Editorial

Is 48-hour targeted temperature management not superior to 24-hour targeted temperature management after out-of-hospital cardiac arrest in adults? Feasible but still inconclusive

Seung-Joon Lee[1], **Young-Min Kim**[2]

[1]Disaster and Emergency Medical Operations Center, National Emergency Medical Center, Seoul, Korea; [2]Department of Emergency Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

Correspondence to: Young-Min Kim, MD, PhD. Department of Emergency Medicine, College of Medicine, The Catholic University of Korea Seoul St. Mary's Hospital, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea. Email: emart@catholic.ac.kr.

Provenance: This is a Guest Editorial commissioned by the Executive Editor Zhongheng Zhang, MD, MM (Department of Emergency Medicine, Sir Run-Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China).

Comment on: Kirkegaard H, Søreide E, de Haas I, *et al.* Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. JAMA 2017;318:341-50.

Received: 15 October 2017; Accepted: 26 October 2017; Published: 22 November 2017.

doi: 10.21037/jeccm.2017.10.06

View this article at: http://dx.doi.org/10.21037/jeccm.2017.10.06

Since positive results of a quasi-randomized controlled trial and a randomized controlled trial were reported in 2002, mild therapeutic hypothermia (TH) has been accepted as an intervention to improve both survival and neurological outcomes following out-of-hospital cardiac arrest (OHCA) with shockable rhythm and has been actively implemented for all cardiac arrest patients around the world over the past decade (1,2). However, many questions for the optimal use of mild TH remain unresolved. Some researchers asserted that the scientific evidence is not sufficient to use mild TH for comatose survivors after cardiac arrest and have undertaken well-designed randomized controlled trials (RCTs) to demonstrate the efficacy and to determine an optimal dose for this intervention (3,4). In 2013, the largest trial including 939 patients after OHCA that compared a target temperature of 33 *vs.* 36 ℃ found no difference in 6-month mortality between the two temperatures (4). The results of the trial cast doubt on the efficacy of mild TH, and a following trial comparing targeted temperature management (TTM) at 33 ℃ with standard normothermia care (<37.5 ℃) will be just started by the same investigators (5). One of the important knowledge gaps for dose of TTM is the optimal duration of treatment.

Neuronal injury mechanisms following brain ischemia after cardiac arrest were affected by hypothermia in multifaceted ways for several days after reperfusion (6). In an animal study, a short duration of hypothermia (1–2 hours) had no neuroprotective effects unless it was started just after global ischemia (7). However, a longer duration (6–36 hours) of hypothermia was beneficial, although the cooling was slightly delayed, even after reperfusion (8). Twenty-four-hour hypothermia resulted in better neurological outcome than 4-hour hypothermia in an animal study using an 8-minute asphyxial cardiac arrest rat model (9). Unlike animal studies, hypothermia tends to be delayed by many reasons in clinical situations, and prolonged hypothermia will inevitably have multifaceted effects on delayed neuronal injury mechanisms. In three landmark trials, 12- or 24-hour durations were used, with the 24-hour duration applied in the two largest trials (1,2,4). On the basis of the available evidence, current guidelines recommended TTM at 32 to 36 ℃ for at least 24 hours (10). However, some animal studies using different arrest models have suggested that 48-hour hypothermia could have additional neuroprotective effects compared with 24-hour hypothermia, and a small prospective observational study suggested that prolonged hypothermia may blunt the inflammatory response after rewarming in patients following cardiac arrest (11-13). Although the prolonged hypothermia could have potential benefits, a longer duration of hypothermia may increase the risk for adverse events. Some observational studies suggested that the cooling duration of the infection

group was longer than that in the non-infection group, and prolonged duration of cooling and rewarming ≥28 hours may increase complications, such as pneumonia and bleeding (14,15). To provide an answer regarding the relative efficacies and the concern about adverse events, a RCT for the prolonged TTM duration is necessary.

In a recent issue of *JAMA*, Kirkegaard *et al.* (16) reported the results of the Time-differentiated Therapeutic Hypothermia 48 (TTH48) trial—a pragmatic, international, multicenter RCT that compared the 6-month favorable neurological outcome (defined as Cerebral Performance Category scores of 1 or 2) of 24 *vs.* 48 hours of TTM with 33 ℃ among unconscious adult survivors treated in ten intensive care units (ICUs) in six European countries.

Based on data from 335 patients, the rates for 6-month favorable neurological outcomes were 69% (120/175) in the 48-hour group and 64% (112/176) in the 24-hour group. The risk ratio for the primary outcome was 1.08 (95% CI, 0.93–1.25) and the risk difference was 4.9% (95% CI, −5–14.8%). The investigators carefully analyzed unadjusted and adjusted 6-month survival rates in both modified intention-to-treat and per-protocol analyses but showed similar results. Secondary outcomes, including mortality during ICU and ward hospitalization or at 6 months, also did not show meaningful differences between the two groups. Based on these results, the investigators concluded that TTM at 33 ℃ for 48 hours did not significantly improve 6-month neurologic outcome compared with TTM at 33 ℃ for 24 hours.

The internal validity of this trial was strong. Among 907 patients registered, 355 patients were randomized into two groups. A total of 351 patients (99%) completed the trial, and only 1 patient was lost to follow-up. Randomization was performed individually within strata defined by age and initial rhythm using a web-based central procedure, and allocation was concealed until randomization. TTM initiation and induction time were relatively short (<2 and <6 hours in the two groups, respectively), and rates of immediate coronary angiography were high (>80% in both groups). Neurologic prognostication was delayed and used a multimodal approach, and decisions to withdraw life-supporting treatment were made by a multidisciplinary team independently and according to established protocols. All of the study protocols and a statistical analysis plans were published in advance (17,18).

The TTH48 trial was the first RCT comparing different durations of TTM after adult OHCA and has many methodological strengths, as mentioned above. Additionally, the trial added to our knowledges of TTM dose after cardiac arrest. Although the incidence of overall adverse events and ICU length of stay were significantly different between the two duration groups, there were no significant differences in the incidence rates of the known major adverse events of prolonged TTM after OHCA, such as pneumonia, bleeding, or severe arrhythmias, as reported in previous studies (14,19,20). The authors reported that most of the adverse events were mild and did not affect the neurological outcomes. These findings suggest that the 48-hour duration could be considered clinically feasible for TTM after OHCA.

However, the superiority of the 48-hour TTM for improving 6-month neurological outcomes in adult OHCA to 24-hour TTM is inconclusive due to the limited statistical power of the trial. The 15% absolute difference in the primary outcome between two different TTM duration groups might be too large considering the study subjects and study settings in this trial. In spite of the pragmatic trial design, the enrolled study subjects had many favorable prognostic characteristics, such as witnessed OHCA (91% in the 48-hour group *vs.* 92% in the 24-hour group) and shockable initial rhythm (91% in the 48-hour group *vs.* 86% in the 24-hour group). Furthermore, the study settings were good systems with a high bystander cardiopulmonary resuscitation rate (87% in the 48-hour group *vs.* 84% in the 24-hour group), short basic life support starting time (median 1 min in both groups), short emergency medical system response time (median 8 min in both groups), and active coronary angiography (83% in the 48-hour group *vs.* 82% in the 24-hour group). Due to the characteristics, the overall outcomes of this study were higher than in previous landmark RCTs (2,4). This particular patient sample may not represent the diverse range of illness severity of post-cardiac arrest patients. Although there is no definitive clinical evidence in adult cardiac arrest, theoretically, prolonged duration of TTM intervention could also be more helpful for patients with moderate-to-severe brain injury (11,13). Thus, the results of this trial do not exclude the possibility that prolonged TTM duration might be beneficial for an individual with moderate-to-severe brain injury. For these reasons, the generalizability of the findings in this trial could be limited to other settings in which patients with moderate-to-severe brain injury are more common. Therefore, further TTM duration trials including patients with moderate-to-severe brain injury and sample sizes estimated from more realistic clinical differences between

the two duration groups (if 10%, the estimated sample size is approximately 800) in different systems are needed to answer to the research question. Although a universal illness severity model for the TTM indicated OHCA patients is not currently recommended, some early prediction models for the patients have suggested it as a triage tool (21,22). Thus, further studies must use an available and reliable model for developing an enrollment criteria or patient stratification. Recently, some experts have requested more sophisticated trial designs for future clinical trials to overcome the limitations due to the diversity of the patients with post-cardiac arrest syndrome and the complexity of post-cardiac arrest care (23,24). In his editorial, Dr. Callaway suggested the necessity of dose-finding trials using appropriate targets or monitors to guide the titration of post-cardiac arrest care to individual responses rather than optimum fixed-dose interventions (23). Recently, individualized and tailored brain resuscitation strategies using various multimodal cerebral monitoring methods have begun to be actively studied in the post-cardiac arrest field (25). Therefore, a trial comparing fixed *vs.* titrated TTM dose according to the illness or brain injury severity and individual responses to the intervention using multimodal brain monitoring is also expected in the future.

In summary, the trial by Kirkegaard *et al.* (16) demonstrated the clinical feasibility of 48-hour TTM as an additional target duration for adult OHCA patients. However, it is still inconclusive whether this prolonged duration is more effective than the 24-hour duration recommended in current guidelines and which subgroups benefit more from the intervention. Therefore, additional multicenter clinical trials with more sophisticated designs using various multimodal cerebral monitoring methods are needed.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557-63.
2. 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.
3. Nielsen N, Friberg H, Gluud C, et al. Hypothermia after cardiac arrest should be further evaluated—a systematic review of randomised trials with meta-analysis and trial sequential analysis. Int J Cardiol 2011;151:333-41.
4. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 °C versus 36 °C after cardiac arrest. N Engl J Med 2013;369:2197-206.
5. Targeted Hypothermia Versus Targeted Normothermia After Out-of-hospital Cardiac Arrest (TTM-2). Available online: https://clinicaltrials.gov/ct2/show/NCT02908308
6. Sekhon MS, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a "two-hit" model. Crit Care 2017;21:90.
7. Kuboyama K, Safar P, Radovsky A, et al. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. Crit Care Med 1993;21:1348-58.
8. Coimbra C, Wieloch T. Moderate hypothermia mitigates neuronal damage in the rat brain when initiated several hours following transient cerebral ischemia. Acta Neuropathologica 1994;87:325-31.
9. Katz LM, Young AS, Frank JE, et al. Regulated hypothermia reduces brain oxidative stress after hypoxic-ischemia. Brain Res 2004;1017:85-91.
10. Callaway CW, Donnino MW, Fink EL, et al. Part 8: post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132:S465-82.
11. Che D, Liu Z, Guo W, et al. Impact of therapeutic hypothermia onset and duration on survival and neurologic function after pulseless electrical activity/asystole cardiac arrest. Crit Care Med 2011;39:1423-30.
12. Suh GJ, Kwon WY, Kim KS, et al. Prolonged therapeutic hypothermia is more effective in attenuating brain apoptosis in a swine cardiac arrest model. Crit Care Med 2014;42:e132-42.
13. Bisschops LL, van der Hoeven JG, Mollnes TE, et al. Seventy-two hours of mild hypothermia after cardiac arrest is associated with a lowered inflammatory response during rewarming in a prospective observational study. Crit Care 2014;18:546.
14. Mongardon N, Perbet S, Lemiale V, et al. Infectious

complications in out-of-hospital cardiac arrest patients in the therapeutic hypothermia era. Crit Care Med 2011;39:1359-64.
15. Kagawa E, Dote K, Kato M, et al. Do lower target temperatures or prolonged cooling provide improved outcomes for comatose survivors of cardiac arrest treated with hypothermia? J Am Heart Assoc 2015;4:e002123.
16. Kirkegaard H, Søreide E, de Haas I, et al. Targeted temperature management for 48 vs 24 hours and neurologic outcome after out-of-hospital cardiac arrest: a randomized clinical trial. JAMA 2017;318:341.
17. Kirkegaard H, Rasmussen BS, de Haas I, et al. Time-differentiated Target Temperature Management After Out-of-Hospital Cardiac Arrest: a multicentre, randomised, parallel-group, assessor-blinded clinical trial (the TTH48 trial): study protocol for a randomised controlled trial. Trials 2016;17:228.
18. Kirkegaard H, Pedersen AR, Pettilä V, et al. A statistical analysis protocol for the time-differentiated target temperature management after out-of-hospital cardiac arrest (TTH48) clinical trial. Scand J Trauma Resusc Emerg Med 2016;24:138.
19. Nielsen N, Sunde K, Hovdenes J, et al. Hypothermia Network. Adverse events and their relation to mortality in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia. Crit Care Med 2011;39:57-64.
20. Kim YM, Youn CS, Kim SH, et al. Korean Hypothermia Network Investigators. Adverse events associated with poor neurological outcome during targeted temperature management and advanced critical care after out-of-hospital cardiac arrest. Crit Care 2015;19:283.
21. Okada K, Ohde S, Otani N, et al. Prediction protocol for neurological outcome for survivors of out-of-hospital cardiac arrest treated with targeted temperature management. Resuscitation 2012;83:734-9.
22. Nishikimi M, Matsuda N, Matsui K, et al. A novel scoring system for predicting the neurologic prognosis prior to the initiation of induced hypothermia in cases of post-cardiac arrest syndrome: the CAST score. Scand J Trauma Resusc Emerg Med 2017;25:49.
23. Callaway CW. Targeted Temperature Management After Cardiac Arrest: Finding the Right Dose for Critical Care Interventions. JAMA 2017;318:334-6.
24. Nolan JP, Berg RA, Bernard S, et al. Intensive care medicine research agenda on cardiac arrest. Intensive Care Med 2017;43:1282-93.
25. Sinha N, Parnia S. Monitoring the Brain After Cardiac Arrest: a New Era. Curr Neurol Neurosci Rep 2017;17:62.

doi: 10.21037/jeccm.2017.10.06
Cite this article as: Lee SJ, Kim YM. Is 48-hour targeted temperature management not superior to 24-hour targeted temperature management after out-of-hospital cardiac arrest in adults? Feasible but still inconclusive. J Emerg Crit Care Med 2017.

