Editorial

Editorial for the paper of Dr. Hans Kirkegaard *et al. JAMA* 2017;318:341-50

Mayuki Aibiki[1,2]

[1]Department of Emergency and Critical Care Medicine, Ehime University, Graduate School of Medicine, Tohon, Japan; [2]Ehime University Hospital, Tohon, Japan

Correspondence to: Mayuki Aibiki. Ehime University Hospital, Shitsukawa 454, Tohon City, Ehime 791-0295, Japan. Email: aibiki@m.ehime-u.ac.jp.

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.

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The International Liaison Committee on Resuscitation (ILCOR) published the Consensus of Science for Treatments and Recommendations (CoSTR) 2015, a body of systematic reviews on resuscitation science. According to the CoSTR, Guidelines 2015 have been developed in several countries, in which targeted temperature management (TTM) at 33 to 36 ℃ has been recommended in unconscious victims after out-of-hospital cardiac arrest (OHCA) at least for 24 hours, but the optimal duration for TTM was unclear. Dr. Hans Kirkegaard *et al.* has tested a hypothesis in an international multicenter randomized control trial (RCT) whether TTM at 33 ℃ for 48 hours could bring more favorable outcomes as compared to that for 24 hours in patients at six months after OHCA from a presumed cardiac origin, in which TTM for 48 hours did not show any benefits on neurologic outcomes over 24 hours (1). This result indicates that TTM of 33 ℃ for 24 hours could be a choice of the treatments for comatose survivors from OHCA. Regarding the 'dosing' of TTM duration in this study, there has already been a thoughtful and excellent editorial written by Dr. Clifton Callaway, Pittsburg Medical Center, in the same issue of JAMA. So, I would like to review the current study from a different point of view as follows.

This RCT was done in ten intensive care units (ICUs) at ten university hospitals in six European countries. Three hundred and fifty-five adult, unconscious patients after OHCA were enrolled from February 2013 to June 2016. This study phase of the current RCT is completely different from the TTM trial done by Dr. Niklas Nielsen *et al.* (2), where a total of 950 patients were enrolled between November 2010 and January 2013 in European countries and Australia. The previous TTM study showed the exact same rates, 47% in the both groups, of favorable neurological outcome (CPC 1 or 2) in 33 and 36 ℃ groups sustaining the body temperature for 24 hours. On the other hand, the current RCT described that 69% (120/175) in the 48-hour group of 33 ℃ TTM had a neurologically favorable outcome at 6 months, though insignificant if compared with 64% (112/176) in the 24-hour group. We need to be very careful if we compare the results in the different studies, but it could be a huge improvement in the rate of CPC 1 or 2 in the 24-hour group in the current study. This present study was excellently performed especially in the body temperature management even in 48-hour group, which might be due not only to an adherence to the protocol for sedation and muscle relaxant administration, but also a continuous administration of sedative agents until the end of rewarming to 37 ℃. This might also cause a difference in the duration of induction to hypothermia of 33 ℃ (approx. 4 hours in the current study; 8 hours in the previous study). Especially, as we indicated in a previous letter (3), huge body temperature variations in the previous TTM trial could affect the potential beneficial effects of therapeutic hypothermia of 33 ℃.

Furthermore, the present study revealed that 6-month

mortality was 27% (48/175) in the 48-hour group and 34% (60/177) in the 24-hour group; but in the previous TTM trail, it was 49% in the 33 ℃ TTM group sustained for 24 hours. In the prognostication of the present study, electroencephalography (EEG) and somatosensory evoked potentials (SSEP) were recommended as prognostic markers for neurological outcome after therapeutic hypothermia. Such tests should be performed at least 48–72 hours after reaching normothermia in this study. These recommendations could prevent an early withdrawal of the life sustaining therapy even in the 48-hour treated group. One more possible reason for the lower mortality or even better neurological outcomes in the current study is fewer complications especially from infection: although the rates of pneumonia in both studies were similar, the occurrence rate of severe sepsis and septic shock in the current study was only 3%, whereas that in the previous TTM trail was approximately 15%. Systematic managements including infection control and hemodynamic adjustments are requisite during therapeutic hypothermia for other types of brain injury (4,5). The current study also indicates that, in the unconscious victims after OHCA, whole body managements during therapeutic hypothermia are crucial for obtaining the potential benefits of hypothermia, which have been established in numerous animal studies.

In an animal study, hypothermia for 48 hours as compared to that for 24 hours starting even after the resumption of spontaneous circulation improved remarkably the numbers of survived hippocampal CA-1 pyramidal neurons (6). Although the authors in the current study could not show any beneficial effects in the 48-hour group over the 24-hour group, they stated a low power in the number of the patients involved for detecting clinically important differences, favorable neurological outcome, between the two groups of 33 ℃ therapeutic hypothermia for the comatose survivors after OHCA. Therefore, this well-done study for the comparison of the duration of therapeutic hypothermia could justify further studies to elucidate possible favorable effects from the longer period of therapeutic hypothermia for the unconscious survivors from cardiac arrest.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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