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Endovascular hypothermia in acute ischemic stroke: A pilot study of selective intra-arterial cold saline infusion

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Abstract

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 (AIS).

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) into the ischemic territory through the angiography 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 appears feasible and safe.

Keywords

selective hypothermia; ischemia/reperfusion injury; endovascular recanalization; neuroprotection

Introduction

Neuroprotective effects of hypothermia in acute ischemic stroke have been demonstrated in various animal experiments, but these results have not been convincingly confirmed in

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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 included: (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) into the ischemic territory at 10 ml/minute through a microcatheter which was put across the thrombus and used to send the stent retriever, thus allowing the cold solutions to infuse into the ischemic territory pre-reperfusion. After that, intra-arterial mechanical clot extraction with a stent retriever was performed to recanalize the occluded vessel. As soon as blood flow was restored, cold 0.9% sodium chloride (4°C) was infused into the ischemic brain tissue through the guiding catheter at 30 ml/minute for 10 minutes.

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 decreased 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 due to 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 about 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 three-dimensional human brain model, another study inferred that ipsilateral cerebral anterior circulation territory temperature decreased by approximately 2°C within 10 minutes. In the present study, we modified this selective brain cooling method by infusing cold saline not only after, but also prior to 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 prior to 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 due to ischemia, and hypothermia induced prior to recanalization may also concur stronger neuroprotection[–]. Due to concerns regarding potential delay in revascularization using saline infusion, cold arterial blood may be used as an alternative coolant to initiate hypothermia prior to 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 acute ischemic patients who often receive antithrombotic treatment. Thus, we used data from a previous study to estimate the temperature reduction. Although rectal temperature could be an easily to monitor whole body temperature, it may be not accurate enough for core temperature. This is a small, non-randomized and single arm observational study on safety and feasibility of endovascular brain cooling procedure. Studies on clinical efficacy of this therapy is warrant in future randomized clinical trials.

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Disclosures

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References

1. Kamatovskaia LV, Wartenberg KE, Freeman WD. Therapeutic hypothermia for neuroprotection: history, mechanisms, risks, and clinical applications. The Neurohospitalist. 2014; 4:153–163. [PubMed: 24982721]
2. Krieger DW, De Georgia MA, Abou-Chebl A, Andrefsky JC, Sila CA, KatzanI L, et al. Cooling for Acute Ischemic Brain Damage (COOL AID): an open pilot study of induced hypothermia in acute ischemic stroke. Stroke. 2001; 32:1847–1854. [PubMed: 11486115]
3. Hemmen TM, Raman R, Guluma KZ, Meyer BC, Gomes JA, Cruzflores S, et al. Intravenous thrombolysis plus hypothermia for acute treatment of ischemic stroke (ICTuS-L): final results. Stroke. 2010; 41:2265–2270. [PubMed: 20724711]
4. Piironen K, Tiainen M, Mustanoja S, Kaukonen KM, Meretoja A, Tatlisumak T, et al. Mild hypothermia after intravenous thrombolysis in patients with acute stroke: a Randomized Controlled Trial. Stroke. 2014; 45:486–491. [PubMed: 24436240]
5. Hong JM, Lee JS, Song HJ, Jeong HS, Choi HA, Lee K. Therapeutic hypothermia after recanalization in patients with acute ischemic stroke. Stroke. 2014; 45:134–140. [PubMed: 24203846]
6. American Heart Association Stroke Council. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment. Stroke. 2015; 46:3020–3035. [PubMed: 26123479]
7. Ding Y, Li J, Luan X, Lai Q, McAllister JP 2nd, Phillis JW, et al. Local saline infusion into ischemic territory induces regional brain cooling and neuroprotection in rats with transient middle cerebral artery occlusion. Neurosurgery. 2004; 54:956–964. discussion 964-955. [PubMed: 15046664]
8. REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. NEngl J Med. 2015; 372:2296–306.
9. Choi JH, Marshall RS, Neimark MA, Konstas AA, Lin E, Chiang YT, et al. Selective brain cooling with endovascular intracarotid infusion of cold saline: a pilot feasibility study. Am J Neuroadiol. 2010; 31:928–934.
10. Konstas AA, Neimark MA, Laine AF, Pile-Spellman J. A theoretical model of selective cooling using intracarotid cold saline infusion in the human brain. J Appl Physiol. 2007; 102:1329–1340. [PubMed: 17170208]
11. Neimark MA, Konstas AA, Lee L, Laine AF, Pile-Spellman J, Choi J. Brain temperature changes during selective cooling with endovascular intracarotid cold saline infusion: simulation using human data fitted with an integrated mathematical model. J Neurointerv Surg. 2013; 5:165–171. [PubMed: 22270331]
12. Ding Y, Li J, Rafols JA, Phillis JW, Diaz FG. Prereperfusion saline infusion into ischemic territory reduces inflammatory injury after transient middle cerebral artery occlusion in rats. Stroke. 2002; 33:2492–2498. [PubMed: 12364743]
13. Ding Y, Li J, Luan X, Lai Q, McAllister JP 2nd, Phillis JW, et al. Local saline infusion into ischemic territory induces regional brain cooling and neuroprotection in rats with transient middle cerebral artery occlusion. Neurosurgery. 2004; 54:956–964. [PubMed: 15046664]

14. Cheng H, Ji X, Ding Y, Luo Y, Wang G, Sun X, et al. Focal perfusion of circulating cooled blood reduces the infarction volume and improves neurological outcome in middle cerebral artery occlusion. Neurol Res. 2009; 31:340–345. [PubMed: 19508815]

Table 1

Baseline characteristics

Characters	Value
Mean age (years, mean ± SD)	58.4±9.56
Female (No,%)	11 (42.3%)
Initial temperature (°C, Interquartile range)	36.9(36.7; 37.0)
ASPECTS (Interquartile range)	6(6; 9)
NIHSS (Interquartile range)	18(12; 22)
Risk factors (No, %)	
Hypertension	16 (61.5%)
Atrial fibrillation	3 (11.5%)
Previous stroke	3 (11.5%)
Diabetes	14 (53.8%)
Smoking	15 (57.7%)
Occluded vessel (No, %)	
ICA	8 (30.8%)
MCA M1	10 (38.5%)
MCA M2	2 (7.6%)
BA/VA	6 (23.1%)
Symptom onset-groin puncture (minutes, median)	383 (195–432)
Recanalization therapy (No, %)	
Mech (Solitaire)	18 (69.2%)
Stenting	3 (11.5%)
Mech + Stenting	5 (19.3%)
TICI(2b/3)	26 (100%)
Infarct volume (mm^3, Interquartile range)	21(14; 25)

ASPECTS: Alberta Stroke Program Early CT Score; **Mech** mechanical clot extraction;**TICI** thrombolysis in cerebral infarction; **MCA** middle cerebral artery; **ICA** internal carotid artery; **BA**; basilar artery; **VA** vertebral artery; **NIHSS** national institute of health stroke scale

Table 2

Changes of vitals and laboratory values during cooling procedure

Variable	Before cooling	During cooling	Post cooling
Vitals			
MAP (mmHg)	102±14	103±10	105±18
Heart rate (beats/min)	74±8	66±8	67±6
Pulse oxygen saturation (%)	99±3	99±2	99±2
Laboratory values			
Hematocrit(%)	43.76±4.96		43.42±4.92
K (mmol/L)	4.37±0.49		4.24±0.52
Na(mmol/L)	139.42±3.55		138.72±2.92
Cl(mmol/L)	102.48±3.71		101.97±3.21

MAP: Mean arterial pressure;

Table 3

Adverse events

Variable	No. of patients (incidence)
Vascular spasm	4(15.4%)
Deep vein thrombosis	1(3.8%)
Coagulation disorder	2(7.7%)
Pneumonia	10(38.5%)
Melena	2(7.7%)
Symptomatic ICH	0
Neurological deterioration	4(15.4%)
Progressive ischemic stroke	0

ICH: Intracranial hemorrhage