patient population were also excluded. One manuscript[15] included 2 study cohorts; one of those was a duplicate of another older study[16] by the same authors and thus was excluded. The quality of the included studies was evaluated based on the adequate description of treatment allocation, blinded outcome assessment, and description of losses to follow-up.

Two independent authors (AM and IYE) extracted data on the study design, sample size, intervention strategies, outcomes, and other study characteristics from the included studies. Discrepancies were resolved by consensus of the authors. The number of events that occurred in each arm of each trial was tabulated for each outcome.

Outcomes and Definitions

The outcomes assessed in this analysis included all-cause mortality and poor neurological outcome, as defined by each study. Most of the included studies used the Pittsburgh cerebral performance category definition of neurological outcome, which is a 5-category scale: category 1 or 2 (good or moderate disability), category 3 (severe disability), and category 4 or 5 (vegetative state or brain death).[17] A poor neurological outcome was defined as cerebral performance category 3-5. Outcomes were reported at 6 months whenever feasible.

Statistical Analysis

All outcomes were analyzed by an intention-to-treat analysis. Summary estimates were primarily constructed using a DerSimonian and Laird random-effects risk ratio (RR) model.[18] Fixed-effects RR were also performed using a Mantel-Haenszel model.[19] Statistical heterogeneity was examined using the I^2 statistic where values <25% and >50% were considered as low and high degree of heterogeneity.[20] This analysis was conducted in concordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.[21] All *P*-values were 2-tailed, with statistical significance set at 0.05, and confidence intervals (CIs) were computed at the 95% level. All analyses were implemented using the Comprehensive Meta-analysis software version 3 (Biostat, Englewood, NJ).

One sub-group analysis was performed for trials in which the majority of patients presented with ventricular fibrillation/pulseless ventricular tachycardia (ie, "shockable rhythms") at time of arrest. Another sub-group analysis was performed by excluding trials that utilized noncontemporary modalities of cooling techniques (ie, cooling helmets and hemofiltration). A sensitivity analysis was performed by excluding the trials that allowed for mild hypothermia in the control arm. Random-effects meta-regression analyses were conducted using the methods of moments approach and Knapp-Hartung method for the main outcomes with prespecified