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Title	Regional transarterial hypothermic infusion in combination with endovascular thrombectomy in acute ischaemic stroke with cerebral main arterial occlusion : protocol to investigate safety of the clinical trial
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BMJ Open Regional transarterial hypothermic infusion in combination with endovascular thrombectomy in acute ischaemic stroke with cerebral main arterial occlusion: protocol to investigate safety of the clinical trial

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ABSTRACT

Introduction Acute cerebral ischaemia with main cerebral artery occlusion requires treatment with intravenous tissue plasminogen activator administration and/or endovascular thrombectomy. However, some patients fail to recover even after recanalisation because of ischaemia/reperfusion (I/R) injury. We hypothesised that regional transarterial hypothermic infusion would be effective for patients with I/R injury. The aim of this study is to validate the safety of this procedure.

Methods and analysis This is a clinical exploratory study to evaluate safety of regional transarterial hypothermic infusion in combination with endovascular thrombectomy. Patients with acute ischaemic stroke and a National Institutes of Health Stroke Scale (NIHSS) score of 5–29 who require endovascular thrombectomy are eligible for the study. When no improvement in NIHSS score after the recanalisation is achieved by thrombectomy, cold saline (15°C) will be administered through a microcatheter located in the ipsilateral internal carotid artery. The primary endpoints of this study are mortality and morbidity. The secondary endpoint is deleterious effects on clinical data such as symptoms, radiographic findings and physiological data. The primary and secondary endpoints will be accumulated as case series because this study will be conducted on a small sample of seven patients.

Ethics and dissemination All protocols and the informed consent form comply with the Ethics Guideline for Clinical Research (Japanese Ministry of Health, Labour and Welfare). Ethics review committees at the Hokkaido University Hospital approved the study protocols. The results of the study will be disseminated at several research conferences and also contributed to peer-reviewed journals. The study will be implemented and reported in line with the SPIRIT statement.

Trial registration number UMIN Clinical Trials Registry (UMIN000018255); pre-results

INTRODUCTION

Since stroke is one of the leading causes of disability and death worldwide,¹¹ the

Strengths and limitations of this study

- This protocol will provide evidence concerning the safety of a new therapeutic strategy for acute ischaemic stroke.
- The study is a multicentre study involving teams with great experience in endovascular management of stroke.
- The study cannot examine the efficacy of regional transarterial hypothermic infusion itself because there is no attention placebo control group.

establishment of treatments and prevention of stroke is a very important issue. In particular, treatment of acute ischaemic stroke (AIS) has attracted much attention because acute intervention for revascularisation offers the chance to reverse the development of infarctions. Patients refractory to intravenous tissue plasminogen activator (tPA) need to be subjected to endovascular thrombectomy to obtain recanalisation. Recently, several randomised controlled trials (RCTs) on endovascular thrombectomy proved the efficacy of this therapy for AIS.^{2–5 5 6} In these RCTs, endovascular thrombectomy using a stent retriever together with medical treatment, including intravenous tPA, was significantly superior to medical treatment alone with respect to functional recovery at 3 months in patients with AIS with occlusion of the intracranial internal carotid artery (ICA) or M1 segment of the middle cerebral artery (MCA). Although the rate of recanalisation was quite high in the RCTs, there were still several patients with poor endpoints after successful recanalisation. It is critical and important to understand the reasons for these poor endpoints after

recanalisation in order to develop a therapeutic strategy to solve this problem. Secondary tissue damage after revascularisation is well documented as ischaemia/reperfusion (I/R) injury in animal transient ischaemic models. Development of neuroprotective therapies against I/R injury has been assessed in animal transient MCA occlusion (MCAO) models.

Previous studies have shown selective brain hypothermia by transarterial cooling to be effective for brain protection in animal experiments.⁷⁻⁹ In addition to these studies, we have demonstrated that transarterial regional hypothermia inhibited sequential microvascular reactions, leading to strong neuroprotective effects in a rat MCAO model.¹⁰ Recently, a pilot feasibility and safety study of selective brain cooling was performed with intra-arterial infusion of cold saline combined with endovascular reperfusion for AIS.¹¹ In this study, cold saline (4°C) was infused into the ischaemic territory through an angiographic catheter to obtain at least a 2°C temperature drop in the ischaemic territory. Although the authors concluded that infusion of 4°C cold saline was safe, there is still a concern that conditions at these low temperatures may mediate endothelial/cell hypothermic injury, which was demonstrated in cultured vascular endothelial cells under conditions of 8°C for 20 min.¹² Therefore, in the present study, we are setting the temperature of infused saline at 15°C to avoid hypothermic injury. We will administer 15°C saline at 10 mL/min for 10 min through a microcatheter located in the ipsilateral ICA for regional transarterial hypothermia.

Objectives

The purpose of this study is to confirm the safety and evaluate the prevention of deleterious effects on clinical data of transarterial cold saline infusion.

METHODS AND ANALYSIS

Study design and setting

As this is a clinical exploratory study to evaluate the safety of the therapy, there is no randomisation and patients who provide informed consent undergo the universal treatment. The study outline of patient flow is shown in [figure 1](#). Patients will be recruited from five hospitals, namely Hokkaido University Hospital (HUH), Otaru General Hospital (OGH), Chitose City Hospital (CCH), Hokkaido Neurosurgical Memorial Hospital (HNMH) and Kashiwaba Neurosurgical Hospital (KNH), which are categorised into three types: a university teaching hospital (HUH), general hospitals (OGH and CCH) and neurosurgical hospitals (HNMH and KNH). Each hospital accepts patients with stroke who require critical care and each can provide both intravenous tPA administration and endovascular thrombectomy immediately, carried out by neurosurgical interventional radiology (IVR) specialists at any time.

Inclusion and exclusion criteria

Patients are eligible to be included in the study if they have AIS with moderate to severe neurological

symptoms, radiologically confirmed occlusion of the proximal or anterior circulation arteries, no large or completed core infarct and indication of intravenous tPA administration. If the artery is not successfully recanalised after the initiation of intravenous tPA, percutaneous thrombectomy will be performed. If the artery is successfully recanalised by thrombectomy but the ischaemic symptoms persist, the patient will proceed to study intervention. It is necessary that the proxies are competent and able to give informed consent. Full and detailed study inclusion and exclusion criteria are listed in [box 1](#). We do not exclude patients medicated by oral anticoagulants or antiplatelets.

Procedures

Recruitment

Because of the nature of our study design, each candidate appears unexpectedly. When a patient who is suspected to have suffered AIS is brought into the hospital, the investigator will quickly assess their eligibility for the study. Cerebral MRI and MR angiography (MRA) will be performed at the same time. Sequences of MR images are as minimal as possible to shorten the time before starting treatment. If the patient is prohibited from undergoing MRI for some reason, CT will be performed. After the diagnosis of AIS is made, and if the candidate has none of the exclusion criteria and satisfies the criteria for intravenous tPA administration, the investigator will provide the patient or the proxies (if it is difficult for the patient to give informed consent) with information about the study. After informed consent is obtained, the investigator will immediately begin intravenous tPA administration (0.6 mg/kg of body weight, the recommended dose in Japanese guidelines) and will proceed with the IVR procedure. If the occluded artery is revealed as intracranial ICA or the M1 segment of the MCA and is still not recanalised after tissue plasminogen activator administration, endovascular thrombectomy will subsequently be performed. If no improvement in National Institutes of Health Stroke Scale (NIHSS) score after the recanalisation is achieved by endovascular thrombectomy, the patient will proceed to the study intervention.

Baseline assessment

Acute neurological status such as the Glasgow Coma Scale, the Japan Coma Scale and the NIHSS will be assessed by the investigator on arrival of the patient, and cerebral MRI/MRA or CT will be performed. Demographic data and medical history will be collected as a part of the baseline assessment. Physical examinations, including blood pressure and laboratory data examination, will be performed as well as the usual stroke treatment.

Randomisation

All eligible patients who consent to participation will proceed to the same study intervention, since the study is exploratory. There is no randomisation.

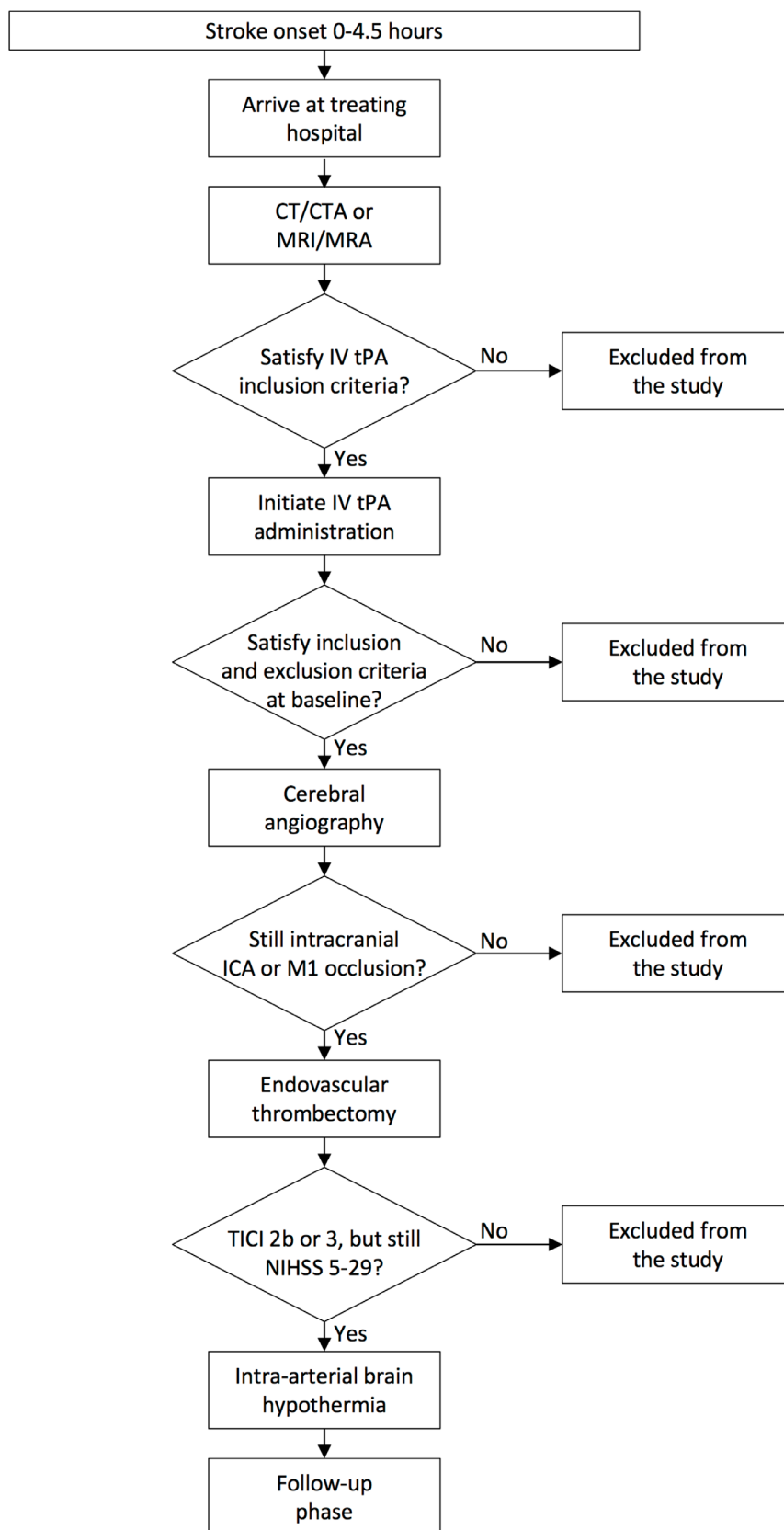


Figure 1 Study design for the study of brief local brain hypothermia in combination with endovascular thrombectomy for patients with tissue plasminogen activator refractory cerebral ischaemia in the internal carotid artery territory (tPA Cool IVR Study). CTA, CT angiography; ICA, internal carotid artery; IV tPA, intravenous tissue plasminogen activator; M1, first segment of the middle cerebral artery; MRA, MR angiography; NIHSS, National Institutes of Health Stroke Scale; TICI, thrombolysis in cerebral infarction.

Box 1 Study inclusion and exclusion criteria*Inclusion criteria at baseline*

- ▶ Age 20–85 years
- ▶ Clinical signs consistent with AIS
- ▶ Prestroke modified Rankin Score 0 or 1
- ▶ Pretreatment NIHSS scores 5–29
- ▶ Initiation of intravenous tPA within 4.5 hours of onset of stroke symptoms (onset time is defined as the last time when the patient was witnessed to be at baseline)
- ▶ Occlusion of the intracranial ICA or the M1 segment of the MCA confirmed by MR or CT angiography
- ▶ Percutaneous thrombectomy is available within 8 hours of onset of stroke symptoms
- ▶ Appropriate informed consent is available from the proxies of the patient before the treatment

Inclusion criteria at thrombectomy phase

- ▶ TICI 2b or 3 flow is obtained after thrombectomy
- ▶ No improvement of NIHSS score after the recanalisation is achieved by thrombectomy

Exclusion criteria at baseline

- ▶ Contraindication to intravenous tPA according to national guidelines
- ▶ Rapid neurological improvement prior to study intervention suggesting resolution of signs or symptoms of stroke
- ▶ Contraindication of using iodine contrast agent
- ▶ Current participation in another clinical study
- ▶ Blood pressure >185 mm Hg as systolic or >110 mm Hg as diastolic even though appropriate therapy before intervention
- ▶ Blood glucose <50 mg/dL or >400 mg/dL even though appropriate therapy before intervention
- ▶ Platelets <5.0 × 10⁴/μl³
- ▶ Renal failure as defined by serum creatinine >2.0 mg/dL or GFR <30
- ▶ Liver dysfunction defined as serum AST and/or ALT >100 IU/L or serum bilirubin >2.0 mg/dL
- ▶ Suspicion of aortic dissection or aortic aneurysm rupture
- ▶ Known history of arterial tortuosity or arterial disease including post-treatment status that would prevent the device delivery to the target artery
- ▶ Abuses of alcohol or illicit drugs
- ▶ Comorbid disease that would confound the neurological assessment or completion of follow-up assessment at 3 months
- ▶ No proxies appear at the emergency room by the time of starting intravenous tPA or thrombectomy

Imaging exclusion criteria

- ▶ Haemorrhagic stroke such as subarachnoid haemorrhage, intracerebral haemorrhage or haemorrhagic infarction, revealed by CT or MRI
- ▶ Intracranial tumour (except small meningioma) revealed by CT or MRI
- ▶ Cerebral vasculitis revealed by CT or MRI
- ▶ CT hypodensity or MR DWI hyperintensity involving greater than one-third of MCA territory (or including other territories, >100 cm³ of brain tissue)
- ▶ ASPECTS <6 by CT or MR DWI
- ▶ Concomitant acute cerebral ischaemia due to vertebral artery, basilar artery or posterior cerebral artery occlusion CT or MRI
- ▶ Judgement by the study neurosurgeon as inappropriate for the study because of the other image findings obtained by CT or MRI

Exclusion criteria by catheter angiography

- ▶ Carotid dissection or complete cervical carotid occlusion that would require carotid artery stenting by catheter angiography
- ▶ Complete or partial recanalisation is obtained after intravenous tPA and there is no occlusion in the intracranial ICA or the M1 segment of the MCA by catheter angiography

AIS, acute ischaemic stroke; ALT, alanine transaminase; ASPECTS, Alberta Stroke Program Early CT score; AST, aspartate transaminase; DWI, diffusion-weighted imaging; GFR, glomerular filtration rate; ICA, internal carotid artery; tPA, tissue plasminogen activator; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; TICI, thrombolysis in cerebral infarction.

Intervention phase

The investigator will perform angiography immediately after checking the inclusion and exclusion criteria. Puncture of the artery does not rely on whether or not intravenous tPA administration is finished. If the occluded artery is not successfully recanalised, endovascular thrombectomy will be performed. If the patient's NIHSS does not improve after endovascular thrombectomy, the patient will proceed to regional transarterial hypothermic infusion. These procedures will be performed by using intravenous administration of diazepam and pentazocine

as well as local anaesthesia (xylocaine injection at puncture site).

With regard to endovascular thrombectomy, the method and technique of thrombectomy in the study do not differ from the usual AIS therapy that is approved in Japan and in the USA. The investigator will use a Penumbra System (Penumbra, Alameda, California, USA) or a stent retriever system including a Solitaire FR (eV3/Covidien Neurovascular, Irvine, California, USA) and a Trevo ProVue Retriever (Stryker, Kalamazoo, Michigan, USA). The thrombectomy technique using these



devices is the same as previously reported.^{13–15} The combination of a Penumbra and a stent retriever or multiple stent retriever systems will be used.

For regional transarterial hypothermic infusion, the investigator will place a microcatheter in the ICA of the ipsilateral side with its tip distal to the origin of the ophthalmic artery. Through the microcatheter, 15°C saline will be administered into the ICA at 10 mL/min for 10 min (100 mL in total). The investigator will strictly monitor the vital signs and neurological status during the administration of 15°C saline. ICA angiography will be performed to confirm the patency of the recanalised artery. If the vital signs or neurological status show abnormalities, or the recanalised artery becomes occluded, spastic or stenotic again, the administration of 15°C saline will be stopped immediately. The vital signs abnormalities are defined as follows: systolic blood pressure under 90 or over 180; heart rate under 50 or over 100 and respiratory failure despite appropriate treatment. Abnormalities of neurological status are defined as seizure, anisocoria or repeating vomiting. After completing cold saline administration, angiography will be performed 10 min later to check the condition of the recanalised artery.

Temperature setting of cold saline

Two papers have previously reported cold saline infusion into cerebral arteries performed in a clinical setting. One was conducted during angiography with an average of 7°C saline,¹⁶ while the other one was reported for endovascular hypothermia with 4°C saline.¹¹ Both studies concluded that the procedure was safe, but Awad *et al* demonstrated hypothermic injury in cultured human vascular endothelial cells under conditions of 8°C for 20 min.¹² Therefore, we decided that the temperature of the infused saline should be higher than 8°C. On the other hand, Ding *et al* reported that 20°C cold saline infusion was effective in reducing infarct volume and enabling neuroprotection in the rat model of temporary MCAO.⁸ Thus, taking both of these results into consideration, we determined that the cold saline temperature in the present study will be set at 15°C.

Follow-up phase

After regional transarterial hypothermic infusion, the patient will be treated in the stroke care unit. The investigator will check the MRI, MRA and CT scans closely and will monitor the vital and neurological signs. Edaravone, a brain-protective agent, will be administered. An anti-epileptic drug will also be used to prevent seizure attacks. If a brain oedema is detected by MRI or CT, glycerine or mannitol will be administered. When progression of brain oedema is severe and brain herniation occurs despite the aforementioned treatment, decompressive craniotomy will be performed. These treatments will be performed in the same way as usually carried out for a patient with AIS, and other therapeutic methods will also be equivalent to the usual protocols. Specific monitoring of the study after intervention is shown in [table 1](#).

In the acute phase, it will be mandatory to conduct physical and neurological examinations, image analysis of MRI/MRA or CT and laboratory data collection at 24 and 48 hours after arrival at the hospital.

Discontinuations

Discontinuation of intervention phase

If the patients meet any of the following criteria, the investigator will discontinue the study intervention. The patients receive appropriate treatment at all times other than the interventional procedure.

1. The patient or the proxies withdraw consent to undergo the study intervention.
2. The investigator judges that it is inappropriate to continue the study intervention due to, for example, a severe vital sign crisis, estimated intracranial haemorrhage or perforation of the cerebral artery, even if effective recanalisation is obtained.
3. The investigator judges that it is difficult to continue the study intervention because of the emergence of adverse events or another appropriate reason that outweighs the benefit of undergoing the study intervention.
4. The investigator judges that it is more appropriate for the patient to undergo direct embolectomy by emergent craniotomy surgery.

Discontinuation of follow-up phase

If the patient withdraws consent to undergo follow-up study assessment, he/she will be considered to have dropped out and will not be contacted for a follow-up assessment in the future.

Safety of the intervention procedure

The procedure before cold saline infusion is the same as usual treatment. Although transarterial cold saline infusion is interventional and has insufficient clinical safety data, the temperature setting of 15°C in this study takes patient safety into careful consideration as mentioned in the section 'Temperature setting of cold saline'. Careful patient monitoring during and after the procedure will also take place, as already mentioned.

Adverse events

The estimated adverse events are as follows:

1. Subarachnoid haemorrhage: the perforation of an artery by placement or removal of a microcatheter during injection of the cold agent.
2. Haemorrhagic infarction: sometimes seen after thrombectomy because of reperfusion injury. Heparin added to the saline for the inhibition of catheter thrombosis may aggravate haemorrhagic infarction.
3. Infection: artificial devices placed in the blood may cause infection. Antibiotics will be administered if this occurs.
4. Seizure: cerebral infarction and recanalisation injury may themselves cause seizures, and brain hypothermia

Table 1 Schedule of the assessments

	Enrolment	Baseline	Intervention	Follow-up			
Time point	-1	0		After 24 hours	After 48 hours	After 1 month	After 3 months
Enrolment							
Eligibility	X						
Informed consent	X						
Interventions							
tPA			X				
Thrombectomy			X				
IABH			X				
Assessments							
Demographics		X					
NIHSS		X		X	X	X	X
Prestroke mRS	X						
mRS						X	X
Physical examination		X	X	X	X	X	X
Neurological examination		X	X	X	X	X	X
Radiological examination		X	X	X	X	X	
Laboratory data		X	X	X	X		
Safety			X	X	X	X	X
Adverse events			X	X	X	X	X

Physical, neurological and radiological examinations, and laboratory data are also assessed at appropriate times during the hospitalisation period. Radiological examination comprises MRI and angiography, but if impossible for any reason, CT scans and angiography are performed instead. Radiological examination includes Alberta Stroke Program Early CT score (ASPECTS) by CT or MRI scoring at baseline. IABH, intra-arterial brain hypothermia; mRS, modified Rankin Score; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.

- may also induce seizures. Antiepileptic drugs will be used prophylactically after the procedure.
5. Cerebrovascular spasm: intra-arterial cold agent irrigation may induce cerebrovascular spasms. Cerebral infarction may occur if the cerebrovascular spasm is severe.
 6. Temperature drop of whole body: the temperature may drop in the brain and in the whole body. Shivering may occur when the temperature is below 35°C. If arrhythmia induced by hypothermia occurs, antiarrhythmics will be used. The body trunk will be covered with a blanket or electric blanket to maintain body temperature.
 7. Other symptoms: various symptoms, such as a headache, nausea or dizziness, may occur as a result of change in the intracranial environment.

Outcome measures

The primary endpoints are mortality and morbidity. The secondary endpoint is deleterious effects on clinical data. Details are described below and are also shown in [table 1](#).

Primary endpoints

Primary endpoints will be measured by mortality 90 days after the treatment and by morbidity as described in 'Adverse events' above or other unexpected adverse

events and complications. Each adverse event or complication will be evaluated using the following three categories: (1) mild case: careful observation is required but there is no necessity for treatment; (2) moderate case: treatment is required but early improvement is expected and (3) severe case: treatment is required and early improvement is not expected. 'Serious adverse events and complications' will also be evaluated. Their definitions are as follows: (1) fatal, (2) life-threatening, (3) permanent or severe disorder or disability, (4) resulting in congenital abnormality in the descendants and (5) requirement of admission or prolonged hospitalisation period.

The adverse events and complications described here are also seen in the usual treatment of AIS caused by major cerebral artery occlusion. They will be evaluated carefully whether or not they are induced mainly by the intervention procedure.

Secondary endpoints

Symptoms

No worsening of NIHSS score during the follow-up compared with the baseline. Each item of NIHSS evaluation such as consciousness, motor paresis, sensory disturbance, dysarthria, aphasia, visual field and ataxia will also be assessed.



Radiographic findings

No worsening of infarct area and brain oedema in the follow-up compared with the baseline. Infarct area and the level of brain oedema will be measured by MRI or CT. Brain oedema is quantified by visualising the midline shift of the brain to the contralateral hemisphere.

Physiological data

No worsening of physiological data. Effects of the brief local brain hypothermia on blood pressure, heart rate, body temperature, wave of the ECG and laboratory data will be evaluated.

Sample size estimation

As this study is an exploratory clinical study, the sample size is set to seven based on the primary endpoint of safety. The statistical calculation is based on seven cases being enough to detect more than one event such that the occurrence rate is about 20% with probability of 79%. This is calculated as follows. The probability for each patient not suffering from the event whereby the occurrence rate is 20% is 80% ($1-0.20=0.80$). Thus, the rate of all seven patients having no such event is $0.80^7 \approx 0.21$. Therefore, we can detect more than one event whereby the occurrence rate is about 20% with the probability of 79% ($1-0.21 \approx 0.79$).

We estimated the event incidence as 20% on the basis of past reported RCTs, namely the Interventional Management of Stroke 3 Study and the Synthesis Expansion Study, which evaluated a new technique associated with endovascular thrombectomy for AIS.^{17 18} In these two RCTs, the mortality rates of groups including thrombectomy were 19.1% and 26%, respectively.^{17 18}

In addition, as this novel treatment is being attempted for the first time in Japanese patients, the safety assessment should be carefully conducted for each case; a larger sample size would be difficult because of the limited funds available and time restrictions associated with patient recruitment and data collection.

Statistical analysis

The primary and secondary endpoints will be accumulated as case series because this study consists of a small sample. For the primary endpoint, the mortality rate and its 95% CI will be calculated. For the sequential data, the transition of the data in each case will be indicated.

Data collection and management

To ensure accurate, complete and reliable data, and to ensure the safety of the participants in the study, the investigator will keep records of the paper instruments and clinical records as source documents for the study in the patient files in the security box at the office of the Department of Neurosurgery, Hokkaido University. Only the authors will be given access to the data sets.

Study monitoring

Periodic meetings will be held with the authors and the data manager at the Hokkaido University

Clinical Research and Medical Innovation Center. The data manager will conduct periodic inspections of the accumulated endpoint data throughout the course of the study the Data Safety Monitoring Committee (DMSC), including expert neurosurgeons who belong to other universities, and they may request additional evaluations and follow-up of patients who have clinically significant events or have been discontinued from the study.

Interim analyses

Data from the first three patients will be presented to the DMSC 1 month after the intervention in order to make a judgement about the safety of continuation of the study. Only when the DMSC approves the continuation of the study will the next patient be allowed to register for the study. When the DMSC judges that the first three patients have undergone safe interventions and approves the continuation of the remaining patients, four more patients will be added and a total of seven patients will be evaluated and judged.

Premature termination of the study

The study will be terminated if the principal investigator (KH), on advice from the DMSC, judges that it is necessary for medical safety, for instance, if a causal relationship between the study intervention and severe side effects is established or there is a serious ethical violation of the Ethics Guideline for Clinical Research (Japanese Ministry of Health, Labour and Welfare, revised in 2008).

Reporting of adverse events

All adverse events reported spontaneously by patients or observed by the investigators will be recorded. If an adverse event occurs, the treating neurosurgeon will take all necessary and appropriate measures to ensure the safety of the patient.

Based on the Ethics Guideline for Clinical Research (Japanese Ministry of Health, Labour and Welfare, revised in 2008), a severe side effect is defined as 'an adverse event that may lead to death or to enduring severe impairment depending on the patient's conditions and circumstances' and will include: (1) death (all deaths, regardless of a causal relationship with the intervention, during the intervention phase or up to 30 days after the completion of the intervention); (2) a life-threatening event and (3) an event leading to an enduring and severe impairment and dysfunction. The investigator will report any severe side effects immediately to the principal investigator (KH), and the principal investigator will notify all collaborating investigators. The principal investigator will report any severe side effects to the ethics review committee and, if it concerns an unforeseeable event, to the Japanese Ministry of Health, Labour and Welfare.

Ethical considerations and dissemination

Ethics approval for the study protocol was obtained from the institutional review board (IRB) of HUH (reference no 014-0426). The IRB of each study hospital, other than

HUH, also approved the study. The study is registered in the UMIN Clinical Trials Registry: UMIN000018255.

Informed consent

The investigator will be responsible for ensuring that the patient or proxies understand the potential risks and benefits of participating in the study and answering any questions the patient or proxies may have throughout the study, as well as sharing in a timely manner any new information that is relevant to the patient's willingness to continue his or her participation in the study.

An informed consent form will be used to explain the potential risks and benefits of the study participation to the proxies in simple terms before the patient is entered into the study and to document that the proxies are satisfied with their understanding of the risks and benefits of participation in the study. An appropriate signature and dates on the informed consent form will be obtained before administration of the intervention. If the patient recovers from AIS and is able to understand his/her situation after the treatment, the investigator will explain the study registration that has been approved by his or her proxies and will receive informed consent again from the patient.

Ethics review

The principal investigator (KH) must agree on the protocol and informed consent form before they are able to submit them to the IRB. They must comply with the Ethics Guideline for Clinical Research (the Japanese Ministry of Health, Labour and Welfare, revised in 2008). The IRB will review the protocol as required. When the protocol needs to be amended for a legitimate reason, such as safety concerns, it will be revised and, after agreement from the principal investigator, will be submitted to the IRB for review.

Compensation and insurance for harmed patients

The medical expenses for the treatment will be paid by the patient because the treatment will be supplied as a healthcare service provided under national health insurance. If a serious complication or severe side effect occurs and damages the health of the patient during or after completion of participation in the study, appropriate measures will be taken. HUH, to which the principal investigator (KH) is affiliated, will prepare a compensation reserve for severe health damage such as death or severe sequelae caused by the study. Other health damage will be covered by the health insurance treatment. There will be no reward payment for the patient or the proxies in the study.

Research fund and conflict of interest

This study will be performed using the commission management fund of the office to which the principal investigator (KH) belongs. All investigators will comply with the policy on conflicts of interest for clinical research guidelines at HUH and will report all necessary items to

the committee of conflict of interest at HUH for investigation and approval.

Dissemination

The results of the study will be disseminated at several research conferences and will also be contributed to peer-reviewed journals. The study will be implemented and reported in line with the SPIRIT statement. Reporting of the study also adheres to the CONSORT extension for pilot and feasibility trials.

DISCUSSION

The present study aims to provide evidence concerning the safety of a new therapeutic strategy for AIS. When the safety is proved, the next clinical study will be planned to verify the effectiveness of regional transarterial hypothermic infusion for patients with AIS. In this study, as a secondary endpoint, deleterious effects will be also examined by symptomatic, radiological and physiological assessment.

There are some limitations of this study. First, the number of patients recruited to the study is small. As the primary endpoint of the study is safety, seven patients are enough to validate this with data analysis. When the safety is proved in this study, the next clinical study will be designed to prove the effectiveness of regional transarterial hypothermic infusion in a greater number of patients. Second, the severity of symptoms caused by AIS at the time of enrolment will vary for each patient. The time from onset to the door will be also different. Although these factors will affect the symptomatic endpoint, the primary endpoint is the safety of the intervention, and the differences among these factors will be evaluated in the future clinical study. The additional neuroprotective effects of edaravone for the endpoints should be considered, but these will be distinguished from the effects of regional brain hypothermia in the future clinical study. The third limitation is the possible technical differences among the investigators. Five hospitals are included in this study and any patient who matches the inclusion criteria will appear unexpectedly, at any time, and require treatment as promptly as possible, so multiple neurosurgeons who can perform IVR of AIS will be required. Their technical skills are more than adequate enough to perform the study protocol and they will also have the ability to manage unexpected situations during the intervention procedure. In addition, before the initiation of patient registration, the technical director of this study (TO) will give technical lectures about the study intervention for every investigator who will potentially perform the study intervention. To surmount some of these limitations, we plan to design the next study with a larger sample size and to assign patients with stratification of symptom severity such as baseline NIHSS score.

If the effectiveness of regional transarterial hypothermic infusion for AIS is proved in humans as well as



the several animal experiments already reported, AIS treatment will undergo a drastic change. It is hoped that the results of the current study will represent the first step of a new treatment approach for patients with AIS.

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Contributors TA and KH conceived and designed the study. TA and TO drafted the protocol of the study and supervised the study implementation. KH and KT refined the protocol and implementation of the study. KO, TA and TO conducted the sample size estimation and will perform statistical analysis. TO provided IVR techniques of the study for each investigator belonging to the hospitals other than Hokkaido University Hospital. KT and KK wrote the manuscript.

Competing interests KH is a member of a board of directors of the Japanese Neurosurgical Society.

Ethics approval The institutional review board (IRB) of Hokkaido University Hospital (reference no 01420426) and the IRB of each study hospital other than Hokkaido University Hospital approved this study.

Provenance and peer review Not commissioned; externally peer reviewed.

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