Targeted Temperature Management in Unconscious Survivors of Postcardiac Arrest: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Background: Targeted temperature management (TTM) is a vital element of postresuscitation management after cardiac arrest. Though international guidelines recommend TTM, the supporting evidence is of low certainty.

Aims and objectives: To estimate the effect of TTM strategy on mortality and neurological outcomes in postcardiac arrest survivors.

Materials and methods: Randomized controlled trials (RCTs) published in English evaluating the use of TTM in adult comatose survivors of cardiac arrest were included. Studies were categorized into two groups, based on hypothermia vs normothermia. The main outcome was death due to any origin. The secondary outcome measures evaluated neurological outcome and complications associated with TTM. Outcomes were analyzed by calculating Odds Ratio (OR) of a worse outcome. ORs with 95% CIs in a forest plot were used to show the results of random-effects meta-analyses.

Results: On pooled analysis of 11 RCTs, no difference was observed in death due to any origin rates in the hypothermia compared to the normothermia group (OR; 0.88, 95% CI: 0.39–1.16). Overall, no difference in poor neurological outcome was observed between the two groups (OR; 0.86, 95% CI: 0.66–1.12). Trial sequencing analysis for mortality and poor neurological outcome showed that number to achieve power to predict futility has been achieved in both the parameters.

Conclusions: This meta-analysis showed that hypothermia compared to normothermia TTM strategies does not improve survival or neurologic outcomes.

Keywords: Hypothermia, Mortality, Neurological outcome, Normothermia, Post cardiac arrest, Targeted temperature management.

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Introduction

Targeted temperature management (TTM) is one of the important components of postresuscitation care after cardiac arrest. Use of TTM for patients who remain unconscious following return of spontaneous circulation is suggested by International Liaison Committee on Resuscitation (ILCOR). Favorable effects of therapeutic hypothermia or TTM on survival and neurologic outcome have been proposed by large randomized controlled trials (RCT). Mortality and morbidity in survivors of postcardiac arrest after return of spontaneous circulation (ROSC) is greatly contributed by hypoxic injury to the brain. Major focus of postcardiac arrest care is prevention of hypoxic brain injury. The evidence to support the recommendations for TTM originated from out of hospital cardiac arrest of supposed cardiac etiology and in patient who had a shockable rhythm. A recent RCT showed that higher percentage of cardiac arrest patients presenting with initial nonshockable rhythm of both in and out of hospital set-up survived with favorable neurological outcome when treated with TTM at 33°C vs 37°C. Based on the results of this RCT, ILCOR guideline 2021 recommends TTM to be tried in patient who stay in unconscious state after successful reversal of cardiac arrest. Though international guidelines recommend TTM, the supporting evidence is of uncertain utility. A recent RCT found that in comatose survivors of out-of-hospital cardiac arrest targeted hypothermia (33°C followed by controlled rewarming) did not reduce deaths by 6 months than targeted normothermia and early treatment of fever.

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Targeted Temperature Management in Postcardiac Arrest Survivors

Materials and Methods
This systematic review was conducted and reported as per the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) reporting guideline.

Eligibility Criteria
We included RCTs published in English from 2000 until July 2021 describing the usage of targeted temperature management following cardiac arrest in adult patients who were eligible for inclusion. Other than English RCTs, unpublished manuscripts, conference abstracts, and studies on pediatric patients were excluded.

Information Sources and Search Strategy
We searched MEDLINE via PubMed, EMBASE, Web of Science, SCOPUS, and the Cochrane Database of Systematic Reviews to identify the studies. Two authors (SBM, RP) used a prespecified list of terms to locate studies. The original database search used original paper, published meta-analysis with systematic reviews, and the references from these sources.

The entire search strategy is explained in detail in Supplemental Table 1. Two authors (SBM, RP) independently identified potentially eligible studies by screening study titles and their abstracts, then these were evaluated through full-text review and retrieved. Any discrepancy between screeners was resolved by discussion and mutual agreement so that an unanimous decision was made.

Selection Process and Data Collection Process
English language RCTs describing the use of targeted temperature management following coma in cardiac arrest adult patients were eligible for inclusion. Data extraction format has been shown in Supplemental Table 2. All cardiac rhythms, including shockable and nonshockable rhythms, and TTM techniques were included. Temperature of 34°C or less was defined as hypothermia, and being 36°C or more was defined as normothermia.

Outcome Measures
The primary outcome measure was death due to any cause following cardiac arrest. The secondary outcome measures evaluated neurological outcome as per any of the following, cerebral performance category (CPC), Pittsburgh cerebral-performance category, or modified Rankin scale (MRS) after targeted temperature management and complications associated with targeted temperature management. CPC scale is a five-point scale graded from I to V and scores on the modified Rankin scale range from 0 to 6. Within these scale, poor neurologic outcomes were defined as CPC categories 3–4 for meta-analyses and MRS grade IV and V for meta-analyses.

Data Extraction and Quality Assessment
After searching the titles and abstracts, two authors (SBM, RP) carried out data extraction. Data were extracted for outcome measures like mortality and neurological outcome in all of the included studies. We also looked for the adverse effect outcomes. All inconsistencies during data extraction were settled by mutual discussion so that a concordant decision was made. The PRISMA checklist for this meta-analysis has been depicted in Supplemental Table 3.

Risk of Bias Assessment
The two authors (SBM, RP) assessed the risk of bias of the studies which were included separately by. Any disagreement was resolved by consensus. The assessment was done in RevMan 5.0.

Effect Measures
We designed to examine dichotomous outcomes by calculating the Odds Ratio (OR) of a worse outcome (i.e., mortality, poor neurological outcome, arrhythmia, bleeding, and pneumonia) for each trial. Mantel-Haenszel odds ratio (OR) was used to analyze the data. The confidence interval for each study and the complete analysis were kept at 95%. The studies that reported the exact numbers for the dichotomous outcomes analyzed were included for analysis.

Data Synthesis and Analysis
The two authors separately did the evaluation and then compared the data. Any discord was resolved by consensus. These tables have summarized the estimated intervention effect and the number of participants and studies for mortality and neurological outcome. ORs with 95% CIs in a forest plot were used to present the results. The tau-squared and the I-squared statistics, respectively, were used for heterogeneity. We have randomly used the I-squared thresholds of >75% to be considered a feature of substantial heterogeneity. All analysis was done in RevMan 5.0.

Funnel plots were done for meta-analyses to assess small-study effects, including all trials of varying sizes. If any asymmetry was found in the funnel plot we designed to assess the cause for it. The methodological or clinical heterogeneity was evaluated as possible causes for publication bias.

Reporting Bias Assessment
The evaluation was done for bias in reporting of the outcomes. The outcomes which were specified in trial protocols with the outcomes reported in the corresponding trial publications were compared. We analyzed the outcomes reported in the methods and results sections of the trial publications in case the protocols could not be assessed.

Certainty Assessment
Two people (SBM, RP) separately evaluated the certainty of the evidence. The five GRADE was used to evaluate the certainty evidence related to the available literature was done. We evaluated the certainty of evidence as high, moderate, low, or very low. The evaluation and grading was done according to the meta-analysis guidelines. We used the GRADEpro GDT software to prepare the “Summary of findings” tables (GRADEpro GDT 2015).

Trial Sequential Analysis
Trial sequencing analysis was done for all-cause mortality taking type I error as 5 and 80% power using O’Brien-Fleming for alpha and beta spending function. Prevalence of mortality in the control group was taken as 60%. Trial sequencing analysis was done for bad neurological outcome taking type I error as 5 and 80% power using O’Brien-Fleming for alpha and beta spending function. The prevalence of bad neurological outcomes in the control group was taken as 70%.

Results
Study Selection
Eleven RCTs with 5,305 patients were eligible for analysis. Flow chart of study enrollment is shown in Flowchart 1. Table 1 represents the characteristics of trials included in the study. The risk of bias has been depicted in Supplemental Figure 1. The results of this meta-analysis are presented as per the updated PRISMA 2020 statement.
Study Characteristics
There was variation in the characteristics of individual studies. All combinations of presenting rhythms were studied. There were dissimilarities in the techniques used for resuscitation and cooling. Hypothermia strategies varied between prehospital and intrahospital cooling. Duration of cooling ranged between 12 hours and 3 days. Various cooling methods in the included studies were an intravenous infusion of cooled fluids, ice packs, a cooling helmet device, an intravascular cooling catheter with or without a closed-loop surface device (Table 1).

Impact on Mortality
Eleven RCTs compared hypothermia with normothermia for all-cause mortality.\(^3\),\(^4\),\(^8\)–\(^10\),\(^16\)–\(^21\) 2,673 patients received hypothermia, and 2,632 received normothermia. 1,504 patients had mortality in the hypothermia group and 1,505 in the normothermia group. On pooled analysis no difference between normothermia and hypothermia was found (OR; 0.88, 95% CI: 0.39–1.16) (Fig. 1).

Impact on Neurological Outcome
Seven RCTs compared neurological outcomes between hypothermia and normothermia strategies.\(^3\),\(^4\),\(^8\)–\(^10\),\(^18\),\(^21\) Overall, 2,531 patients in the hypothermia group and 2,500 in the normothermia group were evaluated for the poor neurological outcome. No difference in neurological outcome between the two groups was found (OR; 0.86, 95% CI: 0.66–1.12) (Fig. 2).

Impact on Complications
Three RCTs have looked into the complications associated with TTM strategy.\(^3\),\(^9\),\(^10\) Two RCTS each have looked into arrhythmia and bleeding while three RCTs have looked into bleeding. Though the incidence of complications was higher in hypothermia group, the pooled analysis did not find any statistical difference. The forest plots are shown in Supplemental Figures 3 to 5.

Heterogeneity among Study Results
Substantial heterogeneity was observed in the treatment effect of mortality among the studies (\(I^2 = 45\%\)). We observed no heterogeneity in trials comparing neurological outcomes between hypothermia and normothermia groups (\(I^2 = 0\%\)). Among the trials evaluating for complications, substantial heterogeneity was observed in the two trials for arrhythmia (\(I^2 = 89\%\)). Less heterogeneity was observed in the trials evaluating bleeding (\(I^2 = 38\%\)) and pneumonia (\(I^2 = 15\%\)).

Trial Sequential Analysis
Trial sequencing analysis for mortality and poor neurological outcome is shown in Figure 3 and Supplemental Figure 6, respectively. The analysis shows the number to achieve the power to predict futility has been achieved in both the parameters. The analysis does not show any superiority of inducing hypothermia.

Certainty of the Evidence
The confidence in the literature was evaluated using GRADE. The death rates had low level of certainty due to significant imprecision concerns regarding the wide 95% CI for the summary Odds Ratio. This would be compatible with substantial benefit or harm. For the secondary analysis that included all seven RCTs, the questions regarding imprecision were decreased and the certainty of the evidence was evaluated as moderate. The GRADE document on certainty of evidence is shown in Supplemental Table 4.
### Table 1: Characteristics of included studies

| Study (reference) (TTM/NT) | Age (years) | Male (%) | Presenting rhythm | Method of cooling | Duration of cooling | Time that cooling was commenced | Target temperature (°C) | Follow-up period | ROSC (time in minutes) (TTM/NT) |
|---------------------------|-------------|----------|-------------------|-------------------|---------------------|-------------------------------|-------------------------|-----------------|----------------------------------|
| Mori et al., 2000<sup>16</sup> (N = 54, TTM/NT = 36/18) | —           | —        | —                 | Water circulating blankets above and below participant with another ice mounted blanket over participant | 3 days | After ROSC | 32–34<sup>4</sup> | 1 month | —                              |
| Hachimi-Idrissi et al, 2001<sup>17</sup> (N = 54, TTM/NT = 36/18) | 76/74       | 76/74    | PEA/Asystole      | Helmet device around head and neck containing a solution of aqueous glycerol | 4 hours | After ROSC | 34<sup>4</sup> | Till discharge | 34/33                           |
| Bernard et al., 2002<sup>4</sup> (N = 77, TTM/NT = 43/34) | 67/65       | 58/79    | VF                | Ice packs          | 12 hours | After ROSC | 33<sup>4</sup> | Till discharge | 27/25                           |
| Holzer et al., 2002<sup>1</sup> (N = 275 TTM/NT = 137/138) | 59/59       | 77/75    | VF/Pulseless VT   | External cooling device | 24 hours | After ROSC | 32–34<sup>4</sup> | 6 months | 21/22                           |
| Hachimi-Idrissi et al, 2005<sup>18</sup> (N = 61, TTM/NT = 30/31) | 67/69       | 77/68    | Asystole/PEA and VF/Pulseless VT | Cooling helmet | Up to 24 hours | After ROSC | 33<sup>4</sup> | 6 months | 29/28                           |
| Laurent et al., 2005<sup>19</sup> (N = 61, TTM/NT = 22/39) | 56/58       | 82/79    | VF/Asystole       | Direct external cooling of blood | 24 hours | After ROSC | 32–34<sup>4</sup> | 6 months | 16/14                           |
| Kamarainen et al., 2009<sup>20</sup> (N = 37, TTM/NT = 19/18) | 59/63       | 95/94    | Asystole/PEA and VF/Pulseless VT | Cooling intravenous fluid infusion | — | After ROSC | 33<sup>4</sup> | Till discharge | 23/22                           |
| Nielsen et al., 2013<sup>10</sup> (N = 933 TTM/NT = 473/466) | 64/64       | 83/79    | Asystole/PEA and VF/Pulseless VT | Ice packs and cooled intravenous fluid infusion | 28 hours | After ROSC | 33<sup>4</sup> | 8.5 months | 25/25                           |
| Kim et al., 2014<sup>21</sup> (N = 1,359, TTM/NT = 688/671) | 66/65       | 64/63    | VF/Non VF         | Cooling intravenous fluid infusion | 24 hours | After ROSC | 34<sup>4</sup> | Till discharge | 27/25                           |
| Lascarrou et al., 2019<sup>8</sup> (N = 581, TTM/NT = 284/297) | 67/67       | 65/63    | Asystole/PEA/unknown not shocked | Active internal cooling with specific device/active external cooling with or without specific device | 24 hours | After ROSC | 33<sup>4</sup> | Till day 90 of randomisation | —                              |
| Danklewicz et al., 2021<sup>9</sup> (N = 1,850, TTM/NT = 925/925) | 64/63       | 80/79    | VF/Non perfusing VT/PEA/Asystole/Unknown rhythm | Surface or intravascular temp management device | 28 hours | After ROSC | 33<sup>4</sup> | 6 months | 25/25                           |

TTM, targeted temperature management; HT, hypothermia; NT, normothermia; ROSC, return of spontaneous circulation; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia
Targeted Temperature Management in Postcardiac Arrest Survivors

Our systematic review and meta-analysis compared the effect of hypothermia vs normothermia TTM strategies and explained TTM on three outcomes: mortality, neurological outcome, and complications.

On pooled analysis, we found no difference in all-cause mortality rates in the hypothermia compared to the normothermia group (OR; 0.88, 95% CI: 0.72–1.07). Earlier trials suggested an increased survival in patients who underwent hypothermia at 33°C.\(^3,4\) The landmark TTM trial published in 2013 found no difference in death rates or neurological outcome between 33°C and 36°C after out-of-hospital cardiac arrest of presumed cardiac cause.\(^10\) This trial altered the practice of therapeutic hypothermia worldwide with adoption of higher temperature target though sizeable heterogeneity in the practice pattern remains.\(^22–24\) Though older cochrane review and meta-analysis support the use of hypothermia,\(^25,26\) it has been noted that the trend in meta-analyses published after 2014 broadly suggests no benefit regarding survival of therapeutic hypothermia.\(^27–30\) Meta-analysis by Kalra et al.\(^29\) found no mortality benefit of hypothermia (RR: 0.88, 95% CI 0.73–1.05). Similar findings of no survival benefit was obtained in meta-analysis by Villalba et al.\(^30\) (RR: 0.81, 95% CI 0.55–1.21). A recently published RCT of 1,900 patients targeted controlled rewarming following induced hypothermia, when compared with targeted normothermia with early treatment of fever (temp >37.8°C) did not lead to a reduction in mortality rates at 6 months.\(^9\) A recently published network meta-analysis of 10 RCTs by Fernando et al. on TTM following out-of-hospital cardiac arrest, impact of various temperature targets on survival, and functional outcome were evaluated. It was observed that compared to normothermia (37–37.8°C), deep hypothermia (31–32°C), moderate hypothermia (33–34°C), and mild hypothermia (35–36°C) may have no effect on survival with good functional outcome.\(^31\) Moreover, on trial sequential analysis in our systematic review, we found that the number to achieve the power to predict futility concerned to mortality was found to be 2,785, which has already reached with included sample of 5,305 patients.
in this meta-analysis. Our findings suggest that there is no need for further trials as the power is adequate to prove no mortality benefit of TTM strategy.

Apart from survival, good neurological outcome benefit is of utmost concern in postcardiac arrest survivors. That is why various prognostic clues for unfavorable neurological outcome at discharge have been proposed and being revised repeatedly.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\) We found no difference in neurological outcome between hypothermia and normothermia TTM strategies (OR: 0.86, 95% CI: 0.66–1.12). Meta-analysis by Kalra et al.\(^2\) found no neurological outcome benefit of hypothermia (RR: 1.26, 95% CI: 0.92–1.72). Similar findings were obtained in meta-analysis by Bhattacharjee et al.\(^2\) (OR: 1.80, 95% CI: 0.97–3.37) and Villalbana et al.\(^2\) (OR: 0.77, 95% CI: 0.47–1.24).

Hypothermia also affects with various pathophysiological processes and this might induce unfavorable effects, such as cardiac dysrhythmia, coagulopathy, and infectious complications.\(^3\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\) We evaluated complications of TTM strategies with respect to bleeding, pneumonia, and arrhythmia. Other meta-analyses found increased complications in the hypothermia group.\(^17\)\(^18\) Compared to the previous meta-analysis, our systematic review included the TTM-2 trial,\(^9\) which has very well addressed complications of hypothermia. We found higher incidence of complications in hypothermia group. However, on pooled analysis, no statistically significant difference was noted.

The results of our review are in accordance with the recently published significant trials.\(^9\)\(^10\) Based on the results of our meta-analysis, as of now, there is sufficient evidence to suggest no benefits of hypothermia compared to the normothermia TTM strategy. We suggest the future guidelines need to address this recommendation. Differences in outcome of TTM could be related to various aspects of TTM strategy such as timing of initiation and duration rather than only provision of TTM. As of results of our meta-analysis and accordance with recent major trials, routine use of TTM is not found to be beneficial. There can be potential specific subgroup of patients where the benefit of TTM cannot be ruled out.

Our systematic review and meta-analysis have several strengths with a broad search and including only RCTs. Recently published RCTs were included in this meta-analysis. We used GRADE document on certainty of evidence and did trial sequencing analysis for mortality and poor neurological outcome assessment.

We recognize that our systematic review and meta-analysis have certain limitations. The duration of cooling, technique of cooling, target temperature, presenting rhythms, and in-hospital vs out-of-hospital cardiac arrest among the included trials had substantial heterogeneousness. There is a high risk of bias in the included trials as well. As most of the included trials are multicenter, the standard of care could not be assured equally. Moreover, not only the postresuscitation care, the factors associated with cardiopulmonary resuscitation (CPR) such as response time, time to initiate resuscitation, duration of resuscitation, and quality of CPR are of utmost important deciding parameters for long-term outcome. As the included trials have inconsistently reported its effects, we could not assess its potential implications on provision of TTM. We did not do any subgroup analysis of the included trials.

**Conclusion**

The meta-analysis of the comprehensible literature shows that hypothermia compared to normothermia does not improve survival or neurological outcomes. Trial sequential analysis of our meta-analysis shows that we have reached the population required to confirm futility of the intervention in providing mortality or neurological benefit. No further studies are warranted. We suggest that existing guidelines need to be updated based on this data. However, though routine use of TTM strategies is not beneficial, future research needs to explore its implications in specific potential subgroups.

**List of Abbreviations**

TTM, targeted temperature management; RCTs, randomized controlled trials; CPC, cerebral performance category; MRS, modified Rankin scale; OR, odds ratio; ILCOR, International Liaison Committee on Resuscitation; ROSC, return of spontaneous circulation; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses.

**Declarations**

**Ethics Approval and Consent**

As it is a systematic review and data compiled from the already published randomized trials, ethical clearance was not obtained for this systematic review.

**Availability of Data and Materials**

Data and materials are available with corresponding author on request.

**Author Contributions**

Shakti Bedanta Mishra: Conceptualisation; Methodology; Software; Formal analysis; Writing Original Draft
Rupali Patnaik: Conceptualisation; Methodology; Formal analysis; Writing Original Draft; Data Curation; Writing - Review & Editing
Arun Rath: Visualisation; Investigation; Supervision
Samir Samal: Visualisation; Investigation; Supervision
Abhilash Dash, Biswajit Nayak: Visualisation; Investigation; Supervision

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**Supplementary Materials**

All the supplemental Tables 1 to 4 and Figures 1 to 6 are available online on the website of www.IJCCM.org.

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Targeted Temperature Management in Postcardiac Arrest Survivors

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