Mild Hypothermia After Intravenous Thrombolysis in Patients With Acute Stroke: A Randomized Controlled Trial

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Background and Purpose—Hypothermia improves outcome in resuscitated patients and newborns with hypoxic brain injury. We studied the safety and feasibility of mild hypothermia in awake patients with stroke after intravenous thrombolysis.

Methods—Patients were randomized 1:1 to mild hypothermia (35°C) or to standard stroke unit care within 6 hours of symptom onset. Hypothermia was induced with a surface-cooling device and cold saline infusions. Active cooling was restrained gradually after 12 hours at <35.5°C. The primary outcome measure was the number of patients with <36°C body temperature for >80% of the 12-hour cooling period.

Results—We included 36 patients with a median of National Institutes of Health Stroke Scale score of 9 one hour after thrombolysis. Fifteen of 18 (83%) patients achieved the primary end point. Sixteen (89%) patients reached <35.5°C in a median time of 10 hours (range, 7–16 hours) from symptom onset, spent 10.5 hours (1–17 hours) in hypothermia, and were back to normothermia in 23 hours (15–29 hours). Few serious adverse events were more common in the hypothermia group. At 3 months, 7 patients (39%) in both groups had good outcome (modified Ranking Scale, 0–2), whereas poor outcome (modified Ranking Scale, 4–6) was twice as common in the normothermia group (44% versus 22%).

Conclusions—Mild hypothermia with a surface-cooling device in an acute stroke unit is safe and feasible in thrombolized, spontaneously breathing patients with stroke, despite the adverse events.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00987922.

Key Words: hypothermia ■ ischemic stroke ■ thrombolytic therapy

Mild to moderate hypothermia improves neurological outcome in resuscitated cardiac arrest patients and newborns with hypoxic brain damage. In traumatic brain injury, 2 large controlled randomized trials recently found no improvement in outcome even with early-induced hypothermia. Acute stroke, a Cochrane database review including 423 patients with acute stroke from pharmacological and physical cooling studies found no risk reduction of death or dependency (odds ratio, 0.9; 95% confidence interval, 0.6–1.4). In a meta-analysis of experimental stroke, however, even mild hypothermia (35°C) improved outcome when initiated within 3 hours. After 3 prospective observational studies on mild or moderate hypothermia in patients with acute ischemic stroke, 3 randomized controlled hypothermia trials in stroke have been reported. In Cooling for Acute Ischemic Brain Damage (COOL AID) II (n=40) and Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (ICTuS-L) (n=59), an endovascular device was used to cool awake patients with ischemic stroke, 72% to 83% receiving thrombolysis before cooling to 33°C for 12 to 24 hours. COOL AID Oresund (n=31) compared endovascular with surface cooling to 33°C for 24 hours in general anesthesia. Seven patients were randomized to endovascular cooling, 10 patients to surface cooling combined with ice-cold saline, and 14 patients to standard care. Half of the patients (45%) received thrombolysis, and only patients with persisting deficits at 3 hours after thrombolysis were included in the trial. All 3 trials showed therapeutic hypothermia in acute stroke to be feasible and safe, although it was related to some adverse events (AEs). Investigators of COOL AID Oresund concluded that although cooling in the intensive care unit provides better antishivering and temperature control, cooling awake patients with stroke allow monitoring of the neurological status.

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There are limited data on randomized trials on neuroprotective hypothermia in patients with acute ischemic stroke and no data on surface cooling in awake patients. The aim of the present trial was to evaluate the safety and feasibility of mild hypothermia using a surface-cooling device in awake, spontaneously breathing patients with a novel antishivering protocol after intravenous thrombolysis.

**Subjects and Methods**

We performed a single-center academic investigator-initiated randomized controlled open safety and feasibility trial with clinical outcome assessment. The study was approved by the Helsinki University Central Hospital (HUCH) Ethics Committee (211/2006, Dnuo 327/ E9/06) and the regulatory authorities of HUCH.

Between October 2007 and May 2011, patients with ischemic stroke thrombolysed with tissue-type plasminogen activator (tPA) at the HUCH neurological emergency room were screened. Informed consent was asked from patients (or next to kin) who met the inclusion criteria if hypothermia could be initiated within 6 hours from the symptom onset in our stroke unit. We included adult patients (aged, 18–85 years) with moderate to severe neurological symptoms (National Institutes of Health Stroke Scale [NIHSS], 7–20 or NIHSS <7 with >2 points from motor score of a single limb, or >1 points for aphasia) 1 hour after initiation of intravenous thrombolysis. Exclusion criteria were as follows: severe congestive cardiac failure, recent history of unstable angina pectoris or sepsis, intracranial hemorrhage or tumor on computed tomographic (CT) scan, pregnancy, hemodynamic instability, severe thrombocytopenia, pre-existing neurological disability with modified Ranking Scale (mRS) >2, or violation of the in-house guidelines of thrombolytic therapy. After informed consent, patients were randomized according to a computer generated sequence on a 1:1 ratio to either hypothermia or control group using sealed and numbered envelopes.

Perrmanned procedures included medical history and physical examination, noncontrast brain CT, NIHSS, 12-lead ECG, chest radiograph, urinary catheter with intravesical temperature probe, noncontrast brain CT, NIHSS, 12-lead ECG, chest radiograph, and routine blood tests. All patients were treated in the acute stroke unit.

Brain CT was repeated within 24 to 30 hours to detect hemorrhage and edema. ECG (12-lead) was repeated the next morning. Control chest radiograph was not part of the protocol and was only repeated if there was a clinical suspicion of pneumonia or congestive heart failure. Arterial oxygenation (P_{O_2}) and carbon dioxide (P_{CO_2}) were measured every 2 to 6 hours during the first 24 hours. The targeted PaO_{2} was 10 to 14 kPa, supported with oxygen mask when needed. The targeted PaCO_{2} was <6 kPa, unless the patient had chronic obstructive pulmonary disease and the target was the prehypothermia value.

Results of P_{O_2} and P_{CO_2} measurements were temperature corrected. Mean arterial pressure was maintained >80 mm Hg, and decrease in systemic blood pressure was treated primarily with saline infusion and secondarily with phenylephrine infusion. Blood pressure was maintained <185/105 mm Hg during the whole cooling period with labetalol infusion or intravenous enalapril as per the in-house protocol. Antibiotics were used on the clinician’s decision with a clinical suspicion of pneumonia or congestive heart failure. Arterial oxygenation (P_{O_2}) and carbon dioxide (P_{CO_2}) were measured every 2 to 6 hours during the first 24 hours. The targeted PaO_{2} was 10 to 14 kPa, supported with oxygen mask when needed. The targeted PaCO_{2} was <6 kPa, unless the patient had chronic obstructive pulmonary disease and the target was the prehypothermia value.

**Cooling Procedures**

The temperature management system composed of a control module (Criticool, Mennen Medical Group, Israel) and cooling blankets wrapped around the patient’s chest, waist, and limbs. The core temperature was monitored continuously from the bladder. The target temperature of the cooling device was lowered gradually until the core temperature reached 35°C to 35.5°C and then set to 34.5°C. For the induction of hypothermia, 2000 mL of cold saline (4°C–6°C) was infused within 2 hours. Shivering was controlled with a 25-mg bolus of intravenous meperidine, by increasing the dexmedetomidine infusion rate by 0.1 μg/kg per hour and by increasing the target temperature temporarily. Active cooling was restrained gradually after 12 hours (1) from the time point where the core temperature reached 35°C; (2) or from 35.5°C in case 35.0°C was not reached; (3) and always after 18 hours from the stroke onset. The targeted rate of rewarming was 0.2°C/h.

**Adverse Events**

Bradycardia was defined as a heart rate <50 bpm; severe bradycardia as heart rate <40 bpm; tachycardia as heart rate >100 bpm; hypertension as blood pressure >185/105 mm Hg; hypotension as mean arterial pressure <80 mm Hg; not adequately specified infection as any trend of increase in infection parameters from baseline without clinical signs of pneumonia or positive radiograph or any other identified infection focus; and abnormal laboratory results as any deviation from the reference ranges.

**Severe AEs**

Severe AE was defined as an AE that was life-threatening or would otherwise affect the prognosis. Pneumonia was defined as a positive chest radiograph finding or clinical signs, suggesting pneumonia with high C-reactive protein (>80 mg/L) or leukocytosis (>11.0 E9/L); congestive heart failure as a positive finding on the chest radiograph; acute myocardial infarction as an increase in troponin T and chest pain or a new finding on ECG; parenchymal hemorrhage as any blood on a follow-up CT; and brain edema as hypointensive brain region causing mechanical pressure on nearby structures. Hypoxemia was defined as P_{O_2}<10 kPa and hypercapnia >6 kPa on ≥2 measurements.

**Outcome Assessment**

The primary outcome measure of this trial was the percentage of patients whose core temperature remained <36°C for >80% of the 12-hour cooling period. Clinical outcome was evaluated at a 3-month outpatient visit including mRS, Glasgow Outcome Scale, NIHSS, and Barthel Index. The scores were evaluated by a stroke neurologist. Good outcome was defined as mRS=0 to 2 and poor outcome as mRS=4 to 6.

**Statistical Analyses**

All analyses were conducted using the intention-to-treat principle. A 2-sided P value of <0.05 was considered statistically significant. Because of non-normal distributions, continuous variables are reported as medians and interquartile range. Mann–Whitney U and χ^2 tests were used for group comparisons. To test the difference between temperatures among the 2 treatment groups, we used repeated-measure ANOVA. As a post hoc sensitivity analysis, we performed an ordinal logistic regression shift analysis on the whole mRS distribution across the treatment groups, both without adjustment for baseline characteristics and then adjusted for age and post-tPA NIHSS. These models were concordant with the proportional odds assumption.
Results
Between October 2007 and May 2011, 992 patients were treated with intravenous tPA at the neurological emergency of HUCH. The most common reasons for exclusion from the study were too mild or severe clinical symptoms at 1 hour from tPA (54%). Other reasons were thrombolysis beyond the time window (7%), age >85 years (5%), or medical reasons such as severe congestive heart failure, thrombocytopenia, or uncontrolled hypertension (16%). We included and randomized 36 patients (4%).

Baseline characteristics of the groups were similar except for higher rates of atrial fibrillation and systolic blood pressure in the hypothermia group (Table 1). One patient in the hypothermia group was treated additionally with thrombectomy after intravenous thrombolysis.

In the hypothermia group, the median dose of dexmedetomidine was 0.39 (interquartile range, 0.29–0.52) μg/kg per hour, meperidine 7.0 (6.0–14.0) mg/h, and buspirone 35 (17–60) mg/d. One patient in the hypothermia group had a constant infusion 22.5 mg/h of meperidine because of uncontrolled shivering. Only 1 patient in the control group received meperidine 6 mg/h for shivering during the first 24 hours. Hypothermia patients received more intravenous fluids during the first 24 hours (2.5 [interquartile range, 2.1–2.7] versus 2.0 [1.7–2.5] mL/kg per hour; \( P = 0.032 \)).

Outcome: Feasibility
In the hypothermia group, 15 of 18 patients reached the primary outcome. The median time from symptom onset to initiation of hypothermia (n=18) was 6 hours (range, 4.5–6.5). Sixteen patients of the hypothermia group reached <35.5°C in a median time of 4.5 hours (3–11), spent 10.5 hours (1–17) at 34.5°C to 35.5°C, and 16.8 hours (3–21) at <36.0°C. Patients were rewarmed by increasing the target temperature for duration of 7 hours (2–9). The median time from the initiation of hypothermia back to normothermia was 23 hours (15–29; Figure 1). Of the 3 patients who did not reach the primary outcome, the first one had severe sleep apnea, and cooling was ceased within 1 hour from the randomization. The second patient did not cool <36°C, despite maximal dosing of medication and no shivering. A malfunction of the cooling device was suspected; however, no technical fault was identified. The third patient had uncontrolled shivering, which resolved only with constant meperidine infusion. This patient reached <36°C at 9 hours and <35.5°C at 11 hours.

Outcome: Safety
AEs were more common in the hypothermia group (Table 2). Most of them were not clinically important, such as bradycardia, mild hypo- or hypertension, shivering, or mild electrolytic disturbances.

There were 19 and 12 severe AEs in the hypothermia and the control group, respectively (pneumonia, congestive heart failure, atrial fibrillation, acute myocardial infarction, symptomatic hemorrhage, symptomatic brain edema, and hemicraniectomy). Furthermore, 8 patients in the hypothermia group were hypoxicemic at some point of the treatment: 5 related to pneumonia and 3 to congestive heart failure. Seven patients had hypercapnia; of which, 5 were related to pneumonia, 1 to heart failure, and 1 to sedation because of meperidine, resolved when the meperidine was halted for a few hours. One patient in the hypothermia group had an acute non–ST-segment–elevation myocardial infarction with elevated creatinine kinase myocardial band and cardiospecific troponin T. In the control group, 1 patient died of massive middle cerebral

Table 1. Baseline Characteristics in Mild Hypothermia Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Hypothermia (n=18)</th>
<th>Control (n=18)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>68 (60–74)</td>
<td>70 (62–74)</td>
<td>66 (55–71)</td>
<td>0.226</td>
</tr>
<tr>
<td><strong>Sex, male</strong></td>
<td>20 (56)</td>
<td>12 (67)</td>
<td>8 (44)</td>
<td>0.180</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (61)</td>
<td>12 (67)</td>
<td>10 (56)</td>
<td>0.494</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (28)</td>
<td>5 (28)</td>
<td>5 (28)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>20 (56)</td>
<td>10 (56)</td>
<td>10 (56)</td>
<td>1.000</td>
</tr>
<tr>
<td>CHD</td>
<td>15 (42)</td>
<td>8 (44)</td>
<td>7 (39)</td>
<td>0.735</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>16 (44)</td>
<td>11 (61)</td>
<td>5 (28)</td>
<td>0.044*</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>9 (25)</td>
<td>7 (39)</td>
<td>2 (11)</td>
<td>0.054</td>
</tr>
<tr>
<td>PAD</td>
<td>1 (2.8)</td>
<td>1 (5.6)</td>
<td>0</td>
<td>0.310</td>
</tr>
<tr>
<td>Smoking</td>
<td>15 (42)</td>
<td>8 (44)</td>
<td>7 (39)</td>
<td>0.735</td>
</tr>
<tr>
<td><strong>Stroke severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS before tPA</td>
<td>12 (8–18)</td>
<td>11 (8–17)</td>
<td>14 (6–18)</td>
<td>0.696</td>
</tr>
<tr>
<td>NIHSS 1h after tPA</td>
<td>9 (7–14)</td>
<td>9 (7–12)</td>
<td>11 (6–16)</td>
<td>0.696</td>
</tr>
<tr>
<td>Symptoms to tPA, min</td>
<td>107 (74–140)</td>
<td>118 (86–148)</td>
<td>92 (67–138)</td>
<td>0.214</td>
</tr>
<tr>
<td>Temperature baseline, °C</td>
<td>36.8 (36.5–37.3)</td>
<td>36.8 (36.6–37.3)</td>
<td>36.7 (36.3–37.2)</td>
<td>0.181</td>
</tr>
<tr>
<td>BP systolic, mmHg</td>
<td>147 (131–177)</td>
<td>163 (139–177)</td>
<td>135 (124–151)</td>
<td>0.024*</td>
</tr>
<tr>
<td>BP diastolic, mmHg</td>
<td>86 (72–99)</td>
<td>88 (73–100)</td>
<td>80 (68–95)</td>
<td>0.252</td>
</tr>
</tbody>
</table>

All values are median (interquartile range) or n (%). BP indicates blood pressure; CHD, coronary heart disease; NIHSS, National Institutes of Health Stroke Scale; PAD, peripheral artery disease; and tPA, tissue-type plasminogen activator.

* \( P < 0.05 \).
artery infarction, 1 of massive intracranial hemorrhage, and in 1 case, a hemicraniectomy was performed.

Seventeen patients in the hypothermia group (7 pneumonias, 2 diarrheas, sinusitis, urinary tract infection, temporal arteritis, and undefined infection) and 7 patients in the control group (2 pneumonias, 3 undefined infection, upper tract infection, and hemicraniectomy) were treated with antibiotics for median of 7 and 4 days, respectively.

There were no differences between the 2 groups in brain edema formation or hemorrhagic transformation on follow-up CTs. None of the patients required intubation. One patient in the control group needed phenylephrine infusion to maintain the mean arterial pressure >80 mmHg. There were no clinically important differences in blood test results before thrombolysis or at 12 to 24 hours between the 2 groups (online-only Data Supplement).

**Clinical Outcome**

There were no differences in favorable outcome defined as mRS=0 to 2 (Figure 2) or Glasgow Outcome Scale=4 to 5 (P=0.298) between the groups at 3 months. Poor outcome (mRS=4–6) was twice as common in the normothermia group (P=0.157). The median NIHSS (2 [1–4] versus 4 [1–11]; P=0.276) and Barthel Index (100 [75–100] versus 97 [63–100]; P=0.958) in the hypothermia and the control group were similar. Comparing the whole mRS distributions simultaneously with the shift analysis did not demonstrate a significant difference between the groups (odds ratio, 1.62 [95% confidence interval, 0.51–5.20] for a better outcome with hypothermia; P=0.41). The shift analysis after adjustment for age and NIHSS produced a similar result (odds ratio, 1.48 [0.44–4.95]; P=0.53). Based on this, a 1:1 trial of 564 patients would have 90% power to detect a statistically significant difference at 2-tailed P=0.05 using ordinal logistic regression; however, the proportional odds assumption would be violated with that sample size and our mRS distribution (P<0.001).

**Discussion**

Our study is the first randomized controlled trial to cool thrombolysed, spontaneously breathing patients with stroke to mild hypothermia with a surface-cooling device. In the 2 previous randomized controlled trials on awake patients with stroke, achieving the target temperature was faster with an endovascular cooling device, being only 77 minutes to 33°C in the COOL AID II and 67 minutes to 33°C to 34.7°C in the ICTuS-L compared with 4.5 hours in our study. Furthermore, we had a patient who failed to cool despite maximal sedative medication; this patient was young (26 years) and obese (body mass index >30), and it is possible that the surface-cooling device was not effective enough.

The rate of few AEs were lower in our trial using mild hypothermia compared with previous hypothermia studies using moderate hypothermia.12–14 The mortality rate of the hypothermia group was 0% in our trial, 28% in the COOL AID II, 21% in the ICTuS-L, and 12% in the COOLAID Oresund trial, but there were some differences in stroke severity (pretreatment mean NIHSS being 12, 15, 14, and 8 [median], respectively). Our pneumonia rate (39%) is comparable with that of the ICTuS-L (50%) and

![Figure 1. Box plot of body temperatures within 24 hours of hypothermia induction. Blue bars represent hypothermia (n=18) and orange bars, control patients (n=18).](http://stroke.ahajournals.org/content/pdf/489)
Stroke February 2014

COOLAID Oresund (33%) but higher than in the COOL AID II trial (11%). Congestive heart failure was more common in our study (38%) than in the COOL AID II study (11%). There were no device-related complications in our study except for shivering. Shivering is the most challenging problem when using the surface-cooling device in awake patients. We used triple medication; namely, dexmedetomidine, meperidine, and buspirone. The first 2 have been reported to reduce the shivering threshold additively to 34.7°C and the latter 2 synergistically to 33.4°C with a single buspirone dose.16,17 Dexmedetomidine is a highly selective α2-adrenoreceptor agonist and has a strong sedative effect without respiratory depression. Sedation with dexmedetomidine improved the patients’ ability to communicate with nursing staff when compared with standard sedation.18 Bradycardia is a typical side effect of both dexmedetomidine and hypothermia. Although we aimed for the maximum rate of dexmedetomidine infusion (0.7 μg/kg per hour at that time, raised since to 1.4 μg/kg per hour), we only achieved the rate of 0.39 μg/kg per hour. Despite severe bradycardia (pulse <40 bpm), hemodynamics remained stable in all patients.

Compared with ICTuS-L and the COOL AID trials, we used smaller doses of buspirone (both 60 versus 35 mg/d) and meperidine (14.5 and 12.2 versus 2.3 mg/kg) and dexmedetomidine as a novelty drug. The total meperidine doses are not strictly comparable because the cooling time was longer and the target temperatures lower compared with ours. The ICTuS-L trial investigators concluded that meperidine caused sedation and therefore increased NIHSS at baseline from 14 to 17 at 24 hours. In our study, the median NIHSS was 11 before treatment and 9 at 24 hours, and we did not observe sedation. Neither did any of our hypothermia patients need intubation, whereas in the COOL AID II trial, 3 patients needed to be intubated during the first 72 hours.

Rapidly infused cold saline (25 mL/kg within 45 minutes) for the induction of hypothermia in acute ischemic stroke did not increase the rate of congestive heart failure, although it did decrease the ejection fraction in some patients.19 In our study, some hypothermia patients with mild congestive heart failure at baseline worsened even when the dose of cold saline infusion was decreased (1000 mL within 2 hours) and intravenous diuretics were used. Hypothermia patients received more intravenous fluids within the first 24 hours, which may have increased the rate and severity of the heart failure.

Of the consecutive thrombolyzed patients at the emergency room of HUCH arriving between 8 AM and 8 PM, 18% were eligible for the study. As 1 investigator recruited all patients, 24/7 recruiting was not possible. Some patients were also missed because of shortage of beds or staff in the stroke unit. Our trial inclusion and exclusion criteria only apply to a small proportion of patients with stroke; however, also recruiting patients with contraindications to thrombolysis, that is, patients arriving between 4.5 and 6 hours from stroke onset, being recently operated, or using anticoagulants, would make the hypothermia treatment available for a larger stroke population.

Our study has limitations. The core temperature was measured from the urinary bladder, which often underestimates...
the brain temperature.\textsuperscript{22} Shivering assessment was not accurate because we did not use a validated scale. The 3-month outcome was not assessed blinded. We did not evaluate the effect of hypothermia on recanalization rates; however, the enzymatic activity of alteplase does not differ in temperatures from 35.5°C to 37.5°C.\textsuperscript{23} Because of the short half-life, it hardly has any thrombolytic effect when the target temperature is reached.

Conclusions

Mild hypothermia for a short duration, small doses of antishivering medication, and tight monitoring of spontaneously breathing patients according to the study protocol cause few serious AEs, such as infections, assumed to be related to intubation, moderate hypothermia or high doses of sedative medication in earlier trials. The rate and severity of AEs were acceptable compared with the normothermia group, and the neurological outcome at 3 months did not differ between the treatment arms. In future studies, prophylactic antibiotics could be considered. Chest radiographs during the first few days to diagnose congestive heart failure and arterial lines with repeated samples to diagnose hypoxemia or hypercapnia should be performed routinely. For patients with severe bradycardia, even mild congestive heart failure, myocardial infarction, or atrial fibrillation, reduced intravenous fluids and high doses of intravenous diuretics should also be considered. The most important observation of the present study is that mild hypothermia in awake patients with stroke with our antishivering protocol proved to be feasible when executed in an acute stroke unit. This makes the treatment feasible for larger stroke population if shown to be effective in large randomized controlled trials. Moderate hypothermia requires intensive unit care, and not even developed countries have enough resources to treat patients with stroke in an intensive care unit. Our results encourage to continue the ongoing European Union grant supported phase III European Stroke Research Network for Hypothermia (EuroHYP)-1 trial, which has similar cooling protocol compared with ours except for the length of cooling (24 hours) and the medication protocol.\textsuperscript{24} Based on our feasibility results, we suggest combining dexmedetomidine to the protocol to avoid excessive sedation.

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Disclosures

M. Kaste’s travel expenses have been covered, and he received honoraria for attending the Steering Committee meetings of DIAS 3/4 trial of H. Lundbeck A/S and serving as a speaker of the Siemens AG Symposium at the ESC 2013. The other authors report no conflicts.

References

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### Supplemental Table I. Baseline and early follow-up laboratory values of patients in the hypothermia and control groups

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia</th>
<th>Control</th>
<th>P Value</th>
<th>Hypothermia</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/L</td>
<td>142 (132-154)</td>
<td>145 (134-151)</td>
<td>0.743</td>
<td>135 (129-145)</td>
<td>128 (122-137)</td>
<td>0.037</td>
</tr>
<tr>
<td>Leukocytes, E9/L</td>
<td>8.7 (6.5-10.3)</td>
<td>6.8 (6.3-8.4)</td>
<td>0.152</td>
<td>11.2 (6.2-12.4)</td>
<td>8.0 (6.7-10.1)</td>
<td>0.143</td>
</tr>
<tr>
<td>Platelets, E9/L</td>
<td>225 (170-273)</td>
<td>220 (179-246)</td>
<td>0.542</td>
<td>204 (159-253)</td>
<td>202 (166-240)</td>
<td>0.938</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>5 (3-25)</td>
<td>3 (3-3)</td>
<td>0.091</td>
<td>9 (3-50)</td>
<td>5 (3-14)</td>
<td>0.104</td>
</tr>
<tr>
<td>Creatinine, µmol/L</td>
<td>84 (74-100)</td>
<td>71 (65-85)</td>
<td>0.034</td>
<td>65 (51-73)</td>
<td>62 (52-78)</td>
<td>0.839</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>7.2 (6.2-8.9)</td>
<td>6.8 (5.9-7.7)</td>
<td>0.293</td>
<td>6.3 (5.8-7.3)</td>
<td>6.4 (5.4-7.2)</td>
<td>0.888</td>
</tr>
<tr>
<td>INR</td>
<td>1.0 (0.9-1.1)</td>
<td>1.0 (0.9-1.1)</td>
<td>0.563</td>
<td>1.1 (1.0-1.2)</td>
<td>1.1 (1.0-1.2)</td>
<td>0.938</td>
</tr>
<tr>
<td>APTT, s</td>
<td>26 (24-29)</td>
<td>25 (24-26)</td>
<td>0.481</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ALAT, U/L</td>
<td>25 (15-32)</td>
<td>16 (12-38)</td>
<td>0.652</td>
<td>21 (14-26)</td>
<td>21 (11-35)</td>
<td>0.650</td>
</tr>
<tr>
<td>TnT, ng/L</td>
<td>0.03 (0.03-0.03)</td>
<td>0.03 (0.03-0.03)</td>
<td>1.000</td>
<td>0.03 (0.03-0.03)</td>
<td>0.03 (0.03-0.03)</td>
<td>0.791</td>
</tr>
<tr>
<td>CK, U/L</td>
<td>86 (54-125)</td>
<td>93 (71-185)</td>
<td>0.355</td>
<td>142 (74-194)</td>
<td>87 (55-191)</td>
<td>0.389</td>
</tr>
<tr>
<td>Na, mmol/L</td>
<td>139 (137-141)</td>
<td>142 (138-142)</td>
<td>0.055</td>
<td>139 (136-142)</td>
<td>139 (138-141)</td>
<td>0.767</td>
</tr>
<tr>
<td>K, mmol/L</td>
<td>4.1 (3.8-5.4)</td>
<td>4.0 (3.7-4.1)</td>
<td>0.074</td>
<td>3.9 (3.5-4.3)</td>
<td>3.8 (3.5-4.3)</td>
<td>0.279</td>
</tr>
<tr>
<td>Ca-ion-a, mmol/L</td>
<td>1.24 (1.20-1.26)</td>
<td>1.22 (1.16-1.26)</td>
<td>0.382</td>
<td>1.19 (1.14-1.20)</td>
<td>1.18 (1.15-1.24)</td>
<td>0.743</td>
</tr>
<tr>
<td>Cl, mmol/L</td>
<td>106 (105-108)</td>
<td>107 (106-108)</td>
<td>0.375</td>
<td>107 (103-110)</td>
<td>106 (104-109)</td>
<td>0.829</td>
</tr>
<tr>
<td>Mg, mmol/L</td>
<td>0.73 (0.67-0.82)</td>
<td>0.80 (0.74-0.86)</td>
<td>0.051</td>
<td>0.73 (0.64-0.83)</td>
<td>0.78 (0.75-0.83)</td>
<td>0.404</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>6 (2-13)</td>
<td>-</td>
<td>-</td>
<td>9 (5-20)</td>
<td>-</td>
<td>0.161</td>
</tr>
<tr>
<td>TSH, mU/L</td>
<td>1.7 (1.0-2.8)</td>
<td>1.4 (0.8-2.2)</td>
<td>0.203</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pi, mmol/L</td>
<td>1.04 (1.0-1.24)</td>
<td>0.99 (0.83-1.02)</td>
<td>0.029</td>
<td>0.96 (0.87-1.15)</td>
<td>0.80 (0.68-1.03)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

All values are median (interquartile range) or n (%). CRP indicates C-reactive protein; INR, International Normalized Ratio; APTT, Activated Partial Thromboplastin Time; ALAT, Alanin Transaminase; ASAT, Aspartate Aminase; TnT, Cardiospesific Troponin T; CK, Creatinin Kinase; ESR, Erythrocyte Sedimentation Rate; TSH, Thyroid Stimulating Hormone.