Effect of Prehospital Induction of Mild Hypothermia on 3-Month Neurological Status and 1-Year Survival Among Adults With Cardiac Arrest: Long-Term Follow-up of a Randomized, Clinical Trial

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Background—Randomized trials of prehospital cooling after cardiac arrest have shown that neither prehospital cooling nor targeted temperature management differentially affected short-term survival or neurological function. In this follow-up study, we assess the association of prehospital hypothermia with neurological function at least 3 months after cardiac arrest and survival 1 year after cardiac arrest.

Methods and Results—There were 508 individuals who were discharged alive from hospitals in King County, Washington; 373 (73%) were interviewed by telephone 123±43 days after the initial event. Overall, 59% of the treatment group and 58% of the control group had Cerebral Performance Category (CPC) 1 or 2 (P=0.70), and 50% of the treatment group and 49% of the control group had slight disability or better by the Modified Rankin Scale (MRS; P=0.35). One-year survival was 87% in the treatment group and 84% in the control group (P=0.42). Of those with CPC 1 at hospital discharge, 68% had CPC 1 or 2 at follow-up, and 50% had MRS of slight disability or better. Of 41 patients with CPC 3 or 4 at discharge, only 12% had CPC 2 at follow-up, and just 5% had MRS of slight disability or better. One-year survival was 92% for CPC 1 at discharge, but only 40% for CPC 4.

Conclusion—In addition to excellent survival, patients who had good neurological function at discharge continued to have good function at least 3 months after the event.

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Key Words: arrhythmia • cardiac arrest • follow-up study

Induction of mild hypothermia after cardiac arrest has become controversial as recent randomized trials have raised questions about timing and temperature goals of induced hypothermia. A large, multicenter, randomized trial in patients admitted to the hospital after cardiac arrest found no neurological or mortality benefit to hypothermia at a targeted temperature of 33°C, compared to a targeted temperature of 36°C. In our randomized trial of prehospital hypothermia in King County, Washington, prehospital cooling was not associated with short-term survival or neurological function at hospital discharge for those with and without ventricular fibrillation (VF). The aim of this article is to characterize neurological function at least 3 months after cardiac arrest and survival at 1 year after cardiac arrest and examine whether prehospital hypothermia was associated with these long-term outcomes. We anticipated that neurological function at discharge would predict these outcomes.

Methods

Patient Population

As detailed previously, eligible patients were randomized from December 7, 2007, through December 7, 2012, and follow-up interviews assessing neurological status were completed by May 1, 2013. Of the 1359 patients in our randomized trial, 508 (37%) were discharged alive from the hospital. Consent was sought from survivors to participate in a telephone interview to assess neurological recovery after discharge. Of the 508 survivors, 86 (17%) did not give consent...
to be interviewed, because they could not be contacted (43%), were deceased (41%), or refused (15%). Another 49 (10%) consented, but were not interviewed. In the end, 373 (73%) patients were interviewed (Figure 1). Trial activities, including the follow-up interviews and vital status ascertainment, were approved by institutional review boards at the University of Washington (Seattle, WA) and participating hospitals in Seattle and King County, Washington.

Variables

Key variables from the hospital phase of the randomized trial included age, sex, initial rhythm, time from call to first unit (either emergency medical technicians or Medics) arrival, bystander cardiopulmonary resuscitation, witnessed arrest, and neurological status at hospital discharge as measured by Cerebral Performance Category (CPC), which was scored as: (1) good cerebral performance; (2) moderate cerebral disability; (3) severe cerebral disability; (4) coma or vegetative state; or (5) deceased.6 The follow-up telephone interviews provided sufficient information to define not only CPC, but also the level of functional independence, as measured by the Modified Rankin Scale (MRS), which was scored as: (0) no symptoms; (1) no significant disability; (2) slight disability; (3) moderate disability; (4) moderately severe disability; (5) severe disability; or (6) deceased. The CPC and MRS were coded according to previously specified criteria.6

Telephone interviews were conducted by a single research assistant who asked questions that were used to define the CPC and MRS. For the CPC, there were either 3 questions for the patient or 4 questions for the caregiver or family member, depending on who was interviewed. For the MRS, there were 27 questions. Interviews were conducted with the patient (85%), caregiver (3%), or family member (12%).

Statistical Methods

We learned of patient deaths as a result of phone calls for the follow-up interviews. In addition, Washington State death records for the years 2007 through 2013 were obtained from the Washington State Department of Health. Patient name, date of birth, and gender were used to match to state death records. Social Security number was also used, but was available for less than 20% of patients. If patients were not identified as deceased by these means, they were presumed to be alive as of December 31, 2013. Survival time was calculated as the time from enrollment to death or December 31, 2013, for those presumed to be alive. Survival curves were constructed with the Kaplan-Meier method. Statistical analyses included chi-square, Student t test, or analysis of variance, as appropriate, and the log-rank statistic.

Results

Patient characteristics according to consent and interview status are shown in Table 1. Included in the 86 patients who did not consent were 41 (48%) who died during the year after discharge. There were 49 patients who consented, but were not interviewed; 17 (35%) died during the year after hospital discharge. As seen in Figure 1, other reasons why patients who consented were not interviewed included: (1) patient or family refusal (6%); (2) inability to contact the patient (35%);
and (3) unknown reason (24%). Compared to patients who were interviewed, patients who were not interviewed had worse neurological function at discharge. In the group that was not interviewed, patients who did not consent had poorer CPC than patients who consented but were not interviewed.

For all 508 patients, baseline characteristics were similar in treatment and control groups (Table 2). There were 373 patients interviewed at a mean of 123 ± 43 days after the initial event; 10 of these patients did not have sufficient information to define CPC or MRS. Overall, 58% of all patients had good outcomes defined as CPC 1 or 2, and 50% had good outcomes defined as MRS slight disability or better (Table 3). Neurological status, as measured by CPC and MRS, was similar in the treatment and control groups, as seen in Table 3. Overall survival at 1 year was 86%; it was 70% in those without VF and 91% in those with VF. Moreover, 1-year survival was not significantly different in treatment and control groups. In patients with non-VF rhythms, 1-year survival was 74% in the hypothermia group and 66% in the control group (P = 0.43 by log rank statistic), and for VF, it was 92% in the treatment group and 90% in the control group (P = 0.48 by log rank statistic).

As shown in Table 4, neurological status at discharge was strongly associated with long-term outcome. Of those with CPC 1 at discharge, 68% had CPC 1 or 2 at follow-up, and 59% had MRS of slight disability or better. Of 41 patients with CPC 3 or 4 at discharge, only 5% or 12% had CPC 2 at follow-up, and only 2% or 5% had MRS of slight disability or better. A similar pattern of results was true for 1-year survival, as seen in Figure 2. Survival declined with increasing levels of disability; 1-year survival was 92% for CPC 1, 85% for CPC 2, 71% for CPC 3, and only 40% for CPC 4. For those with unknown CPC at discharge, 1-year survival was 64%.

**Discussion**

In this follow-up to a randomized trial of prehospital hypothermia, prehospital hypothermia did not improve neurological status or 1-year survival in 508 trial participants who were discharged alive from the hospital. This result was consistent with findings from the hospital phase of the trial, in which prehospital hypothermia was not associated with survival or neurological status at discharge. Overall 1-year survival was 86%. For all 508 patients, 59% had had good outcomes by CPC or MRS. Among patients who were interviewed, 68% had MRS < 3 or slight disability or better. The finding for MRS was somewhat different from results from the Amsterdam Resuscitation Study, in which 81% had MRS < 3 between 6 and 12 months after cardiac arrest. It was expected that the percentage of survivors with good outcomes would rise over time, because those with poor outcomes are more likely to die, not recover, or not participate in the interview.

Both neurological status at follow-up as well as survival were highly dependent upon neurological function at hospital discharge. Patients who had worse neurological function at discharge were less likely to have good outcomes at follow-up.
discharge. Those with a good outcome at hospital discharge by CPC had much better neurological function and survival at follow-up than those without a good outcome at discharge. Again, this result was expected given that those with poor neurological function at discharge are unlikely to improve owing to devastating brain injury.

Those with good function at hospital discharge did not appear to decline, although the measures of neurological
function were based on self-report and did not include objective measures of function or direct observation of the patient. It is hard to know whether those who declined from CPC 1 at discharge to CPC 2 at follow-up experienced a true decline or whether this was because of limitations of the CPC. Rittenberger et al. believe that the CPC has limitations as a gold standard, because its validity and reliability have not been established. They further conclude that neither the CPC nor MRS provide an adequate picture of the post–cardiac arrest patient. Instead, a more relevant measure for the cardiac arrest populations is needed.6 Such a measure might include questions about quality of life and current physical or mental health.8

Another limitation of the study was that only 73% of survivors were interviewed. There were 86 patients who did not consent and another 49 who consented to the interview, but were not interviewed. Of these 135 individuals, 58 (43%) died in the year after cardiac arrest. Patients in both groups had worse neurological function at discharge than their counterparts who were interviewed. We also relied on Washington State death records to assess the occurrence of death after hospital discharge. These records are unlikely to include Washington State residents who died out of state and would not include nonresidents who suffered cardiac arrest while visiting King County and ultimately died in another state or country.

In conclusion, in this prospective follow-up study to a randomized trial of prehospital hypothermia, neurological function and survival were not associated with randomization assignment. Survival 1 year after hospital discharge was 86% for all patients and was 90% for those with good outcome at hospital discharge by CPC. In addition to excellent survival, patients who had good outcome at

| Table 4. Association Between Discharge Neurological Status and Outcome |
|---------------------------------------------------------------|
| At Follow-up | CPC at Hospital Discharge |
|              | 1 | 2 | 3 | 4 | Unknown |
| CPC (%)      |   |   |   |   |        |
| 1            | 166 (50) | 43 (37) | 0 (0) | 0 (0) | 3 (27) |
| 2            | 61 (18) | 18 (16) | 5 (24) | 0 (0) | 1 (9) |
| 3            | 29 (9) | 17 (15) | 7 (33) | 3 (10) | 0 (0) |
| 4            | 2 (1) | 2 (2) | 1 (5) | 5 (17) | 0 (0) |
| Deceased     | 17 (5) | 15 (13) | 5 (24) | 17 (57) | 4 (36) |
| Not interviewed | 55 (17) | 21 (18) | 3 (14) | 5 (17) | 3 (27) |
| MRS (%)      |   |   |   |   |        |
| No symptoms  | 89 (27) | 19 (16) | 0 (0) | 0 (0) | 1 (9) |
| No significant disability | 37 (11) | 12 (10) | 0 (0) | 0 (0) | 3 (27) |
| Slight disability | 68 (21) | 21 (18) | 2 (10) | 0 (0) | 0 (0) |
| Moderate disability | 53 (16) | 21 (18) | 2 (10) | 0 (0) | 0 (0) |
| Moderately severe disability | 5 (1) | 1 (1) | 0 (0) | 0 (0) | 0 (0) |
| Severe disability | 6 (2) | 6 (5) | 9 (43) | 8 (27) | 0 (0) |
| Deceased     | 17 (5) | 15 (13) | 5 (24) | 17 (57) | 4 (36) |
| Not interviewed | 55 (17) | 21 (18) | 3 (14) | 5 (17) | 3 (27) |
| Total        | 330 | 116 | 21 | 30 | 11 |

CPC indicates Cerebral Performance Category; MRS, Modified Rankin Scale.

Figure 2. One-year survival by CPC at hospital discharge. CPC indicates Cerebral Performance Category.
discharge continued to have good function at least 3 months after the event.

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