Hypothermia in patients with cardiac arrest

Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T, Stammet P, Wanscher M, Wise MP, Aneman A, Al-Subaie N, Boesgaard S, Bro-Jepsen J, Brunetti I, Frederik Bugge J, Hingston CD, Juffermans NP, Koopmans M, Køber L, Langørgen J, Lilja G, Møller JE, Rundgren M, Rylander C, Smid O, Werer C, Winkel P, Friberg H, for the TTM Trial Investigators. (Department of Anesthesiology and Intensive Care, Helsingborg Hospital, Helsingborg; Departments of Clinical Sciences and Cardiology, Lund University, Lund; Departments of Neurology, Anesthesiology and Intensive Care and Rehabilitation Medicine, Skåne University Hospital, Lund Department of Anesthesiology and Intensive Care, Sahlgrenska University Hospital, Gothenburg—all in Sweden; Copenhagen Trial Unit, Center of Clinical Intervention Research and Departments of Cardiology and Cardiothoracic Anesthesiology, Heart Center, Department of Anesthesiology, Pharmacology, and Intensive Care, Geneva University Hospital, Geneva, Switzerland; Department of Intensive Care, Academic Medical Center, Amsterdam, the Netherlands; Department of Anesthesiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway; Department of Intensive Care, Medical Center Leeuwarden, Leeuwarden, The Netherlands; Intensive Care Unit, Santa Maria degli Angeli, Pordenone, and Department of Intensive Care, Istituto di Ricovero e Cura a Carattere Scientifico San Martino, Istituto Scientifico Tumori, University of Genoa, Genoa—both in Italy; Department of Anesthesiology and Intensive Care, Centre Hospitalier de Luxembourg, Luxembourg; Adult Critical Care, University Hospital of Wales, Cardiff, UK; Department of Intensive Care, Liverpool Hospital, Sydney; Department of Intensive Care, St George’s Hospital, London, UK; Department of Heart Diseases, Haukeland University Hospital, Bergen, Norway; and 2nd Department of Internal Medicine, Cardiology and Angiology, General University Hospital in Prague, Prague, Prague, Czech Republic.) Targeted temperature management at 33 °C versus 36 °C after cardiac arrest. N Engl J Med 2013; 369:2197–206.

SUMMARY

The Targeted Temperature Management (TTM) trial aimed to determine whether there are differences in all-cause mortality, neurological functional outcome and adverse events between targeted temperature management at 33 °C and 36 °C for 24 hours following return of spontaneous circulation in unconscious patients after cardiac arrest. It was a multicentre, prospective, intention-to-treat, interventional, double-blind, randomized controlled trial that enrolled 950 patients from 36 centres across Europe and Australia. Of 950 patients, only 939 patients were included in the primary analysis; 11 patients were excluded because 7 of them did not receive the assigned intervention while 4 were lost to follow-up.

Patients were recruited on admission to the intensive care unit (ICU) provided they were ≥18 years of age and had suffered out-of-hospital cardiac arrest of presumed cardiac aetiology. Eligible patients had more than 20 consecutive minutes of spontaneous circulation after resuscitation and were unconscious with a Glasgow Coma Scale score of <8. The major exclusion criteria were duration of return of spontaneous circulation to screening ≥240 minutes, asystole, acute stroke and body temperature of <30 °C.

After screening, patients were randomly assigned in a 1:1 ratio to targeted temperature management with a target body temperature of 33 °C or 36 °C, which was maintained for 24 hours along with sedation. Temperature was managed with intravascular cooling catheters (24%) or with a surface cooling system (76%). Core body temperature was measured from the urinary bladder (860 patients), and oesophageal and intravascular compartment (79 patients) with the help of a probe. After 24 hours, patients were re-warmed to 37 °C with an hourly increment of 0.5 °C. At 36 hours, when the body temperature reached 37 °C, sedation was discontinued or tapered. At the end of 72 hours of intervention, a detailed neurological examination was done for the patients who remained unconscious to decide continuation or withdrawal of life-sustaining therapy. All surviving patients were followed for 180 days from the last recruitment. At the end of the trial, all-cause mortality as primary outcome and death or poor neurological function at 180 days as secondary outcomes were evaluated with the cerebral performance category (CPC) scale and modified Rankin scale.

The groups did not differ significantly with respect to composite outcome of death or poor neurological function at the end of the study. Fifty per cent of the patients died in the 33 °C group (235 of 473) as compared with 48% (225 of 466) in the 36 °C group (hazard ratio with temperature of 33 °C 1.06, 95% CI, 0.89–1.28, p=0.51). After 180 days of follow-up, 54% of the patients in the 33 °C group either died or had a poor neurological function on CPC compared with 52% in the 36 °C group (risk ratio of 1.02, 95% CI 0.88–1.16, p=0.78). Analysis by using the modified Rankin scale yielded comparable rates of 52% in both groups (risk ratio 1.01, 95% CI 0.89–1.14, p=0.87). One or more serious adverse events occurred in 439 of 472 (93%) patients in the 33 °C group compared with 417 of 472 (90%) patients in the 36 °C group (risk ratio 1.03, 95% CI 1–1.08, p=0.09). Electrolyte abnormalities, particularly hypokalaemia, were more frequent in the 33 °C group than in the 36 °C group (19% vs. 13%, p=0.02). This trial had a protocol for withdrawal of life-sustaining treatment which was not adopted in all previous studies.

COMMENT

The annual incidence of out-of-hospital cardiac arrest is 92–189 per 100 000 population. Ten per cent of these patients survive to hospital discharge. Effective cardiopulmonary resuscitation and post-resuscitation care are essential in the survival of patients with cardiac arrest. Post-cardiac arrest therapeutic hypothermia protects the brain and other vital organs in patients who remain comatose even after the return of spontaneous circulation (ROSC). Hypothermia reduces brain metabolism (6%–8% per 1 °C), oxygen utilization and consumption of adenosine triphosphate. It inhibits the release of excitatory neurotransmitters, glutamate and dopamine, and induces brain-derived neurotrophic factors which further reduce the release of glutamate. Hypothermia attenuates oxidative stress and lipid peroxidation. Apoptosis is inhibited as a result of a reduction in calcium overload and glutamate release, induction of anti-apoptotic Bcl-2 and suppression of pro-apoptotic factor BAX. Hypothermia decreases inflammation that occurs.
after global cerebral ischaemia and reduces both early hyperaemia and delayed hypoperfusion. Many studies have reported a beneficial effect on outcome from the use of therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest associated with any arrest rhythm. Two randomized controlled trials done in 2002 showed that mild hypothermia (32–34 °C) maintained for 12–24 hours increased survival and improved neurological outcome in selected patients with out-of-hospital cardiac arrest. In a study the ‘Hypothermia after cardiac arrest study group’ showed significant improvement in functional recovery at hospital discharge (55% v. 39%), while the 1-month mortality was found to be much less in hypothermic (41% v. 55%) compared with normothermic patients. Similarly, in 77 patients of out-of-hospital cardiac arrest, 49% were successfully discharged from the hospital in the hypothermic group compared with 26% in the normothermic group. The American Heart Association 2010 guidelines for post-cardio-pulmonary resuscitation care advocate therapeutic hypothermia of 32–34 °C for 12–24 hours in unconscious adults with ROSC after out-of-hospital cardiac arrest. Hypothermia is recommended in patients with cardiac arrest, when the initial rhythm is either ventricular fibrillation (VF) or sustained ventricular tachycardia (VT), particularly with successful ROSC having systolic blood pressure of >90 mmHg (class IIa recommendation). It may also be beneficial in non-VF/VT out-of-hospital cardiac arrest patients (class IIb recommendation). A meta-analysis of randomized controlled trials done in 2011 concluded that therapeutic hypothermia improves both survival and neurological outcome on hospital discharge in post-cardiac arrest patients. However, a large randomized controlled trial published recently did not show improved survival or neurological status from therapeutic hypothermia among patients resuscitated from prehospital cardiac arrest. It was a large randomized controlled trial with 1359 patients of pre-hospital cardiac arrest (583 with VF and 776 without VF). They were randomized so that half of them received standard care alone (control), while half of them got standard care with mild hypothermia of 32–34 °C. Survival to discharge was similar in the intervention and control groups 62.7% v. 64.3% in patients with VF and 19.2% v. 16.3% in non-VF patients. The intervention group was also lagging the control group in terms of full neurological recovery or mild impairment (57.5% v. 61.9%). In this study too, mild hypothermia caused more re-arrest and acute pulmonary oedema.

Despite conflicting reports of outcome from mild hypothermia in various studies, the present study is of interest as it has compared minimal hypothermia (36 °C) with mild hypothermia (32–34 °C) in patients with ROSC after cardiac arrest. The results do not show any survival benefits or better neurological outcome in the group with mild hypothermia. This trial had a protocol for withdrawal of life-sustaining treatment which was not adopted in all previous studies. The authors delineated their approach for 247 (26%) patients who had withdrawal of care before hospital discharge. The reasons for withdrawal of life-sustaining therapy included brain death, multi-organ failure and ethical concerns. The removal of this confounding factor was a major strength of this study.

The present study is relevant for India as it may be easier to induce hypothermia to a temperature of 36 °C instead of 32–34 °C, which often requires several medications to reduce shivering and pain, and to induce sedation. However, the occurrence of similar rates of complications in the two groups is surprising and mandates that all patients undergoing therapeutic hypothermia should be monitored closely for any adverse events.

REFERENCES


NAYER JAMSHED
PRAVEEN AGGARWAL
Department of Emergency Medicine
All India Institute of Medical Sciences
New Delhi
peekay_124@hotmail.com