Prospective Cohort Study

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Impact of immediate postrecanalization cooling on outcome in acute ischemic stroke patients with a large ischemic core: prospective cohort study

Xuesong Bai, MD[a,d], Xin Qu, MD[a,d], Raul G. Nogueira, MD[i], Wenhuo Chen, MD[h], Hao Zhao, MD[a,d], Wenbo Cao, MS[a,d], Peng Gao, MD[a,d,b], Bin Yang, MD[a,d], Yabing Wang, MD[a,d], Jian Chen, MD[a,d], Yanfei Chen, MD[a,d], Yuxin Wang, MS[a], Feng Shang, MD[a,d], Weitao Cheng, MD[a,d], Yueqiao Xu, MD[a,d], Meng Qi, MD[a,d], Lidan Jiang, MD[a,d], Wenjin Chen, MD[a,d], Jie Lu, MD[e,f], Qingfeng Ma, MD[c], Ning Wang, MD, PhD[a,d,*], Liqun Jiao, MD, PhD[a,d,b,g,*]

Background: Patients with large acute ischemic strokes (AIS) often have a poor prognosis despite successful recanalization due to multiple factors including reperfusion injury. The authors aim to describe our preliminary experience of endovascular cooling in patients with a large AIS after recanalization.

Methods: From January 2021 to July 2022, AIS patients presenting with large infarcts (defined as ASPECTS ≤ 5 on noncontrast CT or ischemic core ≥ 50 ml on CT perfusion) who achieved successful recanalization after endovascular treatment were analyzed in a prospective registry. Patients were divided into targeted temperature management (TTM) and non-TTM group. Patients in the TTM group received systemic cooling with a targeted core temperature of 33° for at least 48 h. The primary outcome is 90-day favorable outcome [modified Rankin Scale (mRS) 0–2]. The secondary outcomes are 90-day good outcome (mRS 0–3), mortality, intracranial hemorrhage and malignant cerebral edema within 7 days or at discharge.

Results: Forty-four AIS patients were recruited (15 cases in the TTM group and 29 cases in the non-TTM group). The median Alberta Stroke Program Early CT Score (ASPECTS) was 3 (2–5). The median time for hypothermia duration was 84 (71.5–147.6) h. The TTM group had a numerically higher proportion of 90-day favorable outcomes than the non-TTM group (46.7 vs. 27.6%, $P = 0.210$), and no significant difference were found regarding secondary outcomes (all $P > 0.05$). The TTM group had a numerically higher rates of pneumonia (66.7 vs. 58.6%, $P = 0.604$) and deep vein thrombosis (33.3 vs. 13.8%, $P = 0.138$). Shivering occurred in 4/15 (26.7%) of the TTM patients and in none of the non-TTM patients ($P = 0.009$).

Conclusions: Postrecanalization cooling is feasible in patients with a large ischemic core. Future randomized clinical trials are warranted to validate its efficacy.

Keywords acute ischemic stroke, endovascular treatment, targeted temperature management

Introduction

Acute ischemic stroke (AIS) is a leading cause of morbidity and mortality worldwide[1]. Early recanalization of the occluded artery is crucial to achieve favorable outcomes of AIS[2,3]. After several landmark randomized controlled trials, endovascular thrombectomy (EVT) has been recommended as the first-line therapy for AIS patients due to large vessel occlusion in the anterior circulation[3,4]. Despite the exciting recent advancements, the outcomes of patients with a large ischemic core [the Alberta Stroke Program Early CT Score (ASPECTS) ≤ 5 or ischemic core ≥ 50 ml] still remain a critical concern[5]. Although EVT may achieve successful recanalization in over 80% of the patients, the rates of favorable functional outcome [modified Rankin Scale (mRS) 0–2] in patients with large ischemic infarcts has been reported to be around 14.0–30.0%[4–6]. There are several reasons

[a]Department of Neurosurgery, [b]Department of Interventional Neuroradiology, [c]Department of Neurology, Xuanwu Hospital, Capital Medical University, [d]Department of Neurosurgery, China International Neuroscience Institute, [e]Department of Radiology and Nuclear Medicine, [f]Beijing Key Laboratory of Magnetic Resonance Imaging and Brain Informatics, Beijing, [g]Department of Neurosurgery and Neurology, Jinan Hospital of Xuanwu Hospital, Shandong First Medical University, Jinan, [h]Department of Neurology, Zhangzhou Affiliated Hospital, Fujian Medical University, Zhangzhou City, Fujian Province, People's Republic of China and [i]University of Pittsburgh Medical Center Stroke Institute, Department of Neurology and Neurosurgery, University of Pittsburgh School of Medicine, Pittsburgh, USA

Xuesong Bai and Xin Qu contributed equally and are co-first authors.

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*Corresponding authors. Address: Department of Neurosurgery, Xuanwu Hospital, Capital Medical University No. 45 Changchun Street Xicheng District, Beijing 10053, People's Republic of China. Tel.: +860 108 319 8277; fax: +860 108 319 9233. E-mail: liqunjiao@sina.cn (L. Jiao), and Tel.: +860 108 392 2776; fax: +86 010 63040170. E-mail: ningjing _wd@163.com (N. Wang).

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for the poor outcomes in these patients including the extensive loss of eloquent brain matter as well as ischemic reperfusion injury and/or neuroinflammation supporting the need to explore post-EVT adjunctive therapies.

Immediate cooling after successful recanalization is a promising treatment option. Targeted temperature management (TTM) is a potent neuroprotective method with robust evidence from experimental stroke models, especially in the ischemic-reperfusion stage[7]. It can alleviate the injury through multiple mechanisms, such as inhibiting neuroinflammation and decreasing free radical production[8–11]. A prospective cohort study showed TTM could reduce the risk of cerebral edema and hemorrhagic transformation, and lead to improved clinical outcomes in AIS patients with a median ASPECTS of six after successful recanalization[12]. Few studies have investigated the therapeutic effect of TTM in patients with a large ischemic core and suggested potential benefits. In one study, 10 (55.6%) of 18 patients with substantial ischemia who received postrecanalization cooling achieved a favorable outcome at 3 months[13]. Another study showed TTM could improve functional outcomes in EVT patients with malignant trait defined as[1] baseline Alberta Stroke Program Early CT Score (ASPECTS) below 6 and[2] diffusion-weighted imaging lesion volume measurement (>82 ml) or National Institutes of Health Stroke Scale score >20 and item Ia >0[14]. The current study describes our preliminary experience of post-EVT endovascular cooling in successfully recanalized patients with large ischemic infarcts, to provide clinical evidence for clinicians and guidance for future researches.

HIGHLIGHTS

- The therapeutic effect of targeted temperature management in patients with large ischemic infarcts remains unclear and requires clarification.
- Postrecanalization cooling is feasible in patients with large ischemic infarcts, and numerically increased the chance of a favorable outcome.
- This study adds to the body of literature highlighting the need for well-conducted randomized trials to validate the efficacy.

Methods

Patient selection

The data of this study is from a prospective clinical trial registered in the ClinicalTrial.gov registry. Patients who received successful EVT were recruited. The approval of the local ethics committee of the participating centers was obtained. The work has been reported in line with the strengthening the reporting of cohort, cross-sectional and case–control studies in surgery (STROCSS) criteria[15]. All patients or their legal guardian were informed about the nature, purpose, and potential risks of the trial and signed informed consent forms before participation.

The inclusion criteria were as follows (1): age 18–80 years old (2); AIS Large Vessel Occlusion in the anterior circulation (internal carotid artery, middle cerebral artery M1 or M2 segment) (3); ASPECTS ≤ 5 or ischemic core ≥ 50 ml (ischemic core defined as the relative cerebral blood flow <30% on CT perfusion) (4); Arterial puncture performed within 24 h from symptom onset (5); Baseline National Institutes of Health Stroke Scale (NIHSS) score prior to randomization ≥ 10 and NIHSS 1a ≥ 1 (6); Successful recanalization (modified thrombolysis in cerebral infarction [mTICI] 2b–3) after EVT; mTICI 2b was defined as antegrade reperfusion of at least half of the target territory, mTICI 2c as reperfusion of 90–99% and mTICI 3 as complete reperfusion[16] (7); No immediate intracranial hemorrhage (ICH) after recanalization (8); an informed consent form signed by subjects or their legal guardian. The exclusion criteria were as follows (1): Known presence of an IVC filter (2); End stage renal disease on hemodialysis (3); History of bleeding diathesis, coagulopathy, cryoglobulinemia (4); Use of warfarin with INR >3 (5); Hemodynamically significant cardiac dysrhythmias and severe ventricular dysrhythmias (6); Platelet count $<40\times10^9$/l (7); Evidence of ICH or hemorrhagic transformation immediately after thrombectomy[8]. Expected life expectancy less than 6 months. More details of the inclusion and exclusion could be found from the website.

EVT was performed and the first-line strategy include aspiration, stent-retriever, and a combined approach. Rescue treatment include intra-arterial medications, angioplasty, intracranial/extracranial stenting, or a combination at the discretion of neurointerventionist. After successful recanalization, eligible patients received 'postrecanalization cooling' (TTM group) or not (non-TTM group) based on the recommendation of the neurointerventionist and preference of the patients or their legal guardians. In the TTM group, postrecanalization cooling was done in the ICU immediately after successful recanalization treatment.

All TTM patients received analgesia, sedation, endotracheal intubation, and mechanical ventilation. A silicone urethral catheter with a temperature probe (Guangzhou Weili Medical Equipment Co., Ltd.) was inserted into the bladder to monitor core body temperature in all patients. Sedatives (e.g. midazolam, propofol, and dexmedetomidine) and analgesics (remifentanil and meperidine) were used to prevent shivering before implementing hypothermia treatment. The dose of midazolam was 20–100 μg/kg/h, propofol 4–12 mg/kg/h, dexmedetomidine 0.2–0.7 μg/kg/h, remifentanil 0.02–0.15 μg/kg/h, meperidine 0.03–0.06 mg/kg/h, respectively, depending on the patient's body weight, initial core temperature, blood pressure, heart rate, and shivering status. A heat exchange catheter (Quattro catheter) was placed to the inferior vena cava via femoral vein access and connected to an external heat exchange machine (CoolGard 3000). A maximum rate of 2°/h was used to lower the bladder temperature to 33° rapidly during the induction period, then the core temperature was maintained for at least 48 h. Thereafter, rewarming was started gradually at a rate of 0.1°/h until the bladder temperature reached 36.0° and then heat exchange catheter was removed. Induction time refers to the time from starting body temperature management to reaching the target temperature. The hypothermia duration time is to the time from reaching the target temperature to the start of rewarming. During the cooling period, the patient was closely monitored for any complications.

Both clinical and radiologic data were collected. Clinical data included age, sex, comorbidities (e.g. hypertension, diabetes mellitus, coronary artery disease), baseline NIHSS, baseline ASPECTS, bridging with intravenous thrombolysis, etc. The procedure information of EVT included time from onset to recanalization (OTR) and recanalization status (mTICI grade).

After EVT, a dynamic CT was performed to exclude ICH. For the patients in the TTM group, information related to 'post-recanalization cooling', such as recanalization-to-cooling initiation time, cooling induction time, and cooling duration were specifically documented. Image data included baseline ASPECTS from noncontrast CT scan (NCCT) and occlusion site, which was diagnosed from initial CTA and confirmed with digital subtraction angiography. Recanalization status was evaluated using the mTICI score based on the final angiogram of the procedure and successful recanalization was defined as grade 2b-3. Follow-up NCCT or MRI were performed within 7 day after operation or at discharge to evaluate ICH and cerebral edema. The images were evaluated by an independent imaging core lab (IsCore Image Corelab). Automatic CT perfusion (CTP) evaluation software, RAPID (iSchema View, version, 5.0.2) was used to estimate the ischemic core and hyperperfused volumes. The relative cerebral blood flow (rCBF) <30% for CT perfusion was used to define the ischemic core.

Outcomes

The primary outcome was the rate of favorable outcome (mRS 0-2) at 90 days. Secondary outcomes were ICH within 7 days after EVT or at discharge, 90-day good outcome (mRS 0–3), 90-day mortality (mRS 6), and malignant cerebral edema (MCE) within 7 days or at discharge. MCE were outlined as mass effect during the follow-up NCCT or cerebral herniation caused by the mass effect from edema, needing decompressive craniectomy or leading to death due to the mass effect[17].

Adverse events, including pneumonia, deep vein thrombosis (DVT), electrolyte imbalance, and shivering were also compared. Pneumonia was defined as any clinical findings at auscultation, along with new pulmonary infiltrate on the chest radiograph (persistent on follow-up for more than 48 h), and with an increase in serum white blood cell count[13]. When pneumonia was diagnosed, the patient was immediately treated with appropriate antibiotics. Electrolyte imbalance was defined as any abnormal findings, including hypernatremia, hyponatremia, hyperkalemia, or hypokalemia. DVT was routinely screened by ultrasonography[13]. Shivering was graded using the Bedside Shivering Assessment Scale (BSAS), a 4-point scale ranging from 0 (no shivering noted on palpation of the masseter, neck, or chest wall) to 4 (shivering involves gross movements of the trunk and upper and lower extremities).

Statistical analysis

Patients were classified as TTM and non-TTM groups. Baseline characteristics were analyzed and compared between the two groups. For qualitative variables, data were compared using the χ^2 test or Fisher's exact tests, when appropriate, and presented as frequency and percentage. For quantitative variables, the normality of the data was assessed using the Shapiro – Wilk test. Data with a normal distribution and a non-normal distribution were compared using the Student's *t*-test or Mann – Whitney *U* test, respectively. Data were presented as mean ± SD or as median with interquartile range. The primary and secondary clinical outcomes were analyzed, intergroup differences were compared using univariable logistic regression analysis or the χ^2 test when appropriate. All calculations were performed using SPSS software, version 26.0 (IBM Corporation). A value of two-tailed $P < 0.05$ was considered statistically significant.

Results

From January 2021 to July 2022, a total of 44 AIS patients meeting the inclusion criteria were recruited, including 15 cases in the TTM group and 29 cases in the non-TTM group. The median age of the patients was 59 (53–68) years, and 32 (62.7%) were males. The median NIHSS score was 17 (12–21) and ASPECTS was 3 (2–5). The median time of stroke onset to reperfusion time (OTR) was 462 (365.5–708.2) min. A total of 35 (79.5%) patients achieved mTICI 2c/3 and 9 (20.5%) mTICI 2b.

A comparison of demographic and baseline characteristics between the TTM and non-TTM group are shown in Table 1. There was a higher proportion of males in the TTM than the non-TTM group with a borderline significance (93.3 vs. 62.1, $P = 0.064$). Patients in the TTM group has a higher proportion of smoking (46.7 vs. 13.8%, $P = 0.043$). There were no significant differences in other demographics (e.g. age and comorbidities), clinical procedural characteristics (e.g. NIHSS and ASPECTS), and procedure information (e.g. OTR and mTICI grade).

Details of the parameters of postrecanalization cooling are shown in Table 2. The median time of recanalization-to-cooling initiation was 144 (130–177) min, and the median time of onset-to-cooling initiation was 580 (522–676) min. All patients successfully achieved the target temperature with a median time of induction of 118 (84–120) min. The median time for hypothermia duration was 84 (71.5–147.6) h.

The outcome comparisons between TTM and non-TTM is shown in Table 3. The TTM group had a numerically higher proportion of favorable outcome than the non-TTM group (46.7 vs. 27.6%, $P = 0.210$). There were no significant differences in the rates of good outcome (90-day mRS 0–3: 60 vs. 51.7%, $P = 0.602$), 90-day mortality (20.0 vs. 13.8%, $P = 0.595$), any ICH (46.7 vs. 51.7%, $P = 0.751$), and MCE (40.0 vs. 37.9%, $P = 0.894$). Compared with the non-TTM group, the TTM group had a numerically higher rates of pneumonia (66.7 vs. 58.6%, $P = 0.604$), electrolyte imbalance (60.0 vs. 48.3%, $P = 0.462$), and DVT (33.3 vs. 13.8%, $P = 0.138$). There were four cases of shivering (three cases had BSAS score 1 had BSAS score 2) occurred in the TTM group, with a significant higher proportion of shivering in the TTM group was observed than the non-TTM group (26.7 vs. 0%, $P = 0.009$).

Discussion

In the current study, compared to EVT alone, combined EVT and postrecanalization cooling showed a numerically higher rate of favorable outcome (mRS ≤ 2) at 90 days in AIS patients with a large ischemic core, although the difference was not significant. Meanwhile, a potential increase of adverse effects, such as pneumonia, DVT and shivering, was also observed.

Recently, several trials have been conducted to prove the superiority of thrombectomy over best medical treatment alone (BMT) in patients with large ischemic infarcts[4–6]. However, even with tremendous success in recanalization of occluded arteries over 80%, a high risk of any ICH (49.1–58.0%), and a low chance of a favorable outcome (14.0–30.0%) remained. Therefore, adjunctive therapy to improve the unsatisfactory efficacy of recanalization therapy in this setting is needed. In a prospective cohort study of AIS patients with median ASPECTS of 6, after successful recanalization, TTM may reduce the risk of cerebral edema and hemorrhagic transformation, and led to

Table 1

Baseline characteristics comparison between TTM and non-TTM groups.

	Total $N=44$	TTM $N=15$	Non-TTM N = 29	*P*
Demographics				
Age, median (IQR)	59 (53-68)	56 (49-67)	62 (56-68)	0.181
Male, *n* (%)	32 (62.7)	14 (93.3)	18 (62.1)	0.064
HTN, *n* (%)	24 (54.5)	8 (53.3)	16 (55.2)	0.908
DM, *n* (%)	5 (11.4)	2 (13.3)	3 (10.3)	1.000
Dyslipidemia, *n* (%)	7 (15.9)	4 (26.7)	3 (10.3)	0.333
CAD, *n* (%)	1 (2.3)	1 (6.7)	0 (0)	0.341
AF, *n* (%)	12 (27.3)	2 (13.3)	10 (34.5)	0.256
Smoking , *n* (%)	11 (25.0)	7 (46.7)	4 (13.8)	0.043*
Stroke history, *n* (%)	3 (6.8)	1 (6.7)	2 (6.9)	1.000
Antiplatelet use, *n* (%)	0 (0)	0 (0)	0 (0)	NA
Anticoagulation use, *n* (%)	2 (4.5)	0 (0)	2 (6.9)	0.54
Clinical characteristics				
Intravenous thrombolysis, *n* (%)	14 (31.8)	4 (26.7)	10 (34.5)	0.852
NIHSS, median (IQR)	17 (12–21)	19 (16–20)	15 (12–21)	0.321
ASPECTS, median (IQR)	3 (2–5)	3 (3–4)	3 (2–5)	0.597
Occlusion site, *n* (%)				
ICA	18 (40.9)	9 (60.0)	9 (31.0)	0.064
MCA	24 (54.5)	6 (40.0)	20 (69.0)	
Procedure				
OTD, min, median (IQR)	342 (208–568)	298 (217–369)	360 (172–690)	0.465
OTR, min, median (IQR)	462 (366–708)	447 (379–547)	518 (331–815)	0.586
Recanalization status				0.259
mTICI 2b	9 (20.5)	5 (33.3)	4 (13.8)	
mTICI 2c/3	35 (79.5)	10 (66.7)	25 (86.2)	

AF, atrial fibrillation; ASPECTS, Alberta Stroke Program Early CT score; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; ICA, internal carotid artery; IQR, interquartile rang; MCA, middle cerebral artery; mTICI, the modified Thrombolysis in Cerebral Infarction score; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; OTD, time from onset to door; OTR, time from onset to recanalization; TTM, targeted temperature management.

*P <0.05.

improved favorable outcomes (48.7 vs. 22.2%)[12]. Furthermore, the study of Hwang *et al.*[13] showed that 10 (55.6%) of 18 patients with ASPECTS ≤ 5 achieved a favorable outcome at 3 months after immediate postrecanalization systemic cooling. A multicenter thrombectomy registry showed malignant traits patients in the TTM group could achieve a higher rate of favorable outcome than the non-TTM group (32.1 vs. 7.7%, $P=0.009$) and TTM was found to be independent determinant of favorable outcome[14]. In this study, the numerically higher rates of favorable outcome (46.7 vs. 27.6%) in patients with a large ischemic core and receiving postrecanalization cooling further supported TTM in carefully selected patients. The results of our preliminary study call for validation from more studies, especially randomized trials.

Preclinical and clinical studies suggest that hypothermia is most beneficial in protecting against ischemia-reperfusion injury[7,18]. Our data further support this finding because we only selected those with successful recanalization, similarly to some other studies supporting the advantage of TTM[12,13]. Also, it should be noted that recruited patients had a median time of OTR 447 min and onset to cooling initiation of 580 min. In the study of Hwang *et al.*[13], median time of OTR and onset to cooling initiation was even shorter (211.5 min and 295.0 min, respectively), and a higher rate of favorable functional outcome was achieved (55.6%). The current study had a longer target temperature duration time (84 h vs 34.5 h). In the study of Hong *et al.*[12], endovascular recanalization was required to be within 6 h after symptom onset. A potential concern with the current trial protocol may be the prolonged delay between the recanalization and cooling to attainment of the target temperature. It is assumed that reperfusion injury may begin within the first hours of recanalization[18]. The reported recanalization-to-cooling initiation time is around 2 h[12,13]. So, initiation of hypothermia as soon as possible to reduce the risk of blood-brain barrier disruption immediately after recanalization would be essential. The optimal timing of TTM is worthy further exploration in studies with large sample size.

Table 2

Postrecanalization cooling parameters.

Parameters	$N=15$
Reperfusion-to-cooling initiation time, min, median (IQR)	144 (130–177)
Onset-to-cooling initiation time, min, median (IQR)	580 (522–676)
Induction time, min, median (IQR)	118 (84–120)
Hypothermia duration, h, median (IQR)	84 (71.5–147.6)

Common side effects remain a major concern of TTM application in clinical practice. The most common is pneumonia, possibly due to its detrimental effect on inflammatory reactions such as the secretion of proinflammatory cytokines and leukocyte migration[19]. Meanwhile, some researchers observed a comparable length of hospitalization even with an increased risk of pneumonia, and some studies do not support the increased risk of pneumonia[20]. The current study also showed a similar phenomenon of a higher risk of pneumonia (66.7 vs. 58.6%) without impacting the final functional outcome. Another nonnegligible side effect of TTM is DVT. In this study, the risk of DVT in TTM

Table 3

The outcomes comparison between TTM and non-TTM group.

	Total ($n=44$)	TTM ($n=15$)	Non-TTM ($n=29$)	OR/β (95%CI)	*P*
Favorable outcome, *n* (%)	15 (34.1)	7 (46.7)	8 (27.6)	0.435 (0.119–1.599)	0.210
Good outcome, *n* (%)	24 (54.5)	9 (60.0)	15 (51.7)	0.714 (0.202–2.528)	0.602
Mortality, *n* (%)	7 (15.9)	3 (20.0)	4 (13.8)	1.562 (0.301–8.117)	0.595
ICH, *n* (%)	22 (50)	7 (46.7)	15 (51.7)	0.817 (0.234–2.847)	0.751
MCE, *n* (%)	17 (38.6)	6 (40.0)	11 (37.9)	1.091 (0.304–3.910)	0.894
Complications					
Pneumonia, *n* (%)	27 (61.4)	10 (66.7)	17 (58.6)	1.412 (0.383–5.197)	0.604
Electrolyte imbalance, *n* (%)	23 (52.3)	9 (60.0)	14 (48.3)	1.607 (0.454–5.688)	0.462
Deep vein Thrombosis, *n* (%)	9 (20.5)	5 (33.3)	4 (13.8)	3.125 (0.693–14.082)	0.138
Shivering, *n* (%)	4 (26.7)	4 (26.7)	0 (0)	NA (NA)	0.009*[b]
BSAS score[a], *n* (%)					
0 (none)	40 (90.9)	11 (73.3)	29 (100.0)		
1 (mild)	3 (6.8)	3 (20.0)	0 (0)		
2 (moderate)	1 (2.3)	1 (6.7)	0 (0)		
3 (severe)	0 (0)	0 (0)	0 (0)		

BSAS, Bedside Shivering Assessment Scale; ICH, intracranial hemorrhage; MCE, malignant cerebral edema; NA, not applicable; TTM, targeted temperature management.
*P <0.05.
[a]Score at maximum during cooling.
[b]P value was calculated by chi-square test.

group was much higher than that reported in the study of Hwang *et al*. (33.3 vs 5.6%)[13]. We hypothesize the main reason is due to more extended TTM in this study (hypothermia duration 84.0 vs 51.0 h). The evidence supporting extended hypothermia is hemorrhagic transformation and cerebral edema usually occurs between 2 and 5 days after stroke so longer duration hypothermia could improve clinical outcomes[12,21,22]. How to prevent DVT and the define the optimal duration of TTM still need more studies. Furthermore, a risk of shivering is observed during TTM, but shivering could be well controlled by antishivering medications (three cases with mild shivering and one case with moderate shivering in this study). In short, the risk of side effect of TTM, especially pneumonia and DVT, should be weighed against the potential benefits of neuroprotection. With the accumulation of experience and following standard protocol, TTM may results in neuroprotective benefits as long as being safely implemented.

This study has several limitations and the results should be interpreted with caution. First, despite encouraging results, the efficacy of TTM cannot be concluded given the small sample size of this study. Second, baseline characteristics were not totally balanced (e.g. smoking) and the comparison of outcomes was not adjusted due to the limited sample size. Third, the external validity of our study may be needed. Regardless of the aforementioned shortcomings, the current study provided new perspective and potential settings of clinical application of TTM in AIS. The safety and efficacy of TTM in patients with a large ischemic infarct after recanalization need to be further validated in future studies, especially randomized clinical trials.

Conclusions

In conclusion, postrecanalization cooling is feasible in treating patients with a large ischemic core. Future randomized clinical trials are warranted to validate its efficacy in improving functional outcome.

Ethics approval

The study procedures were approved by Ethics Committee of Xuanwu Hospital, Capital Medical University No. [2020]085.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

X.B., X.Q., N.W. and L.J.: participated in the designation and conceptualization of this study; X.B., X.Q. and W.C.: conducted data curation and statistical analysis; W.C., P.G., J.C., B.Y., T. W., Y.C. Y.W., H.Z., F.S., W.C., Y.X., M.Q., L.J., W.C., Q.M., N.W. and L.J.: provided clinical data; W.C. and J.L.: provided imaging data; X.B., X.Q., W.C., N.W. and L.J.: drafted and collated the manuscript; X.B., X.Q., W.C., R.G.N., and L.J.: edited and revised the manuscript. All the authors read and finally approved the published manuscript and are responsible for ensuring the accuracy and completeness of the work.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Guarantor

Liqun Jiao, Department of Neurosurgery and Department of Interventional Radiology, Xuanwu Hospital, Capital Medical University, No. 45 Changchun Street, Xicheng District, Beijing 100053, People's Republic of China. E-mail: liqunjiao@sina.cn.

Data availability statement

Data are available upon reasonable request.

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