EDITORIAL

Randomized Clinical Trial Progress to Inform Care for Out-of-Hospital Cardiac Arrest

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Approximately 300 000 patients experience out-of-hospital cardiac arrest per year in the United States, and less than 10% survive to hospital discharge.[1] Regional heterogeneity in outcomes, with a 5-fold greater likelihood of survival following ventricular fibrillation arrest in Seattle, Washington, than in counties in Alabama, has underscored the opportunity to improve care.[1] National programs that define best practice around community, emergency medical services (EMS), and hospital strategies to improve care are being implemented[2,3] and promise to substantially improve survival. An important element of evidence-based care is therapeutic hypothermia.[4,5] In this issue of *JAMA*, Kim and colleagues[6] report findings from an ambitious and successful large randomized clinical trial that provides the first good new evidence in more than 10 years, and the first generated in the United States, regarding hypothermia following cardiac arrest.

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The clinical evidence for the benefit of hypothermia has been primarily derived from 2 randomized trials published a decade ago with a total of 352 patients with out-of-hospital cardiac arrest who had ventricular fibrillation (VF) or pulseless ventricular tachycardia. In an Australian trial, 77 patients were randomized (according to day of the week) within 2 hours of return of spontaneous circulation (ROSC) to a group that received surface cooling or to a control group that included passive rewarming.[7] In the cooling group, a temperature of 33.5°C was achieved after 120 minutes of cooling, and cooling was continued for 12 hours. The second trial, from Austria, randomized 275 patients with VF to surface cooling to a target of 32°C to 34°C for core temperature vs normothermia.[8] Cooling began at a median time of 105 minutes and target temperature was achieved a median of 8 hours after ROSC and continued for 24 hours. In each trial, there was a 16% to 24% absolute improvement in favorable neurological outcome.

However, there are many unanswered questions regarding therapeutic hypothermia. Would more trials be helpful to be certain about the degree of benefit of hypothermia in VF arrest? Does cooling work for patients with arrest and asystole or pulseless electrical activity? Is there an optimal duration of treatment? What is the optimal target temperature? Is intravascular cooling as or more effective than surface cooling? Is there greater benefit in earlier initiation of cooling, earlier achievement of target temperature, or both? These questions have not been addressed in adequate randomized clinical trials, although extension or amplification of the benefits seen in the early trials might have major health consequences. In addition, randomized clinical trials of cardiac arrest, particularly in the out-of-hospital setting, are enormously challenging, because of the need both to follow procedures involving authorization for waiver of informed consent and to conduct trials in the underresourced and fragmented environment of EMS.

It is in this context that the trial by Kim and colleagues[6] is an important contribution. A total of 1359 patients, which is more than 3 times as many as in the prior trials[7,8] combined, with out-of-hospital cardiac arrest (583 with VF and 776 without VF) were randomly assigned to prehospital cooling with up to 2 L of 4°C saline or control. Mean core temperature decreased by more than 1°C by the time of hospital arrival with prehospital cooling. The interval required to reach target temperature decreased from 5.5 hours (hospital only cooling) to 4.2 hours (prehospital and hospital cooling) in the VF group and from 4.0 hours to 3.0 hours in the group without VF. Despite these differences in achieving earlier cooling, the primary outcome, survival to hospital discharge, was not improved with hypothermia initiated in the out-of-hospital setting. Among the 583 patients with VF, 62.7% of the intervention group and 64.3% of the control group survived to discharge, whereas among the 776 patients without VF, 19.2% of the intervention group and 16.3% of the control group survived to discharge. There were no significant differences in neurological status at time of discharge between the intervention and control groups.

Why was survival not improved? Either the modestly faster achievement of hypothermia was not sufficiently beneficial to show better survival, or there was harm that balanced the benefit of the faster hypothermia. The hypothesis was a good one. If hypothermia is beneficial after cardiac arrest, it stands to reason that earlier application of hypothermia should be better than delayed cooling. Earlier application of hypothermia has been shown to be beneficial in animal models,[9,10] and more rapid induction of hypothermia could be protective against a cascade of reperfusion injury events, inflammatory insults, and cellular deterioration that develop during the postresuscitation period. However, these animal studies demonstrated no difference in outcome when cooling was performed at 1 hour following ROSC compared with 4 hours following ROSC, which is consistent with the findings in the study by Kim et al. The benefit of earlier cooling in animal studies is associated with cooling immediately upon ROSC[9] or with cooling during the cardiac arrest (termed *intra-arrest cooling*) prior to ROSC.[10] Consistent with the animal data, the current study suggests that improving the time from achieving target temperature from 5 hours to 4 hours does not substantially improve clinical outcome.

Additionally, there is some evidence of harm associated with the cooling method used in the study by Kim et al.[6] There was an 11% higher absolute rate of pulmonary edema on the initial chest radiograph and lower oxygen saturation on emergency department arrival with the intervention group. The volume of saline (2 L given rapidly) appears to have produced negative hemodynamic effects in the period after ROSC for some patients. This is consistent with animal data that demonstrate a reduction in coronary perfusion pressure when saline volume loading is done to achieve cooling.[11] This adverse effect on hemodynamics was not observed when cooling was achieved without delivering a large volume of saline. Thus this may be an adverse effect from the method of cooling selected for the study, not an effect of hypothermia. Alternate methods of cooling such as external skin cooling devices, intravenous cooling catheters, and intranasal cooling devices that do not rely on large volume saline infusions are available. The use of intravenous saline for cooling after cardiac arrest is common in the United States, and this study should provide a note of caution for the use of rapid infusions for hypothermia by all clinicians who use this method. In addition, even though this trial is large, it was powered to show a 30% improvement in outcome and a modest treatment effect may have been missed. Ongoing trials[12] could reinforce or challenge the results of this trial.

How should this trial influence practice? One question is whether the results are broadly generalizable because quality of cardiac arrest care is very high in Seattle, as reflected by 64% hospital survival and 58% survival with good neurological recovery for patients with VF in this trial. Yet the trial provides clear evidence that in the setting of high-quality care, out-of-hospital hypothermia by infusion of cold saline does not substantially improve survival. Emergency medical services agencies should concentrate on other means to improve survival from cardiac arrest. These include optimizing dispatch processes, ensuring quality cardiopulmonary resuscitation, transporting of patients to hospitals capable of providing quality cardiac arrest care, and measuring and continuously improving quality measures of cardiac arrest care.[2] Moreover, the study conclusions apply to out-of-hospital initiation of cooling with rapid infusion of cold saline, and they should not be extended to use of other methods of hypothermia initiated in the emergency department or continued during the initial phase of postresuscitation care in the intensive care unit.

The clinical trial by Kim et al[6] also highlights the importance of conducting rigorous randomized trials of interventions, such as hypothermia, for out-of-hospital cardiac arrest in the United States. Even though thousands of cardiac arrest patients in the United States are treated with hypothermia, it is unfortunate that it has taken 10 years since the publication of the initial randomized hypothermia trials for the first such US study to be published. More trials are needed to answer vital questions regarding the use of hypothermia. This randomized trial, and others being conducted, will lead to better care, more efficient use of resources, and improved outcomes for patients with out-of-hospital cardiac arrest.

ARTICLE INFORMATION

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