Therapeutic hypothermia is independently associated with favourable outcome after resuscitation from out-of-hospital cardiac arrest: a retrospective, observational cohort study
Kerry A Benson-Cooper

ABSTRACT
AIM: To determine the association between use of therapeutic hypothermia (TH) after resuscitation from out-of-hospital cardiac arrest (OHCA) and neurological outcome.

METHOD: Retrospective observational cohort study in a tertiary university-associated Level III general ICU of 179 ICU patients in three cohorts (‘pre’ hypothermia: 58 patients, ‘post’ hypothermia 69 patients, ‘recent’ 52 patients) admitted between 1 January, 2009, and 15 April, 2011, after resuscitation from OHCA. Interventions: TH to 33°C for 12 hours. Main outcome measures: Favourable neurological outcome (transferred home) at hospital discharge.

RESULTS: The frequency of bystander CPR increased (38/58, 56/69, 47/52, p=0.04), as did the use of TH (0/58, 25/69, 39/52, p<0.00001) and the frequency of favourable neurological outcome between the three cohorts (21/58, 28/69, 32/52, p=0.02). The cohorts were similar in age, gender, shockable rhythm and time to ROSC. In multivariate analysis, favourable neurological outcome was independently associated with younger age (in 5-year intervals, OR 0.78 [0.67–0.90], p=0.001), bystander CPR (OR 4.8 [1.5–15], p=0.007), shockable rhythm (OR 3.5 [1.1–11], p=0.04), time to ROSC (OR 0.90 [0.86–0.94], p<0.0005) and use of TH (OR 2.8 [1.2–6.2], p=0.01).

CONCLUSIONS: The use of TH in patients admitted to ICU after resuscitation following OHCA was independently associated with favourable neurological outcome.

In Australasia, out-of-hospital cardiac arrest (OHCA) has a reported annual incidence of 30–148/100,000,1-3 with 29–42% of patients achieving return of spontaneous circulation (ROSC),1,3 but only 8–11%,3,1 surviving to hospital discharge. Outcome is better with cardiac aetiology,4 at a younger age, with bystander CPR, shockable rhythm (VT/VF vs PEA/asystole), and with shorter times to defibrillation and to ROSC.3,4

Post-cardiac arrest admissions constituted 2.4% of 1,001,754 admissions to the ICUs reporting to the ANZICS adult database between 2000 and 2011.3 In patients admitted to ICU, death is predominantly due to hypoxic-ischaemic encephalopathy and usually follows withdrawal of therapy because of severe neurological damage; a few patients become brain dead.4

Two studies published in May, 2002, showed a survival benefit of therapeutic hypothermia (TH) post-ROSC. The European study7 used cooling to 32–34°C within 4 hours of ROSC which was maintained for 24 hours, while the Australian study8 cooled to 33°C within 2 hours of ROSC and maintained this
for 12 hours. Both studies showed improved neurological outcome with TH with absolute increases in favourable CNS outcome of 16% and 23% respectively. A meta-analysis of these trials, and a third smaller trial, showed an NNT of 6 (95%CI 4–13) for TH to produce one additional patient with favourable neurological outcome.

We began using TH in 2002; our protocol involved cooling to 33°C for 12 hours, with opioid, sedation and neuromuscular blockade. These agents were continued during rewarming to 36°C to prevent shivering. Sedative-free clinical assessment commenced after normothermia and advanced supportive treatment was withdrawn in accord with the findings of Levy and the recommendations of the American Academy of Neurology.

In order to establish whether the use of TH was associated with improved neurological outcome at hospital discharge, we reviewed three cohorts of patients admitted between 2000 and 2009.

Methods

We identified, from our prospective ICU database (with ethics committee approval and waived consent), all patients admitted to the ICU who had had a primary OCHA in three cohorts: ‘pre’—58 patients between 1 January 2000 and 16 May 2002 (the first patient treated with TH was on 17 May 2002); ‘post’—69 patients between 17 May 2002 and 31 December 2004; and ‘recent’—52 patients from 1 January 2009 to 15 April 2011. The ICU is a nominal 18-bed (14 ICU, 4 HDU), adult-only, general unit in Auckland City Hospital which provides secondary care to the Auckland District Health Board region (population 476,000 in 2014) as well as extensive tertiary (medical, surgical, oncology, trauma, neuroservices) and national (transplant) services. We obtained demographic data from the ICU database and further information (arrest characteristics, whether TH was given or not, and outcome at hospital discharge) from the clinical notes. Arrest characteristics were bystander CPR (received or not/unknown), first monitored rhythm (shockable (VF/VT) vs non-shockable (all others), and time to ROSC (defined as time of ambulance dispatch to ROSC). The treatment data collected were whether the patient received TH or not. One investigator (KBC) assigned a dichotomised Glasgow Outcome Scale (GOS) outcome at hospital discharge of either favourable (good recovery and moderate disability), or unfavourable (severe disability, persistent vegetative state and dead) from information in the clinical notes. Patients who were discharged home (with either no assistance or some assistance) were assigned to good recovery or moderate disability. Patients who were discharged to any other location (rest homes or private hospitals) were assigned to severe disability (there were no patients in persistent vegetative state). We used Stata® software (StataCorp LP, Texas, US) and Chi-squared to compare categorical variables, and Spearman’s rank correlation to compare age and time to ROSC between the three patient groups. As age, bystander CPR, shockable rhythm and time to ROSC are known predictors of better outcome, we performed univariate and multivariate analysis to determine the influence of these factors, as well as therapeutic hypothermia, on dichotomised GOS. Ethical approval was obtained from the Northern X Regional Ethics Committee on 18 August 2011 (NTX/11/EXP/180).

Results

The demographic characteristics of each of the three cohorts of patients are shown in Table 1, along with the incidence of bystander CPR, shockable first rhythm, time to ROSC and use of therapeutic hypothermia. The cohorts were similar in age, gender, shockable rhythm and time to ROSC. The frequency of bystander CPR increased (38/58, 56/69, 47/52, p=0.04), as did the use of TH (0/58, 25/69, 39/52, p<0.00001) between the three cohorts.

Table 2 shows outcome at hospital discharge for the three cohorts of patients. The frequency of favourable neurological outcome significantly increased between the three cohorts (21/58, 28/69, 32/52, p=0.02).

Table 3 shows the odds ratios for favourable neurological outcome of age, gender, bystander CPR, shockable rhythm, time to ROSC and use of therapeutic hypothermia in a univariate and multivariate analysis. In multivariate analysis, favourable neurological outcome was independently associated with a younger age (in 5-year
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Table 1: Cohort characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>Recent</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>58</td>
<td>69</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39 (67%)</td>
<td>48 (70%)</td>
<td>34 (65%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Median Age–Years (Range)</td>
<td>61 (16–82)</td>
<td>58 (21–82)</td>
<td>60 (20–81)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>38 (66%)</td>
<td>56 (81%)</td>
<td>47 (90%)</td>
<td>p=0.04</td>
</tr>
<tr>
<td>Shockable First Rhythm</td>
<td>46 (80%)</td>
<td>56 (81%)</td>
<td>48 (92%)</td>
<td>p=0.21</td>
</tr>
<tr>
<td>Median Time To Rosc (Mins)</td>
<td>20</td>
<td>18</td>
<td>17</td>
<td>N.S.</td>
</tr>
<tr>
<td>Use Of TH</td>
<td>0</td>
<td>25 (36%)</td>
<td>39 (75%)</td>
<td>P&lt;0.00001 (post vs recent)</td>
</tr>
</tbody>
</table>

Table 2: Outcome at hospital discharge.

<table>
<thead>
<tr>
<th>Dichotomised GOS</th>
<th>Pre</th>
<th>Post</th>
<th>Recent</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfavourable</td>
<td>37</td>
<td>41</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Favourable</td>
<td>21 (36%)</td>
<td>28 (41%)</td>
<td>32 (62%)</td>
<td>p=0.02</td>
</tr>
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</table>

Table 3: Effects of variables on favourable outcome.

<table>
<thead>
<tr>
<th></th>
<th>Univariable</th>
<th>Multivariable Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OOR</td>
<td>95% CI OR p</td>
</tr>
<tr>
<td>Age*</td>
<td>0.81</td>
<td>0.72-0.91 &lt;0.0005</td>
</tr>
<tr>
<td>Male</td>
<td>1.2</td>
<td>0.63-2.3 0.56</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>4.2</td>
<td>1.6-11 0.003</td>
</tr>
<tr>
<td>Shockable Rhythm</td>
<td>3.8</td>
<td>1.4-9.9 0.007</td>
</tr>
<tr>
<td>Time To ROSO</td>
<td>0.91</td>
<td>0.88-0.95 &lt;0.0005</td>
</tr>
<tr>
<td>Use Of TH</td>
<td>3.4</td>
<td>1.8-6.5 &lt;0.0005</td>
</tr>
</tbody>
</table>

* Age difference from median (59.5 years) in increments of 5 years

intervals, OR 0.78 [0.67–0.90], p=0.001), bystander CPR (OR 4.8 [1.5–15], p=0.007), shockable rhythm (OR 3.5 [1.1–11], p=0.04), time to ROSC (OR 0.90 [0.86–0.94], p<0.0005) and use of TH (OR 2.8 [1.2–6.2], p=0.01).

Discussion

The median age of the three cohorts of patients were similar, and similar to the patients in the two sentinel trials of TH, but included a few younger patients. The gender of the patients was similar between the three cohorts and reflected the male predominance found in all studies of OCHA. The time to ROSC was similar between the three cohorts, somewhat longer than in the Australian TH trial8 and shorter than in the European trial. The incidence of shockable rhythm was high, similar between the cohorts, and in keeping with the more recent targeted temperature management (TTM) trial.12

The incidence of bystander CPR was high (~79% overall, with a significant increase between the cohorts), similar to that found in the TTM trial and higher than in the earlier Australian and European trials.

Therapeutic hypothermia was not used prior to the publication of the NEJM trials, and increased between the cohorts.
We decided to confine the use of TH to patients who had been resuscitated from a shockable rhythm, (although 4 patients in the ‘post’ cohort who had non-shockable rhythms were cooled). In the ‘recent’ cohort, 38/48 (79%) patients with shockable rhythms and none with non-shockable rhythms were cooled.

There has been a significant increase in the proportion of patients with a favourable outcome over the three study periods of a similar nature to the original studies. This finding is also consistent with registry data in Australasia, and has also shown a progressive improvement in outcome over the period 2000–2011 for post-arrest patients.

This study confirmed that favourable neurological outcome was not associated with gender, but was more common in younger patients, when there had been bystander CPR and with a shorter time to ROSC. Therapeutic hypothermia was also associated with favourable outcome, including independently by multivariate analysis.

We wrote our TH protocol and treated the first patient in May 2002, three months after the publication of the two sentinel papers. Initially we used TH selectively for patients meeting our protocol, largely out of concern for the development of cardiogenic shock in an elderly comorbid population with a high incidence of myocardial ischaemia. Although heart rate and cardiac index were significantly lower in the hypothermic group in the Australian trial of TH, these haemodynamic consequences did not translate into higher mortality. With experience, our concerns lessened and we increased our use of TH.

We assigned outcome (favourable vs unfavourable) on the basis of review of clinical notes by a single assessor, based on both neurological performance and placement after hospital discharge. Since all patients who were discharged home were assigned good recovery or moderate disability and all patients discharged to other places (or who died in hospital) were assigned to unfavourable outcome and the discharge location was clearly documented and was unalterable by the assessor, there is no possibility of bias in our determination of outcome.

There has been further development of this topic since this study was undertaken. The TTM trial showed that hypothermia (33˚C) did not confer a survival or neurological benefit compared with temperature control at 36˚C in unconscious survivors of OCHA. Although apparently compelling (we are in the process of developing an in-house protocol for TTM, including explicit guidelines for prognostication), we have some reservations about changing from a practice (TH) which, in our experience, is associated with improved outcomes.

We conclude that the use of TH in patients admitted to ICU after resuscitation following OHCA was independently associated with favourable neurological outcome.

Competing interests: Nil
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REFERENCES:


