Endovascular Hypothermia in Acute Ischemic Stroke
Pilot Study of Selective Intra-Arterial Cold Saline Infusion

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Background and Purpose—We conducted a pilot feasibility and safety study of selective brain cooling with intra-arterial infusion of cold saline combined with endovascular reperfusion for acute ischemic stroke.

Methods—Patients with large-vessel occlusion within 8 hours after symptom onset were enrolled. All patients received intra-arterial recanalization combined with infusion of cold isotonic saline (4°C) in the ischemic territory through the angiographic catheter.

Results—Twenty-six patients underwent the procedure, which was technically successful in all. The temperature of ischemic cerebral tissue was decreased by at least 2°C during infusion of the cold solution, and systemic temperature was mildly reduced (maximum 0.3°C). No obvious complications related to intra-arterial hypothermia were observed.

Conclusions—Selective brain cooling by intra-arterial infusion of cold saline combined with endovascular recanalization therapy in acute ischemic stroke seems feasible and safe. (Stroke. 2016;47:1933-1935. DOI: 10.1161/STROKEAHA.116.012727.)

Key Words: endovascular procedures • hypothermia • intra-arterial infusions • neuroprotection • reperfusion injury

Neuroprotective effects of hypothermia in acute ischemic stroke have been demonstrated in various animal experiments, but these results have not been convincingly confirmed in patients. Systemic hypothermia often leads to adverse effects that may offset the potential beneficial effects of hypothermia.

Endovascular recanalization therapy by intra-arterial thrombolysis, stenting, or mechanical clot extraction has proven effective in patients with large proximal vessel occlusion. We have previously shown in animal studies that selective intra-arterial cold saline infusion is feasible during endovascular treatment. In this study, we evaluated the feasibility and safety of this technique in patients.

Methods

Patient Selection
The study was approved by the ethical review board of Xuanwu Hospital, Capital Medical University. Between November 2013 and August 2014, patients with large proximal vessel occlusion within 8 hours after symptom onset were enrolled. We used patient selection criteria as reported previously. Inclusion criteria for the current study were as follows: (1) age between 18 and 80 years; (2) initial National Institute of Health Stroke Scale [NIHSS] score ≥8; (3) patient treated within 8 hours from symptom onset; (4) acute occluded proximal artery could be recanalized through thrombectomy with stent retriever.

Infusion Protocol
We modified the intra-arterial infusion method described previously as follows: patients remained in the supine position and the guiding catheter was positioned in the cervical part of the vertebral or internal carotid artery. Before recanalization, we infused 50 mL cold 0.9% sodium chloride (4°C) in the ischemic territory through the angiographic catheter. We have previously shown in animal studies that selective intra-arterial cold saline infusion is feasible during endovascular treatment. In this study, we evaluated the feasibility and safety of this technique in patients.

Data Collection and Analysis
Before, during, and after infusion of the cold solutions, vital parameters and laboratory tests were recorded. All patients were monitored for potential complications. Rectal temperature was monitored continuously to reflect the systemic temperature during operation. Only descriptive statistics are used in this study.
Results

During the study period, 28 patients underwent thrombectomy. Of these, 26 were included in the study. Two patients were excluded because we were unable to pass the thrombus with the catheter. Mechanical thrombectomy was performed under conscious sedation (16 cases) or general anesthesia (10 cases). Baseline manifestations are provided in Table 1.

The procedure of cold sodium chloride infusion was successful in all patients. During infusion, rectal temperature was decreased to 0.1°C, but returned to normal within 5 minutes after infusion. Vitals were stable and electrolytes and hematocrit did not change significantly before, during, and after treatment (Table 2). Adverse events are listed in Table 3.

Discussion

To the best of our knowledge, this is the first clinical study that examined the feasibility and safety of selective brain cooling by intra-arterial infusion of cold saline in patients with acute ischemic stroke caused by large proximal artery occlusion. Our results suggest that selective brain cooling by intra-arterial infusion of cold saline is feasible and safe in patients with acute ischemic stroke.

Several theoretical models of the human brain demonstrated that an infusion of ice-cold saline at ≈30 mL/min is sufficient to induce moderate hypothermia within 10 minutes. Intra-carotid infusion of cold saline (4–10°C) at 33 mL/min led to a rapid decrease by 0.84±0.13°C in jugular venous bulb temperature in patients undergoing diagnostic cerebral angiograms. Using these data as inputs in a 3-dimensional human brain model, another study inferred that ipsilateral cerebral anterior circulation territory temperature decreased by ≈2°C within 10 minutes. In the present study, we modified this selective brain cooling method by infusing cold saline not only after recanalization but also before recanalization. Thus, we anticipate that we could have achieved at least a 2°C temperature drop in the ischemic territory. Brain temperature drops quickly when cold saline infusion starts and to the lowest point at the end of infusion. After that, brain temperature recovers to normal in several minutes.

Our previous animal studies indicated that intra-arterial local solution infusion before reperfusion could flush the microvasculature in the ischemic region and it may result in neuroprotection by removing accumulated toxins and biochemical byproducts in compromised vascular-parenchymal tissue caused by ischemia, and hypothermia induced before recanalization may also concur stronger neuroprotection. Because of concerns on potential delay in revascularization using saline infusion, cold arterial blood may be used as an alternative coolant to initiate hypothermia before reperfusion being established. This concept was proven effective in our animal study.

During cold saline infusion, vital signs were stable, except that rectal temperature temporarily decreased by a mild amount. In addition, no significant changes in electrolytes and hematocrit were observed. During endovascular procedure and hospitalization, there were no severe complications related to intra-arterial infusion of cold saline.

There are limitations in our study. It was difficult to directly monitor brain temperature considering the risk of intracranial hemorrhage in patients with acute ischemia who

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Cooling</th>
<th>During Cooling</th>
<th>Post Cooling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>102±14</td>
<td>103±10</td>
<td>105±18</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>74±8</td>
<td>66±8</td>
<td>67±6</td>
</tr>
<tr>
<td>Pulse oxygen saturation, %</td>
<td>99±3</td>
<td>99±2</td>
<td>99±2</td>
</tr>
<tr>
<td>Laboratory values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>43.76±4.96</td>
<td>43.42±4.92</td>
<td></td>
</tr>
<tr>
<td>K, mmol/L</td>
<td>4.37±0.49</td>
<td>4.24±0.52</td>
<td></td>
</tr>
<tr>
<td>Na, mmol/L</td>
<td>139.42±3.55</td>
<td>138.72±2.92</td>
<td></td>
</tr>
<tr>
<td>Cl, mmol/L</td>
<td>102.48±3.71</td>
<td>101.97±3.21</td>
<td></td>
</tr>
</tbody>
</table>

bpm indicates beats per minute; Cl, chlorine; K, potassium; MAP, mean arterial pressure; and Na, sodium.
Table 3. Adverse Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients (Incidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular spasm</td>
<td>4 (15.4%)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td>Coagulation disorder</td>
<td>2 (7.7%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10 (38.5%)</td>
</tr>
<tr>
<td>Melena</td>
<td>2 (7.7%)</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>0</td>
</tr>
<tr>
<td>Neurological deterioration</td>
<td>4 (15.4%)</td>
</tr>
<tr>
<td>Progressive ischemic stroke</td>
<td>0</td>
</tr>
</tbody>
</table>

ICH indicates intracranial hemorrhage.

often receive antithrombotic treatment. Thus, we used data from a previous study to estimate the temperature reduction. Although rectal temperature could be an easy way to monitor whole body temperature, it may be not accurate enough for core temperature. This is a small, nonrandomized, and single-arm observational study on safety and feasibility of endovascular brain cooling procedure. Studies on clinical efficacy of this therapy are warrant in future randomized clinical trials.

Sources of Funding

This work was supported by grants from the National Science and Technology Supporting Plan (2011BAI08B07) and Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (ZY201309).

Disclosures

Dr Liebeskind received a research grant from the National Institutes of Health (National Institute of Neurological Disorders and Stroke K24NS072272) and is the consultant for Imaging Core Laboratory for Stryker and Medtronic.

References


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Stroke. 2016;47:1933-1935; originally published online May 19, 2016;
doi: 10.1161/STROKEAHA.116.012727

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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