Decompressive craniectomy combined with mild hypothermia in patients with large hemispheric infarction: A randomized controlled trial

Linlin Fan  
Xuanwu Hospital  
https://orcid.org/0000-0002-0926-9685

Yingying Su (✉ suyingying@xwh.ccmu.edu.cn)  
Yan Zhang  
Xuanwu Hospital

Hong Ye  
Xuanwu Hospital

Weibi Chen  
Xuanwu Hospital

Gang Liu  
Xuanwu Hospital

Research article

Keywords: large hemispheric infarction, decompressive craniectomy, target temperature management, randomized controlled trial, neurological outcome

DOI: https://doi.org/10.21203/rs.3.rs-38307/v3

License: ☺️  This work is licensed under a Creative Commons Attribution 4.0 International License.  
Read Full License
Abstract

Background: The effect of hypothermia on large hemispheric infarction (LHI) remains controversial. Our study aimed to explore the therapeutic outcomes of decompressive craniectomy (DC) combined with hypothermia on LHI.

Methods: Patients were randomly divided into three groups: the DC group, the DC plus head surface cooling (DCSC) group and the DC plus endovascular hypothermia (DCEH) group. The DC group was maintained normothermia. The DCSC group received 24-hour ice cap on the head for 7 days. While the DCEH group were given endovascular hypothermia (34°C). Mortality and modified Rankin Scale (mRS) score at 6 months were evaluated.

Results: Thirty-four patients were included in the study. Mortality of the DC, DCSC and DCEH groups at discharge were 22.2% (2/9), 0% (0/14) and 9.1% (1/11), respectively. However, it increased to 44.4% (4/9), 21.4% (3/14) and 45.5% (5/11) at 6 months, respectively (P=0.367). Pneumonia (8 cases) was the leading cause of death after discharge. Twelve cases (35.3%) achieved good neurological outcome (mRS 0-3) at 6 months. The proportions of good neurological outcome in the DC, DCSC and DCEH groups were 22.2% (2/9 cases), 42.9% (6/14 cases) and 36.4% (4/11), respectively. The DCSC group seemed to have higher proportion of good outcomes, but there was no significant difference between groups (p=0.598). Among survivors, endovascular hypothermia had a higher proportion of good outcome (DC group, 2/5 cases, 40.0%; DCSC group, 6/11 cases, 54.5%; DCEH group, 4/6 cases, 66.7%; p=0.696). The incidence of complications in the DCEH group was higher than those of the DC and DCSC groups (18.9%, 12.0%, and 12.1%, respectively; P=0.025).

Conclusions: There is still no evidence to confirm that hypothermia further reduces long-term mortality and improves neurological outcomes in LHI patients with DC. However, there is a trend to benefit survivors from hypothermia. A local cooling method may be a better option for DC patients, which has little impact on systematic complications.

Clinical Trial Registration- Decompressive Hemicraniectomy Combined Hypothermia in Malignant Middle Cerebral Artery Infarct, ChiCTR-TRC-12002698. Registered 11 Oct 2012- Retrospectively registered, URL: http://www.chictr.org.cn.

Background

Large hemispheric infarction (LHI) is the most malignant type of supratentorial ischemic stroke. The mortality rate in these patients is as high as 53% to 78%, even after the strongest available medical treatments(1-5). Although randomized controlled trials (RCTs) have demonstrated that decompressive craniectomy (DC) can reduce mortality to 17% to 36%, the neurological outcomes in survivors, of whom 33.3% to 70.0% have an mRS of 4-5(2-8), are not ideal.
Preclinical trials have demonstrated that mild hypothermia provides neuroprotective effect and reduces intracranial pressure (ICP). It also effectively prevents disruptions to the blood-brain barrier; reduces cerebral glucose metabolism, oxygen consumption, the accumulation of excitotoxic neurotransmitters, intracellular acidosis, intracellular calcium influx and oxygen-free radical production; alters the expression of “cold shock proteins”; reduces brain edema; minimizes the risk of thrombosis; and decreases the risk of epileptic activity (9-14). Our RCT also showed that in LHI non-DC patients, better neurological outcomes were achieved in the surviving patients in the hypothermia group than in the control group (7/8, 87.5% versus 4/10, 40.0%, \( P = 0.066; \text{OR}=10.5, 95\% \text{CI} 0.9–121.4 \) (8). These results demonstrate that mild hypothermia may improve neurological outcomes in survivors. Thus, we proposed that DC combined with mild hypothermia could improve both mortality and neurological outcomes in LHI patients. Therefore, we conducted this RCT to investigate the effect of DC combined with hypothermia treatment in LHI.

**Methods**

**General Design**

This prospective, single-center RCT was approved by the Ethics Committee of Xuanwu Hospital Capital Medical University, Beijing. Written informed consent was obtained from all patients or designated surrogates. The trial was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR-TRC-12002698). We need to state that some of the method sections have been used in our previous publication (8).

**Patient Population**

From July 2010 to June 2016, patients with acute ischemic stroke in Department of Neurology, Xuanwu Hospital Capital Medical University were screened for eligibility. Eligible criteria was as follows: (1) aged 18 to 80 years old, (2) acute unilateral ischemic stroke within 48 hours after symptom onset, (3) infarction involving at least two-thirds of the middle cerebral artery (MCA) territory on cranial computed tomography or magnetic resonance imaging, (4) a reduced level of consciousness indicated by a National Institutes of Health Stroke Scale (NIHSS) item 1a score \( \geq 1 \), and (5) able to undergo DC within 48 hours after symptom onset.

Patients were excluded if any of the following criteria was met: (1) premorbid mRS score >2; (2) secondary hemorrhage involving more than one-third of the infarction territory with a space-occupying effect; (3) a Glasgow Coma Scale (GCS) without a verbal response item score of <6; (4) rapidly improving symptoms; (5) both pupils fixed and dilated; (6) simultaneous other brain lesion, including tumors and contralateral or infratentorial infarctions; (7) platelet count <75000/mm\(^3\); (8) severe coagulopathy or cardiac, liver or kidney disease; (9) vasospastic disease, hematological disease with increased risk of thrombosis or paramyotonia congenita; (10) sepsis; (11) premorbid treatment with a monoamine oxidase inhibitor or an allergy to pethidine; (12) inferior vena cava fistula or a filter in its place, a mass near the inferior vena cava, or a height of <1.5 m; (13) pregnancy; or (14) a life expectancy <6 months.
Randomization

Enrolled patients were randomly assigned to three groups: DC group, DC plus head surface cooling group (DCSC group) and DC plus endovascular hypothermia group (DCEH group), according to a previously generated randomization scheme. The allocation ratio was 1:1:1. The random number was folded and sealed in an envelope before the initiation of the study. These envelopes were opened by an investigator who was not involved in patient screening, treatment, data collection or analysis.

Standard Medical Treatment

All patients included in the study received standard medical treatment. Patients were admitted into the neurointensive care unit (NCU) immediately after enrollment. Standard medical treatment was initiated as soon as possible. The standard medical treatment is shown in Table 1.

Decompressive craniectomy

All included patients received DC first as soon as possible. DC consisted of a large hemicraniectomy and a duraplasty. The bone flap with a diameter of at least 12 cm, which included temporal, frontal, parietal, and some occipital bones, was removed. The dura was opened, and a dural patch made of a dura substitute was placed into the incision and secured. Resection of infarcted brain tissue was forbidden.

Temperature management

Patients allocated to the DCSC group were sustained using ice caps that were placed around the head. The ice cap was worn 24 hours a day for 7 days. The systematic temperature was sustained normothermia.

Patients randomized to the DCEH group were treated with endovascular hypothermia. Hypothermia was initiated as soon as possible after DC. The target bladder temperature was 34°C with maximal cooling rate. Hypothermia was maintained for a minimum of 24 hours and would be prolonged to 72 hours according to the physician's discretion. The rewarming was controlled 0.5°C every 12 h. In the event of deterioration of rebound ICP, the rewarming process was intermittent until the patient regained a stable status. The time course for rewarming varied from 24 and 72 hours.

The temperature of the patients in the DC group was sustained between 36.5 and 37.5°C to maintain normothermia.

Data Collection

The patient characteristics included age, sex, comorbidities (such as hypertension, coronary heart disease, atrial fibrillation, hyperlipidemia, valvular dysfunction, diabetes mellitus and stroke), radiological data (affected hemisphere and infarcted area), stroke severity at enrollment (GCS score, NIHSS score and Acute Physiology And Chronic Health Evaluation II score), transtentorial herniation, the administration of
thrombolysis, antiplatelet or anticoagulants or defibrinogen and the time interval from symptom onset to DC procedure.

The laboratory data included the erythrocyte count, leukocyte count, platelet count, hemoglobin level, international normalized ratio, thrombin time, prothrombin time, activated partial thromboplastin time, fibrinogen, total bilirubin, alanine aminotransferase, aspartate aminotransferase, creatine kinase, creatinine, urea, glucose, total protein, albumin, sodium, potassium, magnesium, calcium, phosphonium, amylase, lipase, lactate, and arterial blood gas. The tests were run every 12 hours in the DCEH group and every other day in the DC and DCSC group. Chest radiography, electrocardiogram and deep venous ultrasound were also performed every 3 days in all groups.

We also observed severe complications, including hemorrhagic transformation, recurrent infarction, transtentorial herniation post-DC, intracranial hemorrhage or infection post-DC, severe arrhythmia resulting hemodynamic disorder, heart failure (New York Heart Association class IV), hypotension (systolic blood pressure <90 mmHg), pulmonary embolism, gastrointestinal bleeding requiring a blood transfusion (hemoglobin <7 g/L), gastric retention (gastric residual >250 mL), refractory hiccup, acute pancreatitis, acute liver injury, acute kidney injury, platelet <50×10^9/L, disseminated intravascular coagulation, infection (e.g., catheter-related infection, bacteremia, sepsis, pneumonia and urinary infection), severe electrolyte disorder (blood sodium >160 or <125 mmol/L, blood potassium >6.5 or <2.5 mmoL/L), stress hyperglycemia (>11.1 mmol/L), hypoalbuminemia (<30 g/L), and lower extremity deep vein thrombosis.

**Outcome Measurement**

The primary outcomes were all-cause mortality and mRS score at 6 months. An investigator who was not involved in the randomization, treatment or analysis performed the follow-up by calling the patients or surrogates. A mRS 0–3 was regarded as a good neurological outcome. Secondary outcomes were complications.

**Statistical Analysis**

No similar results were found before the study was designed. Based on data from a previous open study of hypothermia in stroke patients, the sample size was calculated to 252 assuming that the difference of the mean mRS of groups was 1 and that the standard deviation was 2 (α=0.05; β=0.10). Because of the slow recruitment, the study was terminated early after a period of 6 years and we are planning a multicenter RCT in China.

Statistic Package for Social Science (SPSS) 25.0 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analyses. Continuous covariates are presented as the mean±SD or the median (range), as appropriate. Categorical covariates are presented as counts and proportions. Comparisons between the three groups were performed using a two-tailed Kruskal-Wallis H test for continuous covariates and the
Pearson's chi-square test for categorical covariates, as appropriate. All tests were two-tailed, and the level of significance was set to a p-value <0.05.

Results

Patient Characteristics

Thirty-four patients were included in this trial. All included patients finished treatment and completed follow-up (Figure 1). Eighteen patients (52.9%) were older than 60 years old. There were more male patients (28 cases, 82.4%) than female patients. The right hemisphere was affected in 20 patients (58.8%), and the total MCA or > MCA territory was involved in 24 patients (70.6%). Seven patients (21.0%) developed transtentorial herniation before inclusion.

There were 9 patients in the DC group, 14 patients in the DCSC group and 11 patients in the DCEH group. The patient baseline characteristics are listed in Table 2. There were no significant differences among the three groups.

Mortality

The mortality rates of all patients at the time of discharge and after 6 months were 8.8% (3/34) and 35.3% (12/34), respectively. The mortality rates in the DC, DCSC and DCEH groups at the time of discharge were 22.2% (2/9), 0% (0/14) and 9.1% (1/11), respectively. There was no significant difference among the groups (P=0.186). At 6 months, the mortality rates in the DC, DCSC and DCEH groups were 44.4% (4/9), 21.4% (3/14) and 45.5% (5/11), respectively (P=0.367). The causes of death are described in the Complications section below.

Neurological Outcome

At 6 months, 12 cases (35.3%) had good neurological outcomes (mRS score of 0-3). The rates of good neurological outcome in the DC, DCSC and DCEH groups were 22.2% (2/9 cases), 42.9% (6/14 cases) and 36.4% (4/11), respectively. The DCSC group seemed to have a higher proportion of good outcome, but there was no significant difference between groups (p=0.598). Among survivors, endovascular hypothermia had a higher proportion of neurological outcome but also without significant difference (DC group, 2/5 cases, 40.0%; DCSC group, 6/11 cases, 54.5%; DCEH group, 4/6 cases, 66.7%; p=0.696) (Figure 2).

Complications

The total cases that experienced complications in the DC, DCSC and DCEH groups were 28 (12.0%), 44 (12.1%), 54 (18.9%), respectively, and the differences between the groups were statistically significant (P=0.025). The DCEH group experienced significantly more complications than the other two groups (Table 3). Twelve patients died of severe complications, and three of these patients died before discharge. In the DC group, herniation and gastrointestinal bleeding were the cause of death in 1 patient
each. In the DCEH group, herniation was the cause of death in 1 patient. The other patients died after discharge from the NCU. In the DC group, pneumonia was the cause of death in 2 patients of the DC group and 3 patients of the DCSC group. In the DCEH group, 3 patients died of pneumonia, and 1 patient died of intracranial infection associated with DC.

Discussion

Our results showed that the mortality rates in the DC, DCSC and DCEH groups were 44.4% (4/9), 21.4% (3/14) and 45.5% (5/11), respectively, without significant difference. The proportions of good neurological outcome in the DC, DCSC and DCEH groups were 22.2% (2/9 cases), 42.9% (6/14 cases) and 36.4% (4/11), respectively, with no significant difference. The DCSC group seemed to have a higher proportion of good outcomes. The incidence of complications in the DCEH group was significantly higher than those of the DC and DCSC groups.

Similar to prior studies (2-8), our results also showed that DC decreased mortality in LHI patients (discharge, 8.8%; 6 months, 35.3%). Additionally, we found that patients in the DCSC and DCEH groups might have lower mortality rates than those in the DC group at the time of discharge. Transtentorial herniation (4 cases, 11.7%) was a severe complication that was associated with death in the acute phase. Therefore, mortality might be further decreased by combining DC with hypothermia during this period. However, we found that severe cerebral edema still did not resolve in some patients, even after they were treated with DC and hypothermia. Meta-analyses have found that hypertonic saline has a better effect than mannitol on decreasing the ICP (15, 16). Additionally, studies using animals have shown that glibenclamide provided a better neuroprotective effect than DC or hypothermia treatment, and it prevented malignant cerebral infarction (17-19). These methods might be an additional option. Our results also showed that lower mortality unfortunately did not extend to the 6-month follow-up. The meta-analysis of Chen et al. showed a similar result. Compared to DC alone, combining DC and hypothermia had a tendency to reduce short-term mortality (RR = 0.52, 95% CI 0.26 to 1.05, P = 0.07) but had no significant effects on long-term mortality (RR = 1.26, 95% CI 0.58 to 2.76, P = 0.56) or neurological outcomes (RR = 0.81, 95% CI 0.53 to 1.24, P = 0.34) (20). We found that pneumonia was the primary cause of death (8 cases, 23.5%), and all of these deaths occurred after discharge. The DESTINY study had the same results: the mortality rate after 30 days was 12%, it increased to 18% after 6 months, and pneumonia was the main cause of death (2). Once patients survive the acute phase, initiating subsequent long-term nursing care and strategies aimed at preventing pneumonia become particularly important, which might be the key to further lower mortality. Studies have shown that rehabilitation enhances airway protection and decreases the incidence of pneumonia (21, 22). Hence, good long-term nursing care and rehabilitation are desired.

In preclinical trials, DC combined with brain hypothermia had significantly additional benefits for the neurologic outcome, infarct volume and degree of neuroinflammation than DC alone in the MCA infarction model (23). In our results, among the 22 surviving patients, the hypothermia group had better neurological outcomes than the DC group (DC group, 2/5 cases, 40.0%; DCSC group, 6/11 cases, 54.5%;
DCEH group, 4/6 cases, 66.7%). Although these results did not reach statistical significance, which might be due to the small sample size, they implied that hypothermia might improve neurological outcomes. This result was consistent with the findings of Thomas et al. In their study, patients in the hypothermia group tended to achieve better neurological outcomes than the normothermia group (NIHSS, 10 vs. 11; P=0.08)(24). The study, which compared endovascular hypothermia with normothermia in LHI patients with contraindications for DC, also found that hypothermia improved neurological outcomes in survivors (hypothermia, 87.5% vs. normothermia, 40.0%; P=0.066)(8). However, Neugebauer et al. conducted a multicenter RCT researching hypothermia in addition to DC in LHI patients and found that the mortality rates at day 14 were similar [hypothermia group, 19% (5/26 case); control group, 13% (3/24 cases); OR=1.65, P=0.70], with no significant difference regarding functional outcome after 12 months of follow-up(25). Furthermore, the hypothermia group suffered more complications. However, there is still controversy regarding the methodology(26), and the sample sizes of all the above studies are small. A well-designed large-sample multicenter RCT is needed.

Previous reports have shown that the complication rate of hypothermia is high(8). Thus, we were concerned about the safety of combining DC with hypothermia treatment. Park et al. found that pneumonia was the most common adverse event in the hypothermia group (5/25 cases, 25%). Additionally, in some cases, hypothermia needed to be discontinued due to side effects (sepsis, hypotension or bradycardia)(27). Our results showed that the rate of complications in the DCEH group was significantly higher than in the other two groups. Gastric retention was significantly higher due to anti-shivering drugs, which inhibits gastrointestinal motility. There also seemed to be more lower extremity deep venous thrombosis in the endovascular hypothermia group, which had an effect on coagulation function. Although the incidence of pneumonia was similar between groups, the pneumonia in the endovascular hypothermia group was more severe due to the use of anti-shivering drugs. Endovascular hypothermia indeed brought more complications. However, we surprisingly found that the DCSC method had only a small influence on the whole system, and patients suffered few severe complications. Thus, it might be the better option for LHI patients after DC.

There are shortcomings to our study. Because we included only patients who received DC, we might have introduced selection bias. Our study was an open RCT, and it was therefore impossible to blind physicians to the treatment assignments. As a result, it is possible that the physicians paid more attention to the patients in the hypothermia group. Additionally, the sample size was too small to make a conclusion. Moreover, the incidence of LHI was low, which made it difficult for a single center to collect a large number of samples. A multicenter RCT including a larger sample population will need to be conducted in the future to confirm our results.

**Conclusions**

There is still no evidence to confirm that hypothermia further reduces long-term mortality and improves neurological outcomes in LHI patients with DC. However, there is a trend to benefit survivors from
hypothermia. A local cooling method may be a better option for DC patients, which has little impact on systematic complications. A multicenter RCT is needed to confirm these results.

**Declarations**

**Authors’ contributions**

SYY made substantial contribution to the conception, study design, interpretation of the data, drafting of the manuscript and revising of the manuscript for intellectual content. FLL made substantial contributions to the study design, sample and data analysis, interpretation of the data, drafting of the manuscript and revising of the manuscript for intellectual content. ZY made substantial contributions to the study design, sample analysis and data collection. CWB, YH and LG made substantial contributions to the study design and data collection. All authors approved the final version to be published.

**Funding**

This study was supported by a grant from the National Key Department of Neurology and Critical Care Medicine funded by the National Health and Family Planning Commission of the People's Republic of China.

**Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

This trial was approved by the Ethics Committee of Xuanwu Hospital Capital Medical University, Beijing. Written informed consent was obtained from all patients or their designated surrogates.

**Consent to publication**

Not applicable.

**Competing Interests**

There is no conflict of interest to disclosure.

**Statement**

Our study adheres to CONSORT guidelines.

**Abbreviations**

Decompressive craniectomy, DC
Large hemispheric infarction, LHI
DC plus head surface cooling, DCSC
DC plus endovascular hypothermia, DCEH
modified Rankin Scale, mRS
Randomized controlled trials, RCTs
Intracranial pressure, ICP
Middle cerebral artery, MCA
National institutes of health stroke scale, NIHSS
Glasgow coma scale, GCS
Neurointensive care unit, NCU
Statistic package for social science, SPSS

Reference
1. Hacke W, Schwab S, Horn M, Spranger M, DeGeorgia M, vonKummer R. 'Malignant' middle cerebral artery territory infarction - Clinical course and prognostic signs. Archives of Neurology. 1996;53(4):309-15.
2. Juttler E, Schwab S, Schmiedek P, Unterberg A, Hennerici M, Woitzik J, et al. Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): a randomized, controlled trial. Stroke. 2007;38(9):2518-25.
3. Vahedi K, Vicaut E, Mateo J, Kurtz A, Orabi M, Guichard JP, et al. Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL trial). Stroke. 2007;38(9):2506-17.
4. Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB, et al. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatenin Edema Trial [HAMLET]): a multicentre, open, randomised trial. The Lancet Neurology. 2009;8(4):326-33.
5. Zhao J, Su YY, Zhang Y, Zhang YZ, Zhao R, Wang L, et al. Decompressive hemicraniectomy in malignant middle cerebral artery infarct: a randomized controlled trial enrolling patients up to 80 years old. Neurocrit Care. 2012;17(2):161-71.
6. Geurts M, van der Worp HB, Kappelle LJ, Amelink GJ, Algra A, Hofmeijer J, et al. Surgical Decompression for Space-Occupying Cerebral Infarction Outcomes at 3 Years in the Randomized HAMLET Trial. Stroke. 2013;44(9):2506-8.
7. Frank JI, Schumm LP, Wroblewski K, Chyatte D, Rosengart AJ, Kordeck C, et al. Hemicraniectomy and Durotomy Upon Deterioration From Infarction-Related Swelling Trial Randomized Pilot Clinical Trial. Stroke. 2014;45(3):781-7.

8. Su Y, Fan L, Zhang Y, Zhang Y, Ye H, Gao D, et al. Improved Neurological Outcome With Mild Hypothermia in Surviving Patients With Massive Cerebral Hemispheric Infarction. Stroke. 2016;47(2):457-63.

9. Delhaye C, Mahmoudi M, Waksman R. Hypothermia therapy: neurological and cardiac benefits. J Am Coll Cardiol. 2012;59(3):197-210.

10. Erecinska M, Thoresen M, Silver IA. Effects of hypothermia on energy metabolism in Mammalian central nervous system. J Cereb Blood Flow Metab. 2003;23(5):513-30.

11. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. Critical Care Medicine. 2009;37(7):S186-S202.

12. Han HS, Karabiyikoglu M, Kelly S, Sobel RA, Yenari MA. Mild hypothermia inhibits nuclear factor-kappaB translocation in experimental stroke. J Cereb Blood Flow Metab. 2003;23(5):589-98.

13. Slikker W, 3rd, Desai VG, Duhart H, Feuers R, Imam SZ. Hypothermia enhances bcl-2 expression and protects against oxidative stress-induced cell death in Chinese hamster ovary cells. Free Radic Biol Med. 2001;31(3):405-11.

14. Chi OZ, Liu X, Weiss HR. Effects of mild hypothermia on blood-brain barrier disruption during isoflurane or pentobarbital anesthesia. Anesthesiology. 2001;95(4):933-8.

15. Kamel H, Navi BB, Nakagawa K, Hemphill JC, 3rd, Ko NU. Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: a meta-analysis of randomized clinical trials. Crit Care Med. 2011;39(3):554-9.

16. Chen H, Song Z, Dennis JA. Hypertonic saline versus other intracranial pressure-lowering agents for people with acute traumatic brain injury. Cochrane Database Syst Rev. 2020;1:CD010904.

17. Wu Z, Zhu SZ, Hu YF, Gu Y, Wang SN, Lin ZZ, et al. Glibenclamide enhances the effects of delayed hypothermia after experimental stroke in rats. Brain Res. 2016;1643:113-22.

18. Simard JM, Woo SK, Tsymbalyuk N, Voloshyn O, Yurovsky V, Ivanova S, et al. Glibenclamide-10-h Treatment Window in a Clinically Relevant Model of Stroke. Translational Stroke Research. 2012;3(2):286-95.

19. Simard JM, Tsymbalyuk N, Tsymbalyuk O, Ivanova S, Yurovsky V, Gerzanich V. Glibenclamide Is Superior to Decompressive Craniectomy in a Rat Model of Malignant Stroke. Stroke. 2010;41(3):531-7.

20. Chen ZY, Zhang XD, Liu CY. Outcomes of therapeutic hypothermia in patients treated with decompressive craniectomy for malignant Middle cerebral artery infarction: A systematic review and meta-analysis. Clinical Neurology and Neurosurgery. 2020;188.

21. Jayasekeran V, Singh S, Tyrrell P, Michou E, Jefferson S, Mistry S, et al. Adjunctive functional pharyngeal electrical stimulation reverses swallowing disability after brain lesions. Gastroenterology. 2010;138(5):1737-46.
22. Hegland KW, Davenport PW, Brandimore AE, Singletary FF, Troche MS. Rehabilitation of Swallowing and Cough Functions Following Stroke: An Expiratory Muscle Strength Training Trial. Arch Phys Med Rehabil. 2016;97(8):1345-51.

23. Park J, Kim JH, Suk K, Han HS, Ohk B, Kim DG. Selective Brain Hypothermia Augmenting Neuroprotective Effects of Decompressive Craniectomy for Permanent Middle Cerebral Artery Infarction in a Rat Model. World Neurosurg. 2019;121:e181-e90.

24. Els T, Oehm E, Voigt S, Klisch J, Hetzel A, Kassubek J. Safety and therapeutical benefit of hemicraniectomy combined with mild hypothermia in comparison with hemicraniectomy alone in patients with malignant ischemic stroke. Cerebrovasc Dis. 2006;21(1-2):79-85.

25. Neugebauer H, Schneider H, Bosel J, Hobohm C, Poli S, Kollmar R, et al. Outcomes of Hypothermia in Addition to Decompressive Hemicraniectomy in Treatment of Malignant Middle Cerebral Artery Stroke: A Randomized Clinical Trial. JAMA Neurol. 2019;76(5):571-9.

26. Engrand N, Mazighi M, Dinkelacker V. Hypothermia After Decompressive Hemicraniectomy in Treatment of Malignant Middle Cerebral Artery Stroke: Comment on the Randomized Clinical Trial. Critical Care. 2019;23(1):164.

27. Park HS, Choi JH. Safety and Efficacy of Hypothermia (34 degrees C) after Hemicraniectomy for Malignant MCA Infarction. Journal of Korean Neurosurgical Society. 2018;61(2):267-76.

Tables
Table 1
Standard Medical Treatment

| • Vital sign monitoring: monitor HR, RR, BP, SpO2, pupils and consciousness |
| --- |
| • Position: elevation of the head at 20–30° |
| • Respiratory function: sustain the SpO2 > 92% monitored with pulse oximetry, keep pH 7.35–7.45, PaCO2 35–45 mmHg and PaO2 80–100 mmHg monitored with blood gas analysis, provide intubation and mechanical ventilation if necessary |
| • Fluid management: maintain normovolemia and avoid hyponatremia |
| • BP: keep the mean BP 90–110 mmHg, treat BP > 180/120 mmHg with antihypertensive agents and treat hypotension (BP < 100/70 mmHg) or low CPP with catecholamines |
| • Blood glucose: keep the glucose level 8.3–10.0 mmol/L |
| • DVT: prophylaxis with subcutaneous low molecular weight heparin |
| • Nutrition: administration of early enteral nutrition (20–25 kcal/kg/d) |
| • Pneumonia: perform sputum culture and treat pneumonia with appropriate antibiotics |
| • Osmotherapy: intravenous mannitol (125 mL every 4–8 hours) to decrease the ICP |

HR, heart rate; RR, respiratory rate; BP, blood pressure; SpO2, pulse oxygen saturation; PaCO2, arterial carbon dioxide pressure; PaO2, arterial oxygen pressure; CPP, cerebral perfusion pressure; ICP, intracranial pressure
### Table 2

**Patient Characteristics**

| Variables                                | DC (n = 9)          | DCSC (n = 14)         | DCEH (n = 11)         | P value |
|------------------------------------------|---------------------|-----------------------|-----------------------|---------|
| Age, years, mean ± SD                    | 63.22 ± 8.66        | 56.07 ± 11.23         | 58.18 ± 9.92          | 0.298   |
| Male, n (%)                              | 8 (88.9)            | 11 (78.6)             | 9 (81.8)              | 0.817   |
| Comorbidity, n (%)                       |                     |                       |                       |         |
| Hypertension                             | 4 (44.4)            | 4 (28.6)              | 3 (27.3)              | 0.663   |
| Coronary heart disease                   | 0                   | 0                     | 0                     |         |
| Valvular dysfunction                     | 1 (11.1)            | 2 (14.3)              | 2 (18.2)              | 0.905   |
| Atrial fibrillation                      | 4 (44.4)            | 5 (35.7)              | 3 (27.3)              | 0.726   |
| Diabetes mellitus                        | 2 (22.2)            | 1 (7.1)               | 1 (9.1)               | 0.519   |
| Hyperlipidemia                           | 0                   | 1 (7.1)               | 0                     | 0.479   |
| Premorbid stroke                         | 2 (22.2)            | 1 (7.1)               | 1 (9.1)               | 0.519   |
| Left hemispheric affected, n (%)         | 4 (44.4)            | 5 (35.7)              | 5 (45.5)              | 0.863   |
| Infarcted area, n (%)                    |                     |                       |                       |         |
| 2/3 MCA                                  | 1 (11.1)            | 4 (28.6)              | 5 (45.5)              | 0.139   |
| MCA                                      | 4 (44.4)            | 5 (35.7)              | 6 (54.5)              |         |
| >MCA                                     | 4 (44.4)            | 5 (35.7)              | 0                     |         |
| GCS, mean ± SD                           | 8.78 ± 2.73         | 10.71 ± 2.59          | 10.55 ± 2.54          | 0.198   |
| NIHSS, mean ± SD                         | 19.78 ± 2.64        | 17.64 ± 3.69          | 18.36 ± 3.01          | 0.337   |
| APACHE II, mean ± SD                     | 14.00 ± 4.18        | 10.43 ± 3.72          | 10.82 ± 4.73          | 0.163   |
| Transtentorial herniation, n (%)         | 2 (22.2)            | 3 (21.4)              | 2 (18.2)              | 0.971   |
| Prior T/A/A/D, n (%)                     | 4 (44.4)            | 7 (50.0)              | 4 (36.4)              | 0.792   |
| Interval time to DC*, hour, mean ± SD    | 23.28 ± 15.60       | 37.32 ± 12.21         | 30.05 ± 12.65         | 0.075   |

GCS, Glasgow Coma Scale; NIHSS, National Institute of Health Stroke Scale; APACHE II, Acute Physiology and Chronic Health Evaluation II; T/A/A/D, treatment with thrombolysis, antiplatelet, anticoagulant or defibrinogen.

*Interval from symptom onset to DC: DC group vs. DCSC group, P = 0.025; DC group vs. DCEH group, P = 0.298; DCSC group vs. DCEH group, P = 0.159.*
| Complications                              | DC (n = 9) | DCSC (n = 14) | DCEH (n = 11) | P value |
|-------------------------------------------|------------|---------------|---------------|---------|
| Recurrent infarction, n (%)               | 0          | 0             | 2 (18.2)      |         |
| Transtentorial herniation post DC, n (%)  | 2 (22.2)   | 0             | 2 (18.2)      |         |
| Intracranial hemorrhage post DC, n (%)    | 0          | 3 (21.4)      | 2 (18.2)      |         |
| Intracranial infection post DC, n (%)     | 0          | 0             | 1 (9.1)       |         |
| Hypotension, n (%)                        | 3 (33.3)   | 0             | 4 (36.4)      |         |
| Pneumonia, n (%)                          | 8 (88.9)   | 10 (71.4)     | 11 (100.0)    | 0.126   |
| Urinary infection, n (%)                  | 0          | 1 (7.1)       | 0             |         |
| Bacteremia, n (%)                         | 0          | 0             | 1 (9.1)       |         |
| Lower extremity deep venous thrombosis, n (%) | 2 (22.2) | 3 (21.4)      | 6 (54.5)      | 0.160   |
| Gastrointestinal bleeding (Hb < 7 g/L), n (%) | 2 (22.2) | 0             | 0             |         |
| Gastric retention, n (%)                  | 2 (22.2)   | 5 (35.7)      | 9 (81.8)      | 0.016   |
| Refractory hiccup, n (%)                  | 0          | 2 (14.3)      | 1 (9.1)       |         |
| Acute liver injury, n (%)                 | 0          | 2 (14.3)      | 2 (18.2)      |         |
| Stress hyperglycemia, n (%)               | 1 (11.1)   | 5 (35.7)      | 3 (27.3)      | 0.425   |
| Hypoalbuminemia, n (%)                    | 8 (88.9)   | 13 (92.9)     | 10 (90.9)     | 0.947   |
| All cases*, n (%)                         | 28 (12.0)  | 44 (12.1)     | 54 (18.9)     | 0.025   |

There was no hemorrhagic transformation, severe arrhythmia resulting hemodynamic disorder, heart failure (NYHA level IV), pulmonary embolism, catheter-related infection, sepsis, acute pancreatitis, acute kidney injury, platelet < 50 × 10⁹/L, disseminated intravascular coagulation and severe electrolyte disorder.

* Incidence of complications = all cases of complications / (26 × number of patients)