Ice-Cold Saline for the Induction of Mild Hypothermia in Patients With Acute Ischemic Stroke

A Pilot Study

Rainer Kollmar, MD; Peter D. Schellinger, MD, PhD; Tobias Steigleder, MD; Martin Köhrmann, MD; Stefan Schwab, MD, PhD

Background and Purpose—Neuroprotective effects of induced hypothermia depend on its time point of initiation after acute brain injury. Preliminary studies in cardiac arrest patients indicate that rapid infusion of ice cold saline (ICS) is safe and effective for induction of hypothermia. We investigated its use in patients with acute ischemic stroke (AIS).

Methods—Patients (n = 10) with AIS were included within 3 hours after symptom onset. After cranial CT, they were treated—if indicated—with rt-PA. ICS of 4°C (25 mL/kg body weight) was administered via peripheral intravenous lines. Patients received buspirone/pethidine to prevent and treat shivering. After infusion of the target volume of ICS, no further efforts were made to maintain hypothermia by other methods.

Results—Ten patients with a median National Institutes of Health Stroke Scale (NIHSS) score of 5.5 (range 4 to 12) on admission were included into the study. NIHSS score improved significantly from a median of 1 (range 1 to 15) at discharge compared to admission (P < 0.02). Tympanic temperature dropped significantly by a maximum of 1.6 ± 0.3°C (P < 0.005) at 52 ± 16 minutes after ICS was started. The procedure was well tolerated. The NIHSS score improved significantly to a median of 1 (range 1 to 15) at discharge compared to admission (P < 0.02).

Conclusions—This pilot study suggests that rapid ICS infusions in combination with pethidine and buspirone lower the body temperature significantly without major side effects.

Key Words: acute care ■ acute stroke ■ brain infarction ■ brain ischemia ■ critical care ■ edema ■ brain embolic stroke ■ emergency medicine ■ hypothermia ■ ICU ■ neuroprotectants ■ neuroprotection ■ neuroprotective agents ■ stroke care ■ thrombolysis

Hypothermia is a powerful neuroprotective method and improved neurological outcome after cardiac arrest. So far, clinical studies on hypothermia and stroke are limited to safety and feasibility. A plausible explanation for this lack of efficacy might be the delayed induction of hypothermia in clinical stroke trials targeting neuroprotection. Recent studies in cardiac arrest patients suggest that ice-cold saline (ICS) infusions represent a fast and safe approach for induction of hypothermia. Therefore, we investigated the effects of ICS for induction of hypothermia in awake patients with acute ischemic stroke. The goal of the study was not achieving or maintaining a specific target temperature, but observing potential temperature changes when ICS is infused.

Methods

After clinical examination, a cranial CT followed by thrombolysis—if indicated—was performed. Cooling was initiated by rapid free floating infusion of ICS (25 mL/kg body weight) via two peripheral venous catheters. The dose was adapted from previous clinical studies. Pethidine was given at 30 mg/h intravenously and buspirone orally once 30 mg to prevent shivering. A surface warming blanket was applied. Patients were monitored for shivering using a 4-point scale: 0, no shivering evident; 1, isolated facial or masticatory fasciculation; 2, peripheral shivering; 3, uncontrolled rigor. In case of shivering, a 10-mg bolus of pethidine followed by an increase of the pethidine drip rate by 5 mg/h was given. Tympanic temperature was measured every 15 minutes. We used tympanic measurement instead of urinary bladder or esophageal measurements to avoid side effects attributable to rt-PA treatment.

Measurements

Primary outcome measures included the tympanic temperature, shivering scores, and vital signs. Blood samples were taken on admission, after 6 to 12 hours, and after 24 hours. Routine transthoracic echocardiography was analyzed for ejection fraction of the left ventricle on day one after symptom onset.

Data Analysis

National Institutes of Health Stroke Scale (NIHSS) scores given as median and range were analyzed by the Wilcoxon signed rank test.

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NIHSS scores on admission were compared to NIHSS score after 24 hours and at discharge. All other data are summarized as means and standard deviation (means ± SD). Physiological data were tested for significance by repeated measures ANOVA. We tested for sphericity with Mauchly test, and as applicable used the Greenhouse-Geisser or Huynh-Feldt correction. The level of significance was set at P = 0.05. For parameters that yielded significant results, we used a simple contrast (relative to the first baseline value) for post-hoc analyses with Bonferroni correction for multiple testing. Tympanic temperature and other physiological parameters on admission were compared to subsequent results at 15 up to 240 minutes after ICS infusion start.

Results

Ten patients (mean age of 66.5 ± 12.5 years) were included into this pilot study. Nine received standard intravenous rt-PA treatment.

The follow-up CT on day one showed signs of an ischemic stroke in 8 patients (n=8). Rt-PA infusion started 104 ± 25 minutes after symptom onset. Pethidine, buspirone, and ICS infusions were given 123 ± 20 minutes after symptom onset and 17 ± 11 minutes after rt-PA treatment was started. The patients received 2163 ± 256 mL of ICS within an average time of 35.6 ± 11.5 minutes.

The temperature decreased from a mean of 37.1 ± 0.7°C by a maximum of 1.6 ± 0.3°C (P < 0.005, paired t-test). The deepest measured temperature was reached 52 ± 16 minutes after ICS infusion start and was 35.4 ± 0.7°C. Temperatures differed significantly at the 10 measured time points (P < 0.001). All temperatures differed significantly from the baseline value (all P < 0.001 except T 210 minutes P = 0.042).

ICS infusions did not affect any of the recorded parameters, including the investigated blood samples (Table 1), with the exception of the tympanic temperature (Table 2, Figure).

Shivering as indicated by a score of 1 appeared in only 2 patients during the first 30 minutes after ICS administration and was effectively treated by pethidine. None of the patients indicated any discomfort during the follow-up period.

Median NIHSS score was 5.5 (range 4 to 12) on admission and improved to 3 (range 1 to 13) after 24 hours (P = 0.07, nonsignificant). Patients were discharged at 4.5 ± 1.5 days after symptom onset. The median NIHSS score at discharge of 1 (range 1 to 15) was significantly lower compared to admission (P < 0.02, Wilcoxon signed rank test).

Routine echocardiograph examination showed an ejection fraction (EF) of ≤ 50% in 4 patients. One patient had an ejection fraction of 20% only. Four patients showed atrial fibrillation on ECG.

Discussion

This is the first report on the effects of rapid ICS infusions in patients with acute ischemic stroke. ICS infusions induced hypothermia fast and without major side effects, and might therefore be useful to deliver hypothermia within a neuroprotective treatment window in stroke.
Vital signs and clinical status of our patients did not indicate fluid load related side effects of ICS even in patients with decreased ejection fraction in echocardiography. These observations are concordant with recent investigations after cardiac arrest,\(^3\) in which transthoracic echocardiography before fluid administration and 1 hour after completion of the 2l ICS infusion did not show significant differences between the 2 time points.\(^3\)

Shivering as a major side effect of hypothermia was treated successfully by a combination of pethidine and buspirone, which are known to decrease the shivering threshold.\(^5\) This procedure was well tolerated in our patient subgroup.

Our results show that induction of mild hypothermia is feasible already during thrombolysis in awake stroke patients. Only Kammersgaard et al induced hypothermia as fast as in our investigation.\(^6\) However, the mean body temperature of 36.8°C dropped significantly only to 36.5°C after 1 hour. The lowest mean body temperature was achieved after 6 hours (35.5°C).

Certainly, this study has limitations. We report the results of a small uncontrolled case series, and therefore results should be taken with caution. The observations of this study are, however, very important for future studies in which rapid induction of hypothermia potentially followed by prolonged hypothermia can be compared to standard treatment in terms of safety and feasibility.

In conclusion, rapid ICS infusions are a simple and effective way for induction of mild to moderate hypothermia in the very early phase of stroke treatment. Further studies are needed to investigate the safety and feasibility of ICS infusions in stroke patients and patients with hemorrhagic stroke. If this is the case, ICS infusion might be considered as an initial treatment in the ambulance car.

### Disclosures

None

### References


### Table 2. Effects of ICS on Temperature and Vital Signs Are Shown

<table>
<thead>
<tr>
<th>Before Start of Infusions</th>
<th>30 Minutes</th>
<th>60 Minutes</th>
<th>90 Minutes</th>
<th>120 Minutes</th>
<th>180 Minutes</th>
<th>240 Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body temperature, °C</td>
<td>37.1±0.7</td>
<td>363±0.9</td>
<td>353±3.8</td>
<td>35.710.8</td>
<td>35.9±0.6</td>
<td>36.110.6</td>
</tr>
<tr>
<td>Difference in body</td>
<td>0</td>
<td>0.8±105</td>
<td>1.4±02</td>
<td>1.3104</td>
<td>1.1104</td>
<td>0.8±0.3</td>
</tr>
<tr>
<td>temperature, °C</td>
<td></td>
<td>(P=0.001)</td>
<td>(P=0.001)</td>
<td>(P=0.001)</td>
<td>(P=0.001)</td>
<td>(P=0.001)</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>117±20</td>
<td>109*20</td>
<td>100*23</td>
<td>104±19</td>
<td>106±17</td>
<td>106±17</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>88±24</td>
<td>95*23</td>
<td>78±22</td>
<td>76±20</td>
<td>80±16</td>
<td>71±17</td>
</tr>
<tr>
<td>Respiration rate, per min</td>
<td>20±15</td>
<td>25±8</td>
<td>20±4</td>
<td>19±4</td>
<td>21*3</td>
<td>19±5</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>99±1</td>
<td>99±1</td>
<td>99±1</td>
<td>99±1</td>
<td>99±1</td>
<td>99±1</td>
</tr>
</tbody>
</table>

All values are given in means±SD. Significant differences for temperature after induction of hypothermia compared to the baseline values are given (1-way repeated-measures ANOVA). The other listed parameters were not significantly different compared to the baseline.

**Figure.** Temperature change is shown over 240 minutes after start of ICS infusion in box-plots with medians and interquartile ranges. Significant differences compared to the baseline values are given (1-way repeated-measures ANOVA): *P=0.001; §P=0.042.**
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