SYSTEMATIC REVIEW/META ANALYSIS

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).[1,2] Favorable effects of therapeutic hypothermia or TTM on survival and neurologic outcome have been proposed by large randomized controlled trials (RCT).[3,4] 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.[5–7] 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.[3,4] 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.[8] 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.[1] 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 (body temperature >37.8°C).[9] Apart from assessing mortality and neurological outcome, limited trials have addressed complications associated with TTM.[3,9,10]

We tried to evaluate the effect of TTM on mortality, neurological outcome, and major complications comparing hypothermia vs normothermia strategy through systematic review and meta-analysis of RCTs.

Our systematic review and meta-analysis had the main objective to assess the effect of TTM strategy on mortality. The evaluation of the consequences of TTM on neurological outcomes and complications associated with TTM strategy were the secondary objectives.

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Materials and Methods

This systemic review was conducted and reported as per the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) reporting guideline.[11]

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.[12]

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 disaccord 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.

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.[13] 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

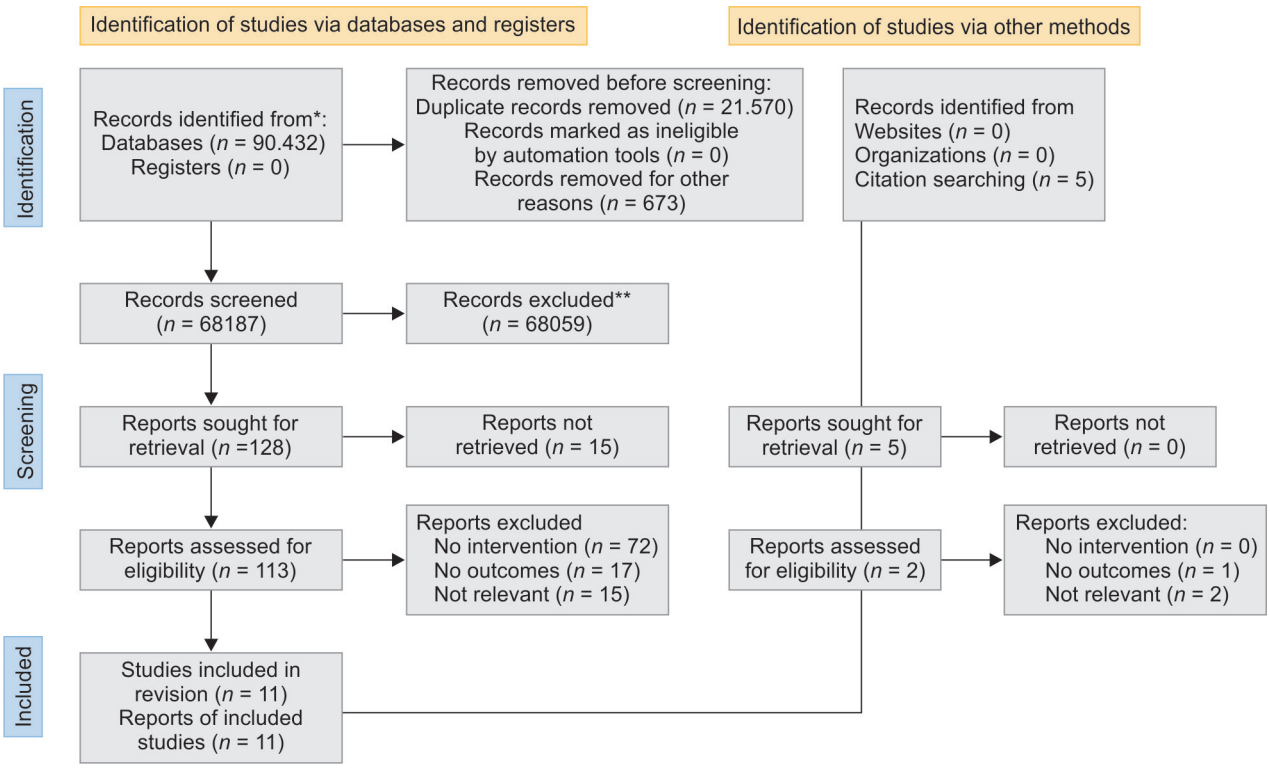
Trial sequencing analysis was done for all-cause mortality taking type I error as 5 and 80% power using O'Brien-Fleming for alpha and beta spending function.[14,15] Prevalence of mortality in the control group was taken as 60%. Trial sequencing analysis was done for bad neurological outcome taking type 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.[3,4,8–10,16–21] 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.

Flowchart 1: Flow diagram for study selection



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). There was lack of any evidence of publication bias in a funnel plot assessment (Supplemental Figure 2).

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) (TTM/NT)*	*Male (%) (TTM/NT)*	*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[16] (*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°	1 month	—
Hachimi-Idrissi et al., 2001[17] (*N* = 54, TTM/NT = 36/18)	76/74	—	PEA/Asystole	Helmet device around head and neck containing a solution of aqueous glycerol	4 hours	After ROSC	34°	Till discharge	34/33
Bernard et al., 2002[4] (*N* = 77, TTM/NT = 43/34)	67/65	58/79	VF	Ice packs	12 hours	After ROSC	33°	Till discharge	27/25
Holzer et al., 2002[3] (*N* = 275 TTM/NT = 137/138)	59/59	77/75	VF/Pulseless VT	External cooling device	24 hours	After ROSC	32–34°	6 months	21/22
Hachimi-Idrissi et al., 2005[18] (*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°	6 months	29/28
Laurent et al., 2005[19] (*N* = 61, TTM/NT = 22/39)	56/58	82/79	VF/Asystole	Direct external cooling of blood	24 hours	After ROSC	32–34°	6 months	16/14
Kamarainen et al., 2009[20] (*N* = 37, TTM/NT = 19/18)	59/63	95/94	Asystole/ PEA and VF/ Pulseless VT	Cooling intravenous fluid infusion	—	After ROSC	33°	Till discharge	23/22
Nielsen et al., 2013[10] (*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°	8.5 months	25/25
Kim et al., 2014[21] (*N* = 1,359, TTM/ NT = 688/671)	66/65	64/63	VF/Non VF	Cooling intravenous fluid infusion	24 hours	After ROSC	34°	Till discharge	27/25
Lascarrou et al., 2019[8] (*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°	Till day 90 of randomisation	—
Danklewicz et al., 2021[9] (*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°	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

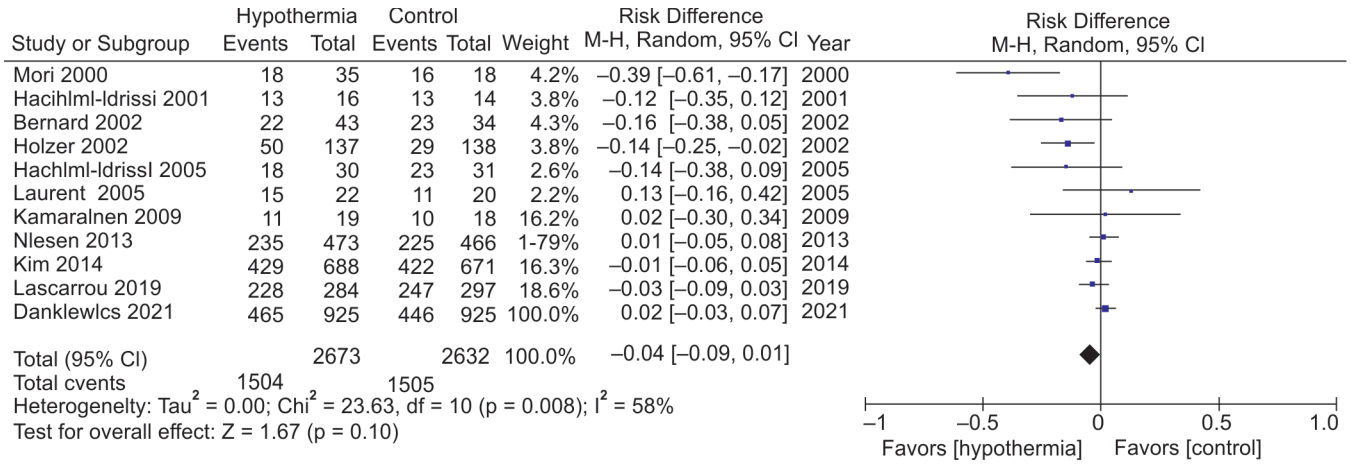


Fig. 1: Forest plot assessment of trials comparing mortality between hypothermia and normothermia strategy

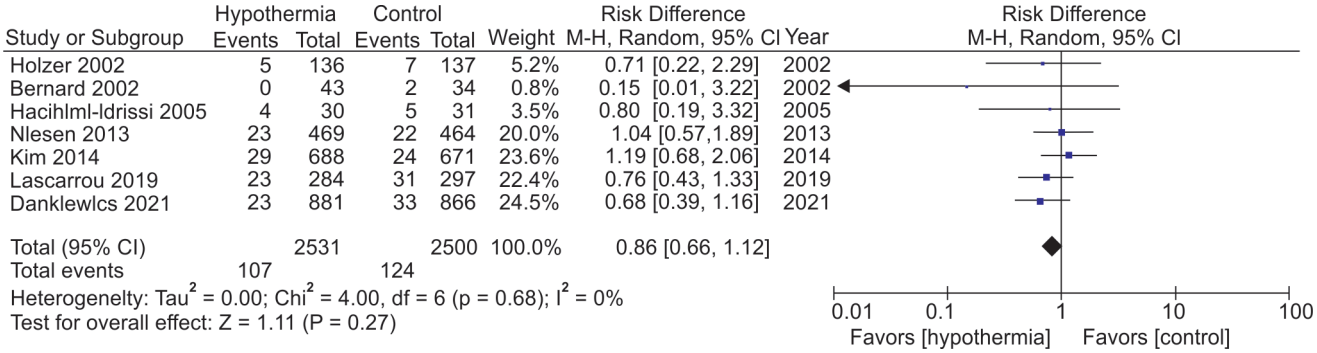


Fig. 2: Forest plot assessment of trials comparing poor neurological outcome between hypothermia and normothermia strategy

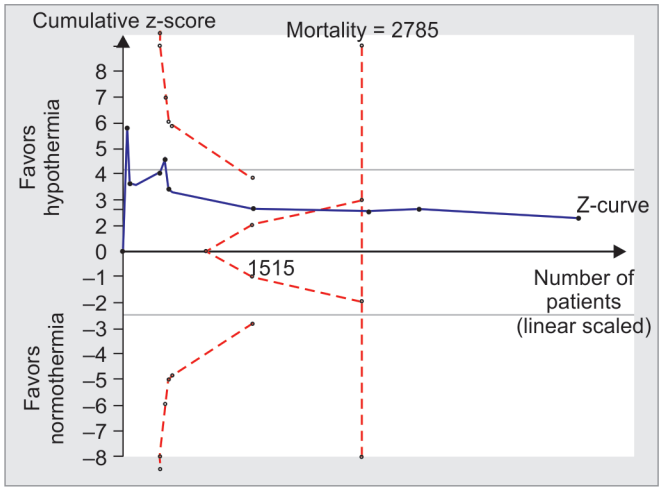


Fig. 3: Trial sequencing analysis for mortality benefit assessment of TTM strategy

Discussion

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 Villablanca 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.[1,32] 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.[29] 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.[28] (OR; 1.80, 95% CI 0.97–3.37) and Villablanca et al.[30] (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.[3,9,10,33] We evaluated complications of TTM strategies with respect to bleeding, pneumonia, and arrhythmia. Other meta-analyses found increased complications in the hypothermia group.[27,28] 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 neurologic 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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References

1. Nolan JP, Sandroni C, Bottiger B W, Cariou A, Cronberg T, Friberg H, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. Intensive Care Med 2021;47(4):369–421. DOI: 10.1007/s00134-021-06368-4.

2. Panchal AR, Bartos JA, Cabañas JG, Donnino MW, Drennan IR, Hirsch KG, et al. Part 3: adult basic and advanced life support: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2020;142 (16_suppl_2):S366–S468. DOI: 10.1161/CIR.0000000000000916.
3. Holzer M, Cerchiari E, Martens P, Roine R, Sterz F, Eisenburger P, et al. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346(8):549–556. DOI: 10.1056/NEJMoa012689.
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(8):557–563. DOI: 10.1056/NEJMoa003289.
5. Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Bottiger BW, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. Circulation 2008;118(23):2452–2483. DOI: 10.1161/CIRCULATIONAHA.108.190652.
6. Parrillo JE, Dellinger RP. Critical care medicine. Principles of diagnosis and management in the adult. 5th ed. Elsevier: Philadelphia; 2019.
7. Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines for post-resuscitation care 2015: section 5 of the European resuscitation council guidelines for resuscitation 2015. Resuscitation 2015;95:202–222. DOI: 10.1016/j.resuscitation.2015.07.018.
8. Lascarrou JB, Merdji H, Le Gouge A, Colin G, Grillet G, Girardie P, et al. Targeted temperature management for cardiac arrest with non-shockable rhythm. N Engl J Med 2019;381(24):2327–2337. DOI: 10.1056/NEJMoa1906661.
9. Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Levin H, Ullen S, et al. Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest (TTM-2). N Engl J Med 2021;384:2283–2294. DOI: 10.1056/NEJMoa2100591.
10. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management 33°C versus 36°C after cardiac arrest. N Engl J Med 2013;369(23):2197–2206. DOI: 10.1056/NEJMoa1310519.
11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. British Medical.Journal 2021;372:n71. DOI: 10.1136/bmj.n71.
12. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. British Medical.Journal 2008;336(7650):924–926. DOI: 10.1136/bmj.39489.470347.AD.
13. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol 2020;119:126–135. DOI: 10.1016/j.jclinepi.2019.10.014.
14. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J Clin Epidemiol 2008;61(1):64–75. DOI: 10.1016/j.jclinepi.2007.03.013.
15. Thorlund K, Devereaux PJ, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? Int J Epidemiol 2009;38(1):276–286. DOI: 10.1093/ije/dyn179.
16. Mori K, Takeyama Y, Itoh Y, Nara S, Yoshida M, Ura H, et al. A multivariate analysis of prognostic factors in survivors of out of out-of-hospital cardiac arrest with brain hypothermia. Crit Care Med 2000;28(12):A168.
17. 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(3):275–281. DOI: 10.1016/s0300-9572(01)00412-9.
18. Hachimi-Idrissi S, Zizi M, Nguyen DN, Schiettecate J, Ebinger G, Michotte Y, et al. The evolution of serum astroglial S-100 beta protein in patients with cardiac arrest treated with mild Hypothermia. Resuscitation 2005;64(2):187–192. DOI: 10.1016/j.resuscitation.2004.08.008.
19. 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(3):432–437. DOI: 10.1016/j.jacc.2005.04.039.
20. Kamarainen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Prehospital therapeutic hypothermia for comatose survivors of cardiac arrest: a randomised controlled trial. Acta Anaesthesiol Scand 2009;53(7):900–907. DOI: 10.1111/j.1399-6576.2009.02015.x.
21. 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. Journal of the American Medical Association 2014;311(1):45–52. DOI: 10.1001/jama.2013.282173.
22. Salter R, Bailey M, Bellomo R, Eastwood G, Goodwin A, Nielsen N, et al. Changes in temperature management of cardiac arrest patients following publication of the target temperature management trial. Crit Care Med 2018;46(11):1722–1730. DOI: 10.1097/CCM.0000000000003339.
23. Nolan JP, Orzechowska I, Harrison DA, Soar J, Perkins GD, Shankar-Hari M. Changes in temperature management and outcome after out-of-hospital cardiac arrest in United Kingdom intensive care units following publication of the targeted temperature management trial. Resuscitation 2021;162:304–311. DOI: 10.1016/j.resuscitation.2021.03.027.
24. Taccone FS, Picetti E, Vincent JL. High quality targeted temperature management (TTM) after cardiac arrest. Crit Care 2020;24(1):6. DOI: 10.1186/s13054-019-2721-1.
25. Arrich J, Holzer M, Havel C, Mullner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. Cochrane Database Syst Rev 2012;9:CD004128. DOI: 10.1002/14651858.CD004128.pub4.
26. Kim YM, Yim HW, Jeong SH, Klem ML, Callaway CW. Does therapeutic Hypothermia benefit adult cardiac arrest patients presenting with non-shockable initial rhythms?: A systematic review and meta-analysis of randomised and non-randomised studies. Resuscitation 2012;83(2):188–196. DOI: 10.1016/j.resuscitation.2011.07.031.
27. Zhang XW, Xie JF, Chen JX, Huang YZ, Guo FM, Yang Y, et al. The effect of mild induced Hypothermia on outcomes of patients after cardiac arrest: a systematic review and meta-analysis of randomised controlled trials. Crit Care 2015;19:417. DOI: 10.1186/s13054-015-1133-0.
28. Bhattacharjee S, Baidya DK, Maitra S. Therapeutic hypothermia after cardiac arrest is not associated with favorable neurological outcome: a meta-analysis. J Clin Anesth 2016;33:225–232. DOI: 10.1016/j.jclinane.2016.03.001.
29. Kalra R, Arora G, Patel N, Doshi R, Berra L, Arora P, et al. Targeted temperature management after cardiac arrest: systematic review and meta-analyses. Anesth Analg 2018;126(3):867–875. DOI: 10.1213/ANE.0000000000002646.
30. Villablanca PA, Makkiya M, Eisenberg E, Briceno DF, Panagiota C, Menegus M, et al. Mild therapeutic hypothermia in patients resuscitated from out-of-hospital cardiac arrest: a meta-analysis of randomized controlled trials. Ann Card Anaesth 2016;19(1):4–14. DOI: 10.4103/0971-9784.173013.
31. Fernando SM, Di Santo P, Sadeghirad B, Lascarrou JB, Rochwerg B, Mathew R, et al. Targeted temperature management following

out-of-hospital cardiac arrest: a systemic review and network meta-analysis of temperature targets. Intensive Care Med 2021;47(10): 1078–1088. DOI: 10.1007/s00134-021-06505-z.
32. Kongpolprom N, Cholkraisuwat J. Neurological prognostications for the therapeutic hypothermia among comatose survivors of cardiac arrest. Indian J Crit Care Med 2018;22(7):509–518. DOI: 10.4103/ijccm.IJCCM_500_17.
33. Saigal S, Sharma JP, Dhurwe R, Kumar S, Gurjar M. Targeted temperature management: current evidence and practices in critical care. Indian J Crit Care Med 2015;19(9):537–546. DOI: 10.4103/0972-5229.164806.