Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (ICTuS-L)

Final Results

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Background and Purpose—Induced hypothermia is a promising neuroprotective therapy. We studied the feasibility and safety of hypothermia and thrombolysis after acute ischemic stroke.

Methods—Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (ICTuS-L) was a randomized, multicenter trial of hypothermia and intravenous tissue plasminogen activator in patients treated within 6 hours after ischemic stroke. Enrollment was stratified to the treatment time windows 0 to 3 and 3 to 6 hours. Patients presenting within 3 hours of symptom onset received standard dose intravenous alteplase and were randomized to undergo 24 hours of endovascular cooling to 33°C followed by 12 hours of controlled rewarming or normothermia treatment. Patients presenting between 3 and 6 hours were randomized twice: to receive tissue plasminogen activator or not and to receive hypothermia or not.

Results—In total, 59 patients were enrolled. One patient was enrolled but not treated when pneumonia was discovered just before treatment. All 44 patients enrolled within 3 hours and 4 of 14 patients enrolled between 3 to 6 hours received tissue plasminogen activator. Overall, 28 patients randomized to receive hypothermia (HY) and 30 to normothermia (NT). Baseline demographics and risk factors were similar between groups. Mean age was 65.5±12.1 years and baseline National Institutes of Health Stroke Scale score was 14.0±5.0; 32 (55%) were male. Cooling was achieved in all patients except 2 in whom there were technical difficulties. The median time to target temperature after catheter placement was 67 minutes (Quartile 1 57.3 to Quartile 3 99.4). At 3 months, 18% of patients treated with hypothermia had a modified Rankin Scale score of 0 or 1 versus 24% in the normothermia groups (nonsignificant). Symptomatic intracranial hemorrhage occurred in 4 patients (68); all were treated with tissue plasminogen activator <3 hours (1 received hypothermia). Six patients in the hypothermia and 5 in the normothermia groups died within 90 days (nonsignificant). Pneumonia occurred in 14 patients in the hypothermia and in 3 of the normothermia groups (P=0.001). The pneumonia rate did not significantly adversely affect 3 month modified Rankin Scale score (P=0.32).

Conclusion—This study demonstrates the feasibility and preliminary safety of combining endovascular hypothermia after stroke with intravenous thrombolysis. Pneumonia was more frequent after hypothermia, but further studies are needed to determine its effect on patient outcome and whether it can be prevented. A definitive efficacy trial is necessary to evaluate the efficacy of therapeutic hypothermia for acute stroke. (Stroke. 2010;41:2265-2270.)

Key Words: hypothermia ■ ischemic stroke ■ neuroprotection ■ thrombolysis

Based on experimental data and early human experience, hypothermia is 1 of the most active modes of neuroprotection.1,2 Hypothermia improves survival and neurological outcome after cardiac arrest3,4 and its use in this setting is recommended by the International Liaison Committee on Resuscitation.5 In infants with hypoxic–ischemic encephalopathy, hypothermia at 33.5°C for 72 hours is safe, reduces mortality, and improves neurodevelopmental outcome.6 Other researchers have used surface cooling methods to reduce brain edema and treat increased intracranial pressure after stroke.7

The Cooling for Acute Ischemic Brain Damage (COOL-AID) study group completed 2 clinical trials of hypothermia in acute ischemic stroke. The first study used surface cooling8 and the second endovascular cooling.9 Both trials demonstrated feasibility but were not powered to answer questions.
regarding safety and efficacy. Side effects of endovascular hypothermia have been pneumonia, cardiac arrhythmia, and deep vein thrombosis.9

Only few patients have been treated with hypothermia <35°C while awake.10,11 Other than small uncontrolled case series, no prior study has confirmed the safety of combining intravascular cooling catheters with thrombolytic therapy for acute stroke.

We sought to determine feasibility and safety of endovascular hypothermia in patients receiving thrombolytic therapy in a randomized, controlled study of endovascular cooling in awake patients after stroke, the Intravascular Cooling in the Treatment of Stroke–Longer tPA window (ICTuS-L) study.12

Materials and Methods

The ICTuS-L trial was a controlled, prospective, randomized trial designed to investigate the feasibility and safety of induced endovascular hypothermia with thrombolysis in patients presenting with acute ischemic stroke <6 hours from onset, age 18 to 80 years, a National Institutes of Health Stroke Scale (NIHSS) score ≥7, and a score of 0 or 1 on NIHSS Item 1a (arousal) at the time of cooling catheter placement. The Institutional Review Boards of the participating centers approved this protocol. All patients or their surrogates gave written informed consent. Enrollment was stratified to the stroke severity. The primary feasibility outcome was the incidence of serious adverse events at 3 months. The primary safety outcome was the incidence of serious adverse events, adverse events, hemorrhages, deaths and 90-day mRS between the HY and NT groups. The Wilcoxon rank sum test was used for the NIHSS comparisons. All statistical analyses were conducted using the statistical software R Version 2.10.1 (www.r-project.org/).

Results

Fifty-nine patients were randomized but 1 patient was found to have pneumonia before receiving any study procedures and was excluded, leaving 58 patients for the intention-to-treat analysis. Cooling was performed in 28 of 58 patients (48.2%); in 22 of the 28 (78.6%), tPA was begun within 3 hours from stroke onset and in 2 patients between 3 and 6 hours (Groups 5 and 6). Four patients in the 3- to 6-hour window underwent cooling alone (Table 1).

The mean (±SE) age was 65 ±14 years with a range from 21 to 81 years. Patients treated with HY were older, 68.93 ±87 years, compared with NT patients, 62.30 ±14.48 years (nonsignificant); 55% were men. Several risk factors were reported by at least 50% of the patients, including hypertension and hyperlipidemia. Between 25% and 50% of the patients reported coronary disease, atrial fibrillation, or myocardial infarction. The prestroke mRS was >1 in 4 HY-treated and 1 NT-treated patient. The baseline (mean ±SE) NIHSS was 14.3 (±5.0) in the HY groups and 13.7 (±5.1) in the NT groups (Table 2).

The mean (±SE) meperidine dose used in HY patients was 14.5 ±6.9 mg/kg. Target temperature was reached in 20 of 28 patients (71.4%). In 2 patients, the hypothermia console failed, 4 had poorly controlled shivering that led to an increase in target temperature, and 2 were maintained at 34°C and 34.1°C. The mean (±SE) temperature that was achieved in these patients was 33.4°C (±0.6). The median time to target temperature after catheter placement was 67 minutes (Quartile 1 57.3 to Quartile 3 99.4); the mean (±SD) was 138.3 ±198.9 minutes (Figure).

In the <3-hour patients (Group 2), the median time from stroke onset to cooling start was 355 minutes (Quartile 1 269 to Quartile 3 399) and to target temperature was 421 minutes (Quartile 1 331 to Quartile 3 594).

The respiratory rate (mean ±SD) in the HY groups was lower throughout the cooling period (at 1 hour 14.15 ±2.85 versus 18.65 ±4.18). There was a trend toward lower respiratory rate during rewarming, but by Hour 36, the respiratory rate was similar between groups. There were no significant differences in blood pressure, oxygen saturation, or heart rate between groups.

There were no differences in outcome or occurrence of adverse events comparing patients who were treated with tPA and those who were not. Forty serious adverse events oc-

<table>
<thead>
<tr>
<th>Hours From Stroke</th>
<th>Group</th>
<th>Patients (No.)</th>
<th>tPA</th>
<th>HY</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3</td>
<td>1</td>
<td>22</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>22</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3–6</td>
<td>3</td>
<td>6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>2</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>4</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>2</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>total</td>
<td></td>
<td>58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Efficacy outcomes of interest were the NIHSS at 24 hours and 30 and 90 days and the modified Rankin Scale (mRS) at 90 days.

Statistical Analysis

Safety, feasibility, and efficacy analyses were conducted using the intent-to-treat principle. Because this was primarily a feasibility study, no adjustments were made for multiple comparisons. A probability value <0.05 was considered to be statistically significant. Baseline comparisons between the HY and NT groups were done using a Wilcoxon rank sum test for continuous outcomes and a Fisher exact test for categorical outcomes. Fisher exact test was used to compare the rates of serious adverse events, adverse events, hemorrhages, deaths and 90-day mRS between the HY and NT groups. The Wilcoxon rank sum test was used for the NIHSS comparisons. All statistical analyses were conducted using the statistical software R Version 2.10.1 (www.r-project.org/).
occurred in 21 of the 28 patients treated with HY versus 21 serious adverse events in 13 of the 30 NT patients. Pneumonia occurred more frequently in the HY patients than in the NT patients (7 of 28 versus 2 of 30, \(P < 0.05\), Fisher exact test). The rate of any intracerebral hemorrhage at 48 hours including both asymptomatic and symptomatic intracerebral hemorrhage was similar in both groups at 30% (33% HY, 25% NT). Symptomatic intracerebral hemorrhage occurred in 4 patients, all treated with tPA within 3 hours from stroke onset, only 1 with HY and 3 in the NT groups.

The risk of deep vein thrombosis, urinary tract infection, pancreatitis, renal failure, or cardiac arrhythmia was not significantly increased in patients treated with HY compared with NT. Deep vein thrombosis occurred in 4 HY and 1 NT patient. It was possibly related to the hypothermia catheter in 2 patients. One received an inferior vena cava filter.

There were no differences in baseline laboratory values between groups. Mild oliguria occurred in almost all patients at the time of undergoing HY but was not associated with renal failure and reversed during rewarming. There was a transient increase in blood urea nitrogen (mean±SD) at Day 2 in the HY group to 23.3 mg/dL (±9.9) versus 12.9 mg/dL (±5.93) in the NT group. No significant change in creatinine was observed and the blood urea nitrogen on follow-up at Day 7 was 16.3 mg/dL (±6.9) in the HT versus 15.1 mg/dL (±8.3) in the NT group. Amylase was increased in patients with HY at Day 2 (243.3±260.9 U/L versus 62.5±25.6 U/L) and remained elevated (99.7±63.0 U/L versus 49.7±28.4 U/L) at Day 7, but no patient was diagnosed with pancreatitis.

Due to sedation with meperidine, the NIHSS at 24 hours was 17.0 (±8.9) in the HY and 11.1 (±8.1) in the NT groups (\(P = 0.02\)). The NIHSS was equivalent in both groups at 30 days. It was 8.0 (±6.5) in the HY and 5.0 (±4.1) in the NT groups (nonsignificant). At 90 days, the NIHSS was 6.3 (±6.6) versus 3.8 (±3.0; nonsignificant).

At 3 months, 18% of patients in the HY groups had a mRS of 0 or 1 versus 24% in the NT groups. The difference was not statistically significant (\(P < 0.77\); Fisher exact test). Six patients treated with HY died; 5 died in the NT group. Of the patients with pneumonia, 11.8% had a mRS of 0 or 1 at 90

### Table 2. Baseline Demographics and Risk Factors Between the HY and NT Groups

<table>
<thead>
<tr>
<th></th>
<th>HY (Groups 2, 5, 6; n=28)</th>
<th>NT (Groups 1, 3, 4; n=30)</th>
<th>Fisher Exact Test</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>56.7%</td>
<td>53.8%</td>
<td>0.999</td>
<td></td>
</tr>
<tr>
<td>Race (white)</td>
<td>89.3%</td>
<td>80.0%</td>
<td>0.707</td>
<td></td>
</tr>
<tr>
<td>Age, years (±SD)</td>
<td>68.9 (7.9)</td>
<td>62.3 (14.5)</td>
<td>0.109</td>
<td></td>
</tr>
<tr>
<td>Known atrial fibrillation</td>
<td>21.4%</td>
<td>13.3%</td>
<td>0.499</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>21.4%</td>
<td>30.0%</td>
<td>0.554</td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>71.4%</td>
<td>63.3%</td>
<td>0.583</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>53.7%</td>
<td>50.0%</td>
<td>0.793</td>
<td></td>
</tr>
<tr>
<td>Present smoking</td>
<td>10.7%</td>
<td>26.7%</td>
<td>0.102</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3.6%</td>
<td>16.7%</td>
<td>0.109</td>
<td></td>
</tr>
<tr>
<td>PVD</td>
<td>3.6%</td>
<td>6.7%</td>
<td>0.411</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>14.3%</td>
<td>16.7%</td>
<td>0.426</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>39.4%</td>
<td>26.7%</td>
<td>0.695</td>
<td></td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>17.9%</td>
<td>20.0%</td>
<td>0.869</td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>3.6%</td>
<td>0%</td>
<td>0.229</td>
<td></td>
</tr>
<tr>
<td>Lung disease</td>
<td>10.7%</td>
<td>13.3%</td>
<td>0.848</td>
<td></td>
</tr>
<tr>
<td>Renal disease</td>
<td>7.1%</td>
<td>13.3%</td>
<td>0.671</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>21.4%</td>
<td>33.3%</td>
<td>0.298</td>
<td></td>
</tr>
<tr>
<td>Prestroke mRS score ≥1</td>
<td>14.3%</td>
<td>3.3%</td>
<td>0.214</td>
<td></td>
</tr>
<tr>
<td>Pretreatment NIHSS (±SD)</td>
<td>14.3 (5.0)</td>
<td>13.7 (5.1)</td>
<td>0.651</td>
<td></td>
</tr>
</tbody>
</table>

PVD indicates peripheral vascular disease.

Figure. Time to target temperature (lowest temperature achieved or first 33°C) in 26 patients in whom cooling was attempted. In 4 patients, effective antishivering was not accomplished, resulting in very long times to target.
that hypothermia can reduce edema after cerebral ischemia.\textsuperscript{7} It may be possible that adjusting the rewarming paradigm to physical examination findings, intracranial pressure monitoring, or other surrogate markers, we could benefit patient outcome. In our own earlier experience, we found that hypothermia reduced brain edema.\textsuperscript{19} The aim of ICTuS-L, however, was acute neuroprotection and edema therapy after completed ischemia was not targeted.

In 8 of 28 patients, target temperature was not reached. In 2 patients, this was due to failure of the cooling console, in 4 patients shivering was poorly controlled, and in 2 the temperature was maintained at 34.0°C and 34.1°C by the investigator. The cooling failure was, in part, attributed to the subjects being obese and the use of the 10.7-Fr catheter. Midway through the trial, a larger and more powerful 14-Fr catheter became available, and it was noted that obese patients were easier to cool. Future studies that examine the efficacy of hypothermic neuroprotection will need to use more reliable cooling devices and use sufficiently powerful cooling catheters in patients with a high body mass index.

Our protocol was designed as a safety study and the aim was to avoid bleeding complications when hypothermia was combined with tPA. The median time to target temperature was over 7 hours (421 minutes) and was mainly driven by the delay in catheter placement. For safety concerns, endovascular cooling in patients with a high body mass index.\textsuperscript{10,11} The median time to target temperature was 6.6 (3.8) hours, and in safety concerns. This finding is consistent with the more aggressive antishivering regimens that cause skin irritation and respiratory suppression.\textsuperscript{8} We used an antishivering treatment with intravenous meperidine, oral buspirone, and surface skin warming without severe respiratory suppression and were able to combine endovascular cooling with thrombolysis in awake patients after acute ischemic stroke.

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Table 3. Outcome Measures Between HY and NT Patients

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>HY (Groups 2, 5, 6; n=28)</th>
<th>NT (Groups 1, 3, 4; n=30)</th>
<th>Fisher Exact Test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS at 90 days (mean±SD)</td>
<td>6.3 (±6.6)</td>
<td>3.8 (±3.0)</td>
<td>0.355</td>
<td></td>
</tr>
<tr>
<td>At least one SAE (%)</td>
<td>75</td>
<td>43.3</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Pneumonia (%)</td>
<td>50</td>
<td>10</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>All ICH (%)</td>
<td>28.6</td>
<td>20</td>
<td>0.752</td>
<td></td>
</tr>
<tr>
<td>Symptomatic ICH (%)</td>
<td>3.6</td>
<td>10</td>
<td>0.609</td>
<td></td>
</tr>
<tr>
<td>Mortality by 90 days (%)</td>
<td>21.4%</td>
<td>16.7</td>
<td>0.744</td>
<td></td>
</tr>
</tbody>
</table>

SAE indicates serious adverse event; ICH, intracerebral hemorrhage.
The increase in pneumonia rate in the HY-treated patients may be affected in part by an ascertainment bias as patients undergoing HY were more closely monitored for side effects; they were all hospitalized in intensive care units for a minimum of 36 hours, whereas NT patients may have been admitted to lower acuity level units. Hypothermia, in addition to stroke, however, is known to suppress the immune system and patients who have sepsis with hypothermia or postoperative hypothermia have increased risks of infections. Furthermore, the use of meperidine reduces respiratory frequency and may contribute to aspiration. Compared with other antishivering treatments, meperidine carries a lower risk of respiratory depression. Our data do not allow us to attribute the pneumonia risk to hypothermic immune suppression, elevated aspiration risk due to the meperidine, or other unknown factors, and further studies are needed to establish the effect of hypothermia on immune suppression. The increased pneumonia rate in hypothermia patients may have obscured any possible beneficial effect on 3-month outcomes.

Conclusions
Endovascular hypothermia can be combined with thrombolytic therapy. The antishivering protocol is feasible in awake patients with stroke. An increased rate of pneumonia in the cooled patients was observed but was not associated with poor outcome. Further studies with larger patient samples and earlier cooling are needed to evaluate the efficacy of hypothermia after ischemic stroke.

Appendix
The ICTuS-L Investigators are as follows: University of California San Diego, Calif, and Scripps Mercy Hospital, San Diego, Calif: T.M. Hemmen, T. Rzesiewicz, K.Z. Guluma, and B.C. Meyer; University of Texas Medical School, Houston, Texas: J. Grotta, M.J. Hess, S. Martin-Schild, A. Barreto, H. Hallely, N. Gonzales, and S. Savitz; University of Connecticut, Hartford, Conn: J. Gomes and J. Blum; University of Pittsburgh, Pittsburgh, Pa: M. Hammer and E. Gruen-dler; Stanford University Medical Center, Palo Alto, Calif: C.A.C. Wijman, G.W. Albers, M.S. Buckwalter, J.S. Castle, A. Finley Caulfield, M. Garcia, S. Kemp, M.A. Kumar, M. G. Lansberg, N.E. Schwartz, and C. Venkatasubramanian; St Louis University, St Louis, Mo: S. Cruz-Flores and E. Holzemer; and UCSD Stroke Clinical Trials Coordinating Center, San Diego, Calif: P.D. Lyden and K.S. Rapp.

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Disclosures
None.

References


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배경과 목적
저온법(hypothermia)은 유망한 신경보호 치료술이다. 저자들은 급성 허혈뇌졸중(ischemic stroke)에서 저온법과 혈전용해술(thrombolysis)의 실험 가능성을 평가하기 위해 연구하였다.

방법
Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (ICTuS–L)는 허혈뇌졸중 발병 6시간 이내에 저온법과 정맥내 조직플라스미노겐활성제 (intravenous tissue plasminogen activator)를 사용하는 것에 대한 무작위 배정 다기관 연구이다. 0 ~ 3시간 및 3 ~ 6시간으로 치료 시간대를 축소하여 환자를 모집하였다. 중상 발현 3시간 이내에 내원한 환자에게 표준 용량의 alteplase를 정맥내 주사한 후 24시간 동안 33°C의 혈관내 저온법과 연이은 12시간 동안의 통제된 rewarming을 받도록 하거나 정상 체온 (normothermia) 치료를 받도록 무작위 배정하였다. 3 ~ 6시간 내에 내원한 환자는 정맥내 조직플라스미노겐활성제 치료를 받을 것인지 아닌지, 저온법을 받을 것인지 아닌지에 대하여 두 번 무작위 배정하였다.

결과
총 59명의 환자를 모집하였다. 한 환자는 동통은 하였으나 치료 직전에 병발을 발견하여 치료는 하지 않았다. 3시간 이내에 동통된 44명 모두와 3 ~ 6시간에 동통된 14명 중 4명에게 조직플라스미노겐활성제 치료를 하였다. 결과 28명을 저온법에 무작위 배정하였고, 30명을 정상 체온 치료에 배정하였다. 기저 인구학적 특성과 위험인자는 두 군에서 동일하였다. 평균 연령은 65.5±12.1세였고, 기저 National Institutes of Health Stroke Scale 점수는 14.0±5.0이었다. 32명 (55%)는 남성이었다. 저온법은 기술적인 문제가 있던 두 명을 제외하고 모든 환자에서 성공하였다. 도판 삽입 후 목표 체온에 도달하기까지 걸린 시간의 중앙값은 67분 (사분위1 57.3, 사분위3 99.4)이었다.

결론
이 연구는 뇌졸중 이후 정맥내 혈전용해술과 혈관내 저온법 병합 요법의 실험 가능성을 평가한 결과, 허혈뇌졸중에서 더 신속하게 치료가 가능하다는 결론을 내렸다. 폐렴이 보존된 경우, 저온법은 뇌졸중의 예후에 미치는 영향과 허혈에 예방할 수 있을지에 대하여 더 많은 연구가 필요하다. 급성 뇌졸중에서 지료적 저온법의 효능에 대한 명확한 임상시험 이 필요하다.
Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (ICTuS-L) 
Final Results
Thomas M. Hemmen, Rema Raman, Kama Z. Guluma, Brett C. Meyer, Joao A. Gomes, Salvador Cruz-Flores, Christine A. Wijman, Karen S. Rapp, James C. Grotta, Patrick D. Lyden; ICTuS-L Investigators

背景和目的：诱导低温是一种有前景的神经保护治疗。我们研究了低温结合溶栓治疗急性缺血性卒中的可行性和安全性。

方法：ICTuS-L 是一项在缺血性卒中发生 6 小时内的患者中进行的随机、多中心临床试验，研究采用低温及静脉组织型纤溶酶原激活剂 (tPA) 联合治疗。入选者按照治疗时间窗 0-3 小时和 3-6 小时进行分层。症状发生后 3 小时内就诊的患者接受标准剂量静脉滴注阿替普酶, 并被随机分配至两组，一组维持正常体温，另一组给予血管内降温至目标体温 33 ℃共计 24 小时, 而后给予 12 小时的控制复温。在 3-6 小时就诊的患者被双重随机分组：tPA 溶栓与无 tPA 溶栓治疗，低温与非低温治疗。

结果：研究共纳入 59 例患者。1 例入选者由于治疗前发现其患肺炎, 并未进行治疗。发病 3 小时内就诊的全部 44 例患者以及发病后 3-6 小时就诊的 14 例患者中的 4 例接受了 tPA 治疗。共有 28 例患者被随机分配至低温 (hypothermia, HY) 组, 30 例被纳入正常体温 (normothermia, NT) 组。组间的基线数据及危险因素相似。平均年龄为 65.5±12.1 岁，基线 NIHSS 评分为 14.0±5.0，32 例(55%) 患者为男性。2 例因技术失败而未实现降温。放置导管后达到目标体温的中位时间为 67 分钟 (第 25 百分位和第 75 百分位分别为 57.3 和 99.4)。3 个月时, 18% 的低温治疗患者改良 Rankin 量表 (mRS) 评分为 0 或 1 分, 在常温组上述比例为 24% (P=0.001)。4 例患者在 3 个月内死亡 (无显著性差异)。4 例低温治疗的患者和 3 例常温患者发生肺炎 (P=0.001)。肺静脉发生率对 3 个月内 mRS 评分的不良影响并不显著 (P=0.32)。

结论：该研究初步证实了卒中后血管内低温结合静脉内溶栓治疗的可行性及安全性。低温治疗后的肺炎发生率升高，但其对患者临床预后的影像及其是否能被预防仍需进一步的研究证实。对于急性卒中患者低温治疗的确切疗效仍需试验评估。
ICTuS-L(Intravascular Cooling in the Treatment of Stroke-Longer tPA window) 研究试图通过对卒中后接受血管内降温治疗且神志清醒的患者进行随机、对照试验，从而证实对已接受溶栓治疗的患者给予血管内低温治疗的可行性及安全性[12]。

**材料与方法**

ICTuS-L 研究是一项随机、对照、前瞻性试验，旨在探索对急性缺血性卒中发作 6 小时内给予溶栓联合诱导血管内低体温治疗的可行性及安全性。入选者年龄介于 18-80 岁，NIHSS 评分 ≥7 分，在放置降温导管时的 NIHSS 中条目 1a(觉醒)评分为 0 或 1 分。上述治疗方案经各研究中心的评审委员会批准。所有患者或其代理人签署了知情同意书。入选者根据 tPA 治疗的时间窗 0-3 小时和 3-6 小时进行分层。发病 3 小时内的患者接受 0.9 mg/kg(最大剂量 90 mg) 静脉 tPA 治疗，并被随机分为两组：一组应用摄氏温度控制系统 (Innercool, San Diego, Calif) 血管内降温至 33℃，维持 24 小时，随后 12 小时以每小时 0.3℃的速率给予复温;对照组不进行降温处理。发病 3-6 小时的患者被随机分组两次：应用 tPA 与不应用 tPA 治疗。低温治疗 (HY) 与常温治疗 (NT)。入选者通过一个随机化列表被随机分组，该列表由加利福尼亚大学-圣地亚哥分校的 SPOTRIAS(Specialized Program of Translational Research in Acute Stroke)数据中心产生并支持。

我们应用一个之前发表过的方案结合哌替啶、丁螺环酮及保温毯抗寒战治疗[10]。在 tPA 治疗的患者中，tPA 滴注完成后 30-180 分钟置入导管。所有患者在治疗前、卒中发生后的 36(±12) 小时及 30 天进行头颅 CT 检查，并在治疗前、卒中发生后的 24 小时以及 7, 30 和 90 天进行临床评估。该临床试验方法的详细描述已经发表[23]。主要安全性终点事件为 3 个月内发生严重不良事件。主要可行性终点为实现降温，即尽可能达到目标体温 33℃。

所关注的次要安全性终点包括：(1) 卒中发生后 36 小时的头颅 CT 上出现血肿及血肿的体积 ; (2) 发生不良事件;(3)90 天的死亡率。有效性终点为 24 小时、30 小时及 90 天的 NIHSS 评分及 90 天时的 mRS 评分。

**统计分析**

安全性、可行性及有效性分析遵循意向 - 治疗原则。该研究主要为可行性研究，因此并未以多重比较为目的进行调整。P<0.05 被认为在统计学上有显著性意义。在 HY 与 NT 两组之间的基线数据比较方面，统计分析采用 Wilcoxon 秩和检验，分类终点应用 Fisher 精确检验。 Fisher 精确检验被用于比较 HY 和 NT 两组的严重不良事件、不良事件、出血、死亡的发生率及 90 天的 mRS 评分。 Wilcoxon 秩和检验被用于 NIHSS 评分的比较。所有的数据分析均应用统计软件 R 2.10.1 版本 (www.r-project.org/).

**结果**

59 例患者参与随机化分组，1 例患者因在治疗前患有肺炎被排除，其余 58 例进行意向 - 治疗分析。58 例患者中的 28 例 (48.2%) 接受低温治疗，其中 22 例 (78.6%) 在卒中发生 3 小时内应用 tPA，2 例在卒中发生 3-6 小时应用 tPA(即组 5 和组 6)；4 例患者在 3-6 小时的时间窗内仅接受低温治疗（表 1）。

表 1 根据卒中后发生 tPA 治疗时间的随机分组

<table>
<thead>
<tr>
<th>卒中后时间</th>
<th>组别</th>
<th>患者数量</th>
<th>tPA</th>
<th>HY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 小时</td>
<td>1</td>
<td>22</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>3-6 小时</td>
<td>3</td>
<td>6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>合计</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

入选者年龄从 21 至 81 岁，平均 (±SE) 年龄为 65±14 岁。接受 HY 治疗的患者年龄大一些，平均 68.93±7.9 岁；而 NT 治疗组的平均年龄为 62.30±14.48 岁 (无显著性差异)。55% 的患者为男性。至少 50% 的患者有危险因素，包括高血压及高脂血症。25%-50% 的患者有冠心病，心房颤动或心肌梗死。4 例 HY 治疗组及 1 例 NT 治疗组患者卒中前 mRS>1 分。基线 (均值±SE) NIHSS 在 HY 组为 14.3(±5.0)，在 NT 组为 13.7(±5.1)（表 2）。

HY 组的平均 (±SE) 喷替啶剂量为 14.5±6.9 mg/kg。28 例患者中的 20 例 (71.4%) 达到目标体温。2 例患者降温操作失败，4 例患者因无法控制寒战而不得不升高目标体温。3 例患者体温维持在 33.5℃到 34℃。降温成功患者的平均 (±SE) 体温为 33.5℃ (±0.6)。导管置入后达到目标体温的中位时间为 67 分钟 (第 25 百分位和第 75 百分位分别为 57.3 和 99.4)；平均 (±SD) 为 138.3±198.9 分钟 (图)。

在卒中发生 3 小时内的患者 (组 2) 中，从卒中发生至开始降温的中位时间为 355 分钟 (第 25 百分位和第 75 百分位分别为 269 和 399)，至达到目标体温的中位时间为 421 分钟 (第 25 百分位和第 75 百
与 NT 组相比，HY 组深静脉血栓、泌尿道感染、胰腺炎、肾功能衰竭及心律失常的发生率无显著性升高。4 例 HY 组及 1 例 NT 组患者发生深静脉血栓。其中的 2 例可能与低温导管相关。1 例患者放置了下腔静脉滤器。

两组间的基线实验室指标无差异。几乎所有的患者在接受 HY 治疗时均发生轻度少尿，但其发生与肾功能衰竭无关，并可在复温时恢复。第 2 天时 HY 组有一过性血尿素氮升高（均值 ±SD），达 23.3 mg/dL（±9.9），而 NT 组为 12.9 mg/dL（±5.93）。血肌酐无显著变化。随诊至第 7 天，HY 组的血尿素氮为 16.3 mg/dL（±6.9），NT 组为 15.1 mg/dL（±8.3）。HY 组患者第 2 天的淀粉酶升高（243.3±260.9 U/L vs 62.5±25.6 U/L），且在第 7 天仍较高（99.7±63.0 U/L vs 49.7±28.4 U/L），但并无患者被诊断为胰腺炎。

由于哌替啶的镇静作用，HY 组 24 小时的 NIHSS 评分为 17.0（±8.9），NT 组为 11.1（±8.1）(P=0.02)。两组的 NIHSS 评分在第 30 天相当，在 HY 组为 8.0（±6.5），
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表 3 HY 组与 NT 组患者的预后比较

<table>
<thead>
<tr>
<th></th>
<th>HY 组</th>
<th>NT 组</th>
<th>Fisher 精确检验 P 值</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 天 mRS 0-1 分</td>
<td>(2.5, 5 组)</td>
<td>(1, 3, 4 组)</td>
<td></td>
</tr>
<tr>
<td>n=28</td>
<td>n=30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 天 NIHSS (平均 ±SD)</td>
<td>6.3(±6.6)</td>
<td>3.8(±3.0)</td>
<td>0.355</td>
</tr>
<tr>
<td>少于 1 次严重不良事件 (%)</td>
<td>75</td>
<td>43.3</td>
<td>0.018</td>
</tr>
<tr>
<td>肺炎 (%)</td>
<td>50</td>
<td>10</td>
<td>0.001</td>
</tr>
<tr>
<td>全部脑出血 (%)</td>
<td>28.6</td>
<td>20</td>
<td>0.752</td>
</tr>
<tr>
<td>假性脑出血 (%)</td>
<td>3.6</td>
<td>10</td>
<td>0.609</td>
</tr>
<tr>
<td>90 天死亡率 (%)</td>
<td>21.4</td>
<td>16.7</td>
<td>0.744</td>
</tr>
</tbody>
</table>

NT 组为 5.0(±4.1)(无显著性差异)。在第90天，两组的 NIHSS 评分分别为 6.3(±6.6) vs 3.8(±3.0)(无显著性差异)。

在第3个月，HY 组有 18% 的患者，NT 组有 24% 的患者 mRS 评分为 0 或 1 分，差异无统计学意义 (P<0.077；Fisher 精确检验)。

讨论

本项研究是有关清醒的卒中患者接受低温治疗的最大的随机对照研究，目标体温为 33℃。既往的研究应用体表降温及积极的抗寒战治疗，会导致皮肤刺激症状及呼吸抑制 [8]。我们通过静脉给予哌替啶、口服丁螺环酮及皮肤表面取暖的方法抗寒战，解决了严重呼吸抑制的弊端，且能够实现对急性缺血性卒中的清醒患者给予血管内低温结合溶栓治疗。

该试验方案设计为安全性研究，目的是在进行低温结合 tPA 治疗时避免出血并发症。达到目标体温的中位时间超过 7 小时 (421 分钟)，其限速步骤为导管置入过程。出于安全性考虑，血管内低温治疗只能在 tPA 滴注完成后 30-180 分钟进行。在接受溶栓治疗的患者中，未发现因股静脉导管插入术而导致的腹股沟血肿及其它出血并发症，降温过程因预防该类并发症而显著延迟。然而，在于低温合并置入后的 20 分钟内我们未记录体温，降温过程可能因此被高估 (图 4)。延迟降温可能降低了潜在的神经保护作用。

应用无创的方法，例如静脉内给予冷盐水或体外降温进行低温诱导可能会进一步增加到达目标体温的时间。

临床前期研究显示，在卒中发生后越快实施低温治疗，效果越优，提示如何能够迅速启动低温治疗是未来的研究方向之一 [13-16]。

除治疗时间窗之外，低体温的持续时间可能影响患者预后 [17]。临床前期研究显示增加低体温持续时间可提高神经保护效果 [18]。我们的研究中，低温持续 24 小时。接下来的研究应该关注急性缺血性卒中后的最佳低体温持续时间。

尽管现有研究中所有患者的复温方式相同，Schwab 等指出低体温可以降低缺血后脑水肿 [17]。我们或许可以根据体格检查结果，颅内压监测或其它替代指标来调整复温方式，以使患者临床预后更佳。我们自己之前的经验也认为低温治疗可降低脑水肿 [19]。然而 ICTuS-L 研究中，在缺血后给予急性神经保护及水肿治疗的目的并未实现。

低温治疗可延长 tPA 治疗的时间窗为该研究的最初假设之一。然而由于卒中发生后 3-6 小时入组的患者数量较少，我们无法验证该假设。试验启动后，观察资料证实极少患者在卒中发生后 3-6 小时就诊 [20]。NIHSS 评分较高的患者更多地在 3 小时内接受治疗 [21-23]。由于试验设计要求 NIHSS 评分 ≥7 分，在 3-6 小时就诊的患者极少符合入组条件。因此，我们无法证实应用低温治疗可延长静脉给 tPA 的治疗时间窗。在数量有限的 3-6 小时入组的患者中，未观察到更多的安全问题。该发现与 ECASS(European Cooperative Acute Stroke Study)III 研究的结果是一致的，ECASS III 证实了卒中发作后 3-4.5 小时静脉给予 tPA 的安全性及有效性。

在该项小样本的可行性及安全性研究中，并未发现给予 HY 治疗与未进行 HY 治疗的患者死亡率及 mRS 评分存在差异。HY 组 24 小时的 NIHSS 评分升高，这可能与抗寒战措施所导致的轻微镇静作用相关，因为在之后的随访过程中，NIHSS 评分并无显著性差异。

严重不良事件在 HY 组发生率更高，以肺炎最常见。肺炎的发生对 90 天预后并无显著影响。卒中所引起的一过性免疫抑制增加了罹患肺炎的风险 [25,26]。有关肺炎对于卒中临床预后影响方面的资
料尚存在争议。GAIN(Glycine Antagonist In Neuro-protection) 研究发现肽疹与泌尿道感染与卒中预后不良相关[23]。PANTHERIS (Preventive ANtibacterial THERapy in acute Ischemic Stroke) 研究显示，卒中后预防性应用抗生素可降低肺炎的发生[27]，从而改善临床预后。然而该益处并未在 Chamorro 等的类似研究中得到证实[28]。

**HY** 组患者肺炎发生率的增高某种程度上可能与确认偏倚相关，这是因为我们对接受低温治疗的患者副作用的监测更加密切；他们在 ICU 住院治疗至少 36 小时，而 NT 组患者则更长住普通病房。然而除卒中外，低体温也会抑制免疫系统[29]，低体温的感染性血症或术后低体温的感染风险增加[10]。此外，哌替啶的应用降低了呼吸频率，这可能导致误吸发生。与其它抗寒战治疗相比，哌替啶的呼吸抑制风险更低[11-33]。该项研究的资料不足以让我们判断假定的肺炎的发生属于由低体温导致的免疫抑制，或或将误吸风险的增高关乎于哌替啶或其它未知因素。

**参考文献**


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23. Hemmen et al      Hypothermia After Ischemic Stroke