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 neurologic 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 fatality, 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 translational Research in Acute Stroke (SPOTRIAS) Data Core.

We used a previously published antishivering protocol combining meperidine, busipiron, and warming blankets.10 In tPA-treated patients, the catheter insertion was initiated between 30 and 180 minutes after completion of the tPA infusion. Patients received a head CT before treatment, at 36 (±12) hours and at 30 days, and a clinical evaluation before treatment and at 24 hours and 7, 30, and 90 days after stroke. A full description of the clinical trial methods has been published.12 The primary safety outcome was the incidence of a serious adverse event at 3 months. The primary feasibility outcome was achievement of cooling defined as reaching a target temperature as close to 33°C as possible.

Secondary safety outcomes of interest included (1) the incidence and volume of hemorrhages on head CT 36 hours after stroke onset; (2) the incidence of adverse events; and (3) 90-day mortality.

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/).

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-
curred 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, \( P = 0.099 \), 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, one 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 |
|-----------------|-----------------|-----------------|-----------------|
| HY (Groups 2, 5, 6; n=28) | NT (Groups 1, 3, 4; n=30) | Fisher Exact Test |
| Male gender | 56.7% | 53.8% | 0.999 |
| Race (white) | 89.3% | 80.0% | 0.707 |
| Age, years (± SD) | 68.9 (7.9) | 62.3 (14.5) | 0.109 |
| Known atrial fibrillation | 21.4% | 13.3% | 0.499 |
| Diabetes | 21.4% | 30.0% | 0.554 |
| Arterial hypertension | 71.4% | 63.3% | 0.583 |
| Hyperlipidemia | 53.7% | 50.0% | 0.793 |
| Present smoking | 10.7% | 26.7% | 0.102 |
| Congestive heart failure | 3.6% | 16.7% | 0.109 |
| PVD | 3.6% | 6.7% | 0.411 |
| Coronary artery disease | 14.3% | 16.7% | 0.426 |
| Prior stroke or TIA | 17.9% | 20.0% | 0.869 |
| Liver disease | 3.6% | 0 | 0.229 |
| Lung disease | 10.7% | 13.3% | 0.848 |
| Renal disease | 7.1% | 13.3% | 0.671 |
| Gastrointestinal disease | 21.4% | 33.3% | 0.298 |
| Prestroke mRS score >1 | 14.3% | 3.3% | 0.214 |
| Pretreatment NIHSS (± SD) | 14.3 (5.0) | 13.7 (5.1) | 0.651 |

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.
days versus 25% of those without pneumonia (nonsignificant; Table 3).

**Discussion**

This study is the largest randomized controlled study of awake patients with stroke who received hypothermia targeted at 33°C. Past studies used surface cooling methods with aggressive antishivering regimens that cause skin irritation and respiratory suppression. 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.

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 hypothermia was not begun until 30 to 180 minutes after completion of the tPA infusion. Although we did not observe groin hematoma or other bleeding complications attributable to the femoral venous catheterization in patients who had received thrombolytic therapy, cooling was significantly delayed due to this precaution; however, our calculation of the times to cooling may have been an overestimate because we did not record temperature for 20 minutes after cooling catheter placement (Figure). The delayed cooling may have reduced the potential for neuroprotective benefit in our patients.

Hypothermia induction with noninvasive methods such as intravenous cold saline or external cooling may have further increased the time to target temperature. Preclinical studies have shown that hypothermia is more effective the sooner it is implemented after stroke, suggesting that future studies should contain provisions for more prompt cooling initiation.13–16

In addition to the time window, cooling duration may affect patient outcome.17 Preclinical studies have shown that longer cooling increases neuroprotective effects.18 The patients in our study were cooled for 24 hours. Future research should focus on the optimal cooling duration after ischemic stroke in humans.

Although the rewarming paradigm used in the present study was the same in all patients, Schwab et al have shown that hypothermia can reduce edema after cerebral ischemia.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.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, 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.

One initial hypothesis of our study was that cooling extends the time window for tPA. We were not able to test this hypothesis because enrollment into the treatment groups between 3 and 6 hours was low. After our trial was initiated, survey data confirmed that few patients with stroke arrive between 3 and 6 hours. One initial hypothesis of our study was that cooling extends the time window for intravenous tPA is possible with the addition of hypothermia. In the limited number of patients studied between 3 and 6 hours, we did not observe an excess in safety concerns. This finding is consistent with the more recent European Cooperative Acute Stroke Study (ECASS) III study that demonstrated the safety and efficacy of intravenous tPA between 3 and 4.5 hours.24

We did not find a difference in mortality and mRS in patients treated with or without HY in this small safety and feasibility study. The increased NIHSS score at 24 hours in the HY groups may have been due to mild sedation caused by the antishivering protocol because we found no significant difference in NIHSS scores at follow-up.

Serious adverse events were more common in the HY groups and the most common serious adverse event was pneumonia. The occurrence of pneumonia did not significantly affect outcome at 90 days. Stroke causes a transient immune depression, which leads to increased pneumonia risk.25 Data regarding the effect of pneumonia on stroke outcome is conflicting. The Glycine Antagonist In Neuroprotection (GAIN) investigators found an increased risk of poor outcome after stroke associated with pneumonia and urinary tract infection.25 The Preventive ANtiBacterial THERapy in acute Ischemic Stroke (PANTHERIS) study showed a reduction of pneumonia after stroke when prophylactic antibiotics were used.27 The reduction was associated with a trend toward better outcome. This benefit was not confirmed, however, in a similar study by Chamorra et al.28

**Table 3. Outcome Measures Between HY and NT Patients**

<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 P</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0–1 at 90 days</td>
<td>5</td>
<td>7</td>
<td>0.747</td>
</tr>
<tr>
<td>NIHSS at 90 day (mean±SD)</td>
<td>6.3±6.6</td>
<td>3.8±3.0</td>
<td>0.355</td>
</tr>
<tr>
<td>At least one SAE (%)</td>
<td>75</td>
<td>43.3</td>
<td>0.018</td>
</tr>
<tr>
<td>Pneumonia (%)</td>
<td>50</td>
<td>10</td>
<td>0.001</td>
</tr>
<tr>
<td>All ICH (%)</td>
<td>28.6</td>
<td>20</td>
<td>0.752</td>
</tr>
<tr>
<td>Symptomatic ICH (%)</td>
<td>3.6</td>
<td>10</td>
<td>0.609</td>
</tr>
<tr>
<td>Mortality by 90 days (%)</td>
<td>21.4%</td>
<td>16.7%</td>
<td>0.744</td>
</tr>
</tbody>
</table>

SAE indicates serious adverse event; ICH, intracerebral hemorrhage.

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**Medical Subject Headings (MeSH)**

- Hypothermia
- Stroke
- Intravenous Therapy
- Nitrogen Dioxide
- Stroke Therapy
- Neuroprotection
- Intravenous Therapy, Nitrogen Dioxide
- Stroke Therapy, Nitrogen Dioxide
- Nitrogen Dioxide
- Stroke Therapy
- Intravenous Therapy
- Hypothermia
- Stroke
- Nitrogen Dioxide
- Stroke Therapy
- Nitrogen Dioxide
- Stroke Therapy
- Intravenous Therapy
- Nitrogen Dioxide
- Stroke Therapy
- Nitrogen Dioxide
- Stroke Therapy
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. Hallevi, N. Gonzales, and S. Savitz; University of Connecticut, Hartford, Conn: J. Gomes and J. Blum; Stanford University Medical Center, Palo Alto, Calif: C.A.C. Hemmen et al Hypothermia After Ischemic Stroke 2269

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Disclosures

None.

References


13. Dietrich WD, Busto R, Alonso O, Globus MY, Ginsberg MD. Intraischemic cooling catheters and devices for this clinical trial but no other financial or other support.


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**Abstract 4**

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

최종 결과

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

Final Results

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*(Stroke. 2010;41:2265-2270.)*

Key Words: hypothermia ■ ischemic stroke ■ neuroprotection ■ thrombolysis

배경과 목적

저온법(hypothermia)은 유방한 신경보호 치료술이다. 저온법은 급성 혈관뇌졸증(ischemic stroke)에서 저온법과 혈전용해술(thrombolysis)의 실험 가능성을 입증하려고 연구하였다.

방법

Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (ICTuS-L)는 혈관뇌졸증 병발 6시간 이내에 저온법과 정맥내 조직플라스마미노전환계 (intravenous tissue plasminogen activator)를 사용하는 것에 대한 무작위 배정 다기관 연구이다. 0~3시간 및 3~6시간간으로 치료 시간대를 총합하여 환자를 모집하였다. 중앙 발현 3시간 이내에 내원한 환자에게 표준 용량의 alteplase를 정맥내 주사한 후 24시간 동안 35°C의 혈관내 저온법과 연이은 12시간 동안의 장애된 rewarming을 받도록 하거나 정상 체온 (normothermia) 치료를 받도록 무작위 배정하였다. 3~6시간 내내원한 환자는 조작플라스마미노전환계 치료를 받을 것인지 아닌지, 저온법을 받을 것인지 아닌지에 대하여 두 번 무작위 배정하였다.

결과

총 59명의 환자를 모집하였다. 한 환자는 동시에 환자들은 동종을 하였으나 치료 직전에 페렴을 발견하여 치료는 하지 않았다. 3시간 이내에 등록된 44명 모두와 3~6시간에 등록된 14명 중 4명에게 조직플라스마미노전환계 치료를 하였다. 결국 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%)은 남성이었다. 저온법은 기술적인 문제가 있던 두 명을 제외하고 모든 환자에서 성공하였다. 도와 삽입 후 목표 체온에 도달하기까지 걸린 시간의 중앙값은 67분(범위 157.3, 사분위 99.4)이었다. 3개월째에 수정 랜덤화도(modified Rankin Scale) 점수가 0 또는 1인 환자의 비율은 저온법을 받은 환자가 18%, 정상 체온 치료를 받은 환자가 24%였다(통계적으로 의미 없음). 중앙성 두개내출혈(intracranial hemorrhage)은 4명(6%)에서 발생하였고, 모두 3시간 이내에 조직플라스마미노전환계 치료를 받은 1명은 저온법을 받았다. 저온법을 받은 환자 중 6명과 정상 체온 치료를 받은 환자 중 5명이 90일 이내에 사망하였다(통계적으로 의미 없음). 실험은 저온법을 받은 환자 중 14명, 정상 체온 치료를 받은 환자 중 3명에서 발생하였다(P=0.001). 실험 발병은 3개월 수정 랜덤화도 점수에 영향을 주지 않았다(P=0.32).

결론

이 연구는 뇌졸중 이후 정맥내 혈전용해술과 혈관내 저온법 병합 요법의 실험 가능성을 입증하고자 하였다. 실험은 저온법에서 더 혼자 있는 긍정적인 결과가 있음에 따라 더 많은 연구가 필요하다. 긍정 뇌졸중에서 치료적 저온법의 효능에 대한 명확한 임상시험이 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

Background and Objective: Induced hypothermia is a promising neuroprotective strategy. We studied the feasibility and safety of hypothermia combined with thrombolysis for acute ischemic stroke.

Methods: ICTuS-L was a randomized, multicenter clinical trial of patients with ischemic stroke within 6 hours. Patients were assigned to 3-6 hours, and those within 3 hours were randomized to receive standard dose intravenous tissue plasminogen activator (tPA) with or without hypothermia. Patients received tPA and were randomized to normothermia (NT) or hypothermia (HY) for 24 hours followed by 12 hours of controlled rewarming. In 3-6 hour patients, patients were double randomized to receive tPA and hypothermia or not.

Results: Of 59 patients, 1 was excluded due to pneumonia before thrombolysis. Within 3 hours, 44 patients (55%) received tPA and were randomized to HY or NT. A total of 28 patients (57%) were randomized to HY; 30 patients were randomized to NT. Baseline data and risk factors were similar between groups. The average age was 65.5±12.1 years, and baseline NIHSS was 14.0±5.0. Of 32 patients (55%), 2 were due to technical failure. Temperatures were achieved at median 67 minutes (25th to 75th percentile at 57.3 and 99.4 respectively). At 3 months, 18% of HY patients had modified Rankin Scale (mRS) score of 0 or 1 compared to 24% (P = 0.32) in the NT group. Four patients (6.8%) developed symptomatic intracranial hemorrhage (sICH), all in the tPA group (P = 0.001). 9 of 30 (30%) patients randomized to hypothermia and 5 of 30 patients randomized to NT died within 90 days (P = 0.32). Seventeen patients (14 in HY and 3 in NT) developed pneumonia (P = 0.001). Pneumonia was not associated with worse long-term mRS (P = 0.32).

Conclusion: This study demonstrates the feasibility and safety of intravenous thrombolysis plus hypothermia for acute ischemic stroke. Higher rate of pneumonia in the hypothermia group and its potential impact on functional outcome require further study.

Keywords: Hypothermia, ischemic stroke, neuroprotection, thrombolysis
表 1  根据卒中发生后 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>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></td>
<td>58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 ℃的速度给予复温；对照组不进行降温处理。发病 3-6 小时的患者被随机分配两次：应用 tPA 与不应用 tPA 治疗，低温治疗 (HY) 与常温治疗 (NT)；共 6 组；表 1)。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 [12]。主要安全性终点事件为 3 个月时发生严重不良事件。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、可行性和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，连续终点应用 Wilcoxon 科和检验，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 科和检验被用于 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)。

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) 哌替啶剂量为 14.5±6.9 mg/kg。28 例患者中的 20 例 (71.4%) 达到目标体温。2 例患者体温操作失败，4 例患者因无法控制寒战而不得不升高目标体温。2 例患者体温维持在 34 ℃到 34.1 ℃。降温成功患者的平均 (±SE) 体温为 33.4 ℃。4 例患者体温维持在 34 ℃到 34.1 ℃。降温成功患者的平均 (±SE) 体温为 33.4 ℃ (±0.6)。导管置入后达到目标体温的中位时间为 67 分钟 (第 25 百分位数和第 75 百分位数分别为 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 百分位数和第 75 百分位数分别为 269 和 399)，至达到目标体温的中位时间为 421 分钟 (第 25 百分位数和第 75 百
与未接受 tPA 治疗的患者中无差异。28 例接受 HY 治疗的患者中有 21 例共发生 40 次严重不良事件, NT 治疗组 30 例患者中的 13 例共发生 21 次不良事件。HY 组的肺炎发生率高于 NT 组 (7/28 vs 2/30, P<0.05, Fisher 精确检验)。48 小时的症状性及无症状性颅内出血的发生率两组相似, 均为 30% 左右 (HY 组 33%, NT 组 25%)。4 例发生症状性颅内出血, 均为卒中发生 3 小时内应用 tPA 治疗的患者, 其中 1 例在 HY 组, 3 例在 NT 组。

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 天时仍较高 (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 评分平均为 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),
Stroke October 2010

Table 3 HY组与NT组患者的预后比较

<table>
<thead>
<tr>
<th></th>
<th>HY组 (2.5.6组)</th>
<th>NT组 (1.3.4组)</th>
<th>Fisher精确检验 n=28 (n=30) P值</th>
</tr>
</thead>
<tbody>
<tr>
<td>90天mRS0-1分</td>
<td>5</td>
<td>7</td>
<td>0.747</td>
</tr>
<tr>
<td>90天NIHSS(平均±SD)</td>
<td>6.3(±6.6) 3.8(±3.0)</td>
<td>0.355</td>
<td></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>症状性脑出血 (%)</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)。HY组有6例死亡，NT组有5例死亡。在患肺炎的患者中，11.8%在第90天的mRS评分为0或1分，而在非肺炎患者中上述比例为25%(无显著性差异，表3)。

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清醒患者的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滴注完成后的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，由于在降温导管置入后的20分钟内我们未记录体温，降温时间可能因此被高估(图)。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达到目标体温的时间。

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，体温持续24小时。接下来的研究应该关注急性缺血性卒中后低体温持续时间。

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[7]。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，以使患者脑温后更佳。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过少，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内给予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) 研究发现肺炎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 治疗至少 36 小时，而 NT 组患者则多入住普通病房。然而除卒中外，低体温也会抑制免疫系统 [29]，低体温的脓毒血症患者或术后低体温者的感染风险增加 [30]。此外，哌替啶的应用降低了呼吸频率，这可能导致误吸。与其它抗寒战治疗相比，哌替啶的呼吸抑制风险更低 [31-33]。该项研究的资料不足以让我们对肺炎的发生归咎于低体温导致的免疫抑制，或将误吸风险的增高归咎于哌替啶或其它未知因素。低体温的免疫抑制作用有待于进一步的研究证实。低体温的肺炎发病率的增高可能掩盖了该治疗方法给 3 个月时临床预后带来的获益。

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论
血管内低温可以与溶栓治疗联合应用。抗寒战治疗方法在清醒卒中患者中的应用是可行的。在给予低温治疗的患者中，肺炎的发生率升高，但与预后不良无关。需要进一步更大样本量，更早给予低温治疗的研究来评估缺血性卒中低体温治疗的有效性。

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