Local mild hypothermia therapy as an augmentation strategy for minimally invasive surgery of hypertensive intracerebral hemorrhage: a meta-analysis of randomized clinical trials

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Background: Previous studies reported that the mild hypothermia therapy (MHT) could significantly improve the clinical outcomes for patients with hypertensive intracerebral hemorrhage (HICH). Therefore, this meta-analysis was conducted to systematically assess whether the addition of local MHT (LMHT) could significantly improve the efficacy of minimally invasive surgery (MIS) in treating HICH.

Methods: Randomized clinical trials on the combined application of MIS and LMHT (MIS+LMHT) vs MIS alone for treating HICH were searched up to September 2016 in databases. Response rate and mortality rate were the primary outcomes, and the neurologic function and Barthel index were the secondary outcomes. Side effects were also analyzed.

Results: Totally, 28 studies composed of 2,325 patients were included to compare the efficacy of MIS+LMHT to MIS alone. The therapeutic effects of MIS+LMHT were significantly better than MIS alone. The pooled odds ratio of response rate and mortality rate was 2.68 (95% confidence interval [CI]=2.22–3.24) and 0.43 (95% CI=0.32–0.57), respectively. In addition, the MIS+LMHT led to a significantly better improvement in the neurologic function and activities of daily living. The incidence of pneumonia was similar between the two treatment methods.

Conclusion: These results indicated that compared to MIS alone, the MIS+LMHT could be more effective for the acute treatment of patients with HICH. This treatment modality should be further explored and optimized.

Keywords: LMHT, pneumonia, HICH, neurologic function, Barthel index

Introduction

Intracerebral hemorrhage (ICH) is a common cerebrovascular disease with a high mortality and poor outcomes in clinical practice, and also the leading cause of death and disability in elderly patients.¹ It was reported to account for about 10% of all strokes and 30% of all cerebrovascular diseases.²,³ The mortality rate could be up to 50%, and the mortality rate in one month could be up to 40%.³,⁴ Moreover, there could be up to 40% of severely disabled survivors.³ Normally, the edema and hematoma expansion are the two major factors contributing to worsened outcomes and secondary damage.⁵

Many factors could lead to ICH, but hypertension is the major cause of ICH, and the hypertensive ICH (HICH) is a common neurological disease. To date, there are still no effective drug therapies for HICH.⁶ Moreover, HICH is characterized by high incidence, high mortality and high morbidity, which seriously endangers the health of
patients and causes substantial economic burden for families and society. Therefore, it is urgently necessary to develop an effective therapy for this disease.

During the treatment, the key point is to quickly clear the hematoma and reduce the intracranial pressure. Along with minimally invasive technique, minimally invasive surgery (MIS) for HICH is gaining increasing attention. It could effectively decrease the mortality rate in the acute treatment of patients with HICH. Additionally, some previous studies reported that the mild hypothermia therapy (MHT) could be useful for neuroprotection and be used to treat cerebral edema after acute brain injury. Previous study reported that the addition of MHT could significantly improve the efficacy of MIS in treating HICH. Therefore, the aim of this study was to review the available published studies and conduct a meta-analysis to systematically assess whether the combined application of MIS and local MHT (LMHT) (MIS+LMHT) could result in a better efficacy than MIS alone.

Methods
Study selection
The first step of this meta-analysis was to obtain the eligible clinical trials. We conducted electronic searches in the following databases: Cochrane Controlled Trails Register, PubMed, Embase, Web of Science, Chinese Biomedical Literature Database on Disc and Chinese National Knowledge Infrastructure (dated up to September 2016). The search terms that we used were “hypothermia”, “minimally invasive” and “hypertensive cerebral hemorrhage”. No language restriction was set to avoid the potential language bias. Reference documents listed in the eligible studies and conference summaries were also reviewed. The inclusion criteria included the following items: 1) randomized clinical trials comparing the MIS+LMHT with MIS alone; 2) patients with hypertensive cerebral hemorrhage over 18 years of age; 3) the outcomes including at least one of these three indexes: response rate, mortality rate and neurologic function; and 4) patients could provide informed consent. The exclusion criteria included the following items: 1) no control group or not used MIS as the control group and 2) case reports, reviews and duplicate studies.

Outcome measures
Response rate and mortality rate were chosen as the primary outcomes. The response rate was defined according to the criteria of the included studies. The neurologic function, Barthel index and side effects were chosen as the secondary outcomes. The neurologic function was assessed according to the China Stroke Scale (CSS). The Barthel index was used to assess the activities of daily living (ADL) after treatment. Because pneumonia might be the main side effect caused by hypothermia, we only analyzed the incidence of pneumonia to assess the acceptability of these treatment methods.

Data extraction
In order to ensure the high accuracy of the extracted data, two authors (Yu Han and Ke Sheng) were arranged to independently screen the potential studies according to the aforementioned inclusion/exclusion criteria and extract the data. Any disagreement was resolved by discussion. The extracted data included the demographic data of the patients, the parameters of the MIS and LMHT, the first author and outcomes (primary and secondary outcomes). Good-faith efforts were made to obtain the data which were not available from the included studies.

Statistical analysis
RevMan 5.1 software was used to conduct the meta-analysis. For discontinuous data, the summary odds ratio (OR) was used as the effect size; for continuous data, the weighted mean difference (WMD) was used as the effect size. The chi-square test and I² index were used to assess the heterogeneity. If the corresponding P-value was more than 0.10 and I² was less than 50%, then the Mantel–Haenszel fixed-effects model was used; otherwise, the random-effects model was used. The potential presence of publication bias was assessed using funnel plot. This meta-analysis was conducted according to the recommendations.

Results
Literature search
At first, we obtained 157 potentially relevant randomized clinical trials. Based on the inclusion and exclusion criteria, 129 studies were excluded. The reasons for exclusion included the following: 1) no randomization, 2) no control group, 3) compared the MIS+LMHT with the conservative treatment, 4) no available data, 5) did not use MIS and 6) being a retrospective study. Finally, 28 clinical trials composed of 2,325 adult patients with hypertensive cerebral hemorrhage were included in this meta-analysis. The matched demographic data were observed in the included studies (Table 1). More than half of the included studies used cooling blanket as the device of LMHT. The detailed information of treatment methods is provided in Table 2.
Response rates
Response rate was available for 23 trials (Figure 1). Overall, 916 of 1,156 (79.2%) patients receiving the MIS+LMHT and 673 of 1,129 (59.6%) patients receiving MIS alone were classified as responders. No heterogeneity ($I^2=0\%, P=0.63$) existed. Then, the fixed-effects model was used. The pooled OR was 2.68 with 95% confidence interval (CI) = 2.22–3.24, which indicated that the MIS+LMHT could yield a higher response rate than MIS alone. The funnel plot showed that there was no publication bias (Figure 2).

Mortality rates
Mortality rate was available for 18 trials (Figure 3). Overall, 79 of 883 (8.9%) patients receiving the MIS+LMHT and 162 of 868 (18.7%) patients receiving MIS alone died after treatment. No heterogeneity ($I^2=0\%, P=0.83$) existed. Then, the fixed-effects model was used. The pooled OR was 0.43 with 95% CI = 0.32–0.57, which indicated that the MIS+LMHT could yield a lower mortality rate than MIS alone. The funnel plot showed that there was no publication bias (Figure 2).

Neurologic function
Among the included studies, 11 studies used CSS to assess the neurologic function of patients (Figure 4). Eight of 11 studies assessed the neurologic function one month after treatment; two studies conducted the assessment 21 days later and one study 14 days later. Heterogeneity ($I^2=91\%, P<0.0001$) existed. Then, the random-effects model was used. The pooled WMD was −5.83 with 95% CI = −7.18 to −4.47, which indicated that the MIS+LMHT could be more effective than MIS alone in improving the neurologic function of patients. The funnel plot showed that there was no publication bias (Figure 2).

Barthel index
Seven studies assessed ADL using Barthel index one month after treatment (Figure 5A). Heterogeneity ($I^2=67\%, P=0.006$)

Table 1 Characteristics of patients in included studies

| Study       | N | Female/ Male | Mean age (SD) (years) | Mean OT (SD) (hours) | GCS | NF (MIS-HT vs MIS) |
|-------------|---|--------------|----------------------|----------------------|-----|------------------|
| Chen16      | 96 | 29/67        | 56.3 (6.4)           | NA                   | NA  | 33.2 vs 31.5 (CSS) |
| Chen17      | 89 | 34/55        | 56.15 (8.0)          | NA                   | NA  | 5 ≤ GCS ≤ 8     |
| Wang18      | 60 | 23/37        | 52.7 (10.82)         | 6.96 (0.84)          | GCS ≤ 8 | 42.2 vs 42.1 (ESS) |
| Yu et al19  | 112 | 53/59   | 59.80 (4.13)         | NA                   | NA  | 43.4 vs 42.4 (ESS) |
| Peng and Zhou20 | 48 | 18/30        | 57.24 (11.24)        | 8.55 (2.14)          | GCS ≤ 8 | 35.0 vs 34.9 (CSS) |
| Chen et al21 | 100 | 39/41       | 53.65 (10.12)        | 5.3 (0.8)            | GCS ≤ 8 | 35.1 vs 33.6 (CSS) |
| Liu22       | 80 | 19/61        | 59.3 (3.5)           | NA                   | NA  | NA               |
| Jia and Ding23 | 140 | 42/98        | 65.31 (6.75)         | 3.1 (0.59)           | NA  | 28.5 vs 28.9 (CSS) |
| Yang24      | 80 | 31/49        | 55.18 (10.84)        | NA                   | NA  | 18.8 vs 18.7 (NIHSS) |
| Ou25        | 98 | 39/59        | 66.15 (7.6)          | NA                   | NA  | 36.8 vs 37.6 (CSS) |
| Zhao et al26 | 98 | 34/62        | 65.09 (5.31)         | NA                   | NA  | NA (CSS)         |
| He27        | 76 | 29/47        | 58.3 (17.5)          | NA                   | NA  | NA (CSS)         |
| Shen28      | 80 | 43/37        | 56.65 (7.4)          | 3 ≤ GCS ≤ 12         | 38.4 vs 38.0 (CSS) |
| Lin29       | 86 | 37/49        | 60.65 (10.67)        | NA                   | NA  | NA               |
| Xu30        | 60 | 23/37        | 56.3 (1.6)           | NA                   | NA  | NA               |
| Ye31        | 98 | 30/68        | 58.7 (9.6)           | NA                   | NA  | 48.9 vs 51.3 (ESS) |
| Bei and Zhao32 | 48 | 22/26        | 53.2 (6.5)           | NA                   | NA  | 27.9 vs 28.1 (CSS) |
| Zhang and Xie33 | 120 | 43/77 | 55.28 (11.24) | 6.87 (0.37) | GCS ≤ 8 | 33.5 vs 32.7 (CSS) |
| Xie34       | 80 | 34/46        | 56.4 (6.4)           | NA                   | 3 ≤ GCS ≤ 8 | 44.3 vs 43.4 (ESS) |
| Zhang35      | 51 | 19/32        | 57.7 (5.6)           | NA                   | GCS ≤ 8 | 38.6 vs 36.0 (CSS) |
| Zhou and Chen36 | 40 | 18/22        | 57.2 (11.2)          | 8.56 (2.14)          | NA  | 35.0 vs 34.9 (CSS) |
| Ning et al37 | 304 | 132/172 | 64.1 (7.54)          | NA                   | 3 ≤ GCS ≤ 8 | 34.1 vs 33.5 (CSS) |
| Bai38       | 86 | 36/50        | 50.03 (10.31)        | NA                   | GCS ≤ 8 | NA               |
| Chen et al39 | 134 | 51/83        | 57.48 (18.75)        | 7.09 (8.05)          | GCS ≤ 8 | NA (CSS)         |
| Zhang and Feng40 | 152 | 55/97       | 65.44 (4.38)         | 3.16 (0.57)          | GCS ≤ 8 | 27.6 vs 28.5 (CSS) |
| Yao41        | 79 | 35/44        | 73.7 (6.83)          | NA                   | 5 ≤ GCS ≤ 8 | 13.8 vs 13.6 (NIHSS) |
| Zuo42       | 53 | 19/34        | 66.7 (NA)            | NA                   | GCS ≤ 8 | NA               |
| Yang et al43 | 89 | 35/54        | 64.09 (7.62)         | NA                   | NA  | 34.1 vs 33.5 (CSS) |

Abbreviations: SD, standard deviation; OT, onset time; GCS, Glasgow Coma Scale; NF, neurologic function; MIS, minimally invasive surgery; HT, hypothermia therapy; NA, not available; CSS, China Stroke Scale; ESS, European Stroke Scale; NIHSS, National Institutes of Health Stroke Scale.
Table 2 Characteristic of included controlled trials

| Study          | MIS CT location | Puncture needle | HT Device | BT (°C) | Duration (days) | Random |
|----------------|-----------------|-----------------|-----------|---------|-----------------|--------|
| Chen¹⁴         | Yes             | YL-1            | YZK-1086  | 32–35   | 3–5             | Yes    |
| Chen¹⁷         | Yes             | YL-1            | Ice hat   | 33–35   | 3–5             | Yes    |
| Wang¹³         | Yes             | YL-1            | HGT-200⁰ | 33–34   | 3–5             | Yes    |
| Yu et al¹⁹     | Yes             | YL-1            | HGT-200I  | 32–35   | 2–7             | Yes    |
| Peng and Zhou²⁰| Yes             | NA              | CB        | 33–35   | 3–5             | Yes    |
| Chen et al²¹   | Yes             | NA              | CB        | 33–35   | 3–5             | Yes    |
| Liu²²          | Yes             | NA              | CB        | 32–35   | 3–5             | Yes    |
| Jiao and Ding²³| Yes             | YL-1            | YZK-1066  | 33–35   | 2–3             | Yes    |
| Yang²⁴         | Yes             | YL-1            | CB        | 33–35   | 3–5             | Yes    |
| Ou²⁵           | Yes             | YL-1            | YZK-1086  | 32–35   | NA              | Yes    |
| Zhao et al²⁶   | Yes             | NA              | CB        | 33–35   | 3–7             | Yes    |
| He²⁷           | Yes             | YL-1            | HDB-01    | 33–35   | 3–5             | Yes    |
| Shen²⁸         | Yes             | NA              | CB        | 32–35   | 2–5             | Yes    |
| Lin²⁹          | Yes             | NA              | CB        | 33–35   | 2–5             | Yes    |
| Xu³⁰           | Yes             | NA              | CB        | 33–35   | 2–5             | Yes    |
| Ye³¹           | Yes             | YL-1            | CB        | 33–35   | 2–5             | Yes    |
| Bei and Zhao²² | Yes             | YL-1            | CB        | 33–35   | 3–5             | Yes    |
| Zhang and Xie³³| Yes             | YL-1            | HGT-200⁰ | 33–34   | 3–5             | Yes    |
| Xie³⁴          | Yes             | YL-1            | CB        | 33–35   | 3–5             | Yes    |
| Zhang³⁵        | Yes             | NA              | NA        | 32–35   | NA              | Yes    |
| Zhou and Chen³⁶| Yes             | YL-1            | CB        | 33–35   | 3–5             | Yes    |
| Ning et al³⁷   | Yes             | YL-1            | CB        | 33–35   | 3–5             | Yes    |
| Bai³⁸          | Yes             | YL-1            | CB        | 33–35   | 2–5             | Yes    |
| Chen et al³⁹   | Yes             | YL-1            | CB        | 33–35   | 3–5             | Yes    |
| Zhang and Feng⁴⁰| Yes             | YL-1            | YZK-1066  | 33–35   | NA              | Yes    |
| Yao⁴¹          | Yes             | YL-1            | CB        | 33–35   | 3–5             | Yes    |
| Zuo⁴²          | Yes             | YL-1            | CB        | 33–35   | 3–7             | Yes    |
| Yang et al⁴³   | Yes             | YL-1            | ICE-I     | 33–35   | 2–5             | Yes    |

Abbreviations: MIS, minimally invasive surgery; HT, hypothermia therapy; CT, computed tomography; BT, body temperature; NA, not available; CB, cooling blanket.

Figure 1 Response rate of 23 trials.

Abbreviations: MIS, minimally invasive surgery; M–H, Mantel-Haenszel; HT, hypothermia therapy; CI, confidence interval; df, degrees of freedom.
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Figure 2 Funnel plots showing no publication bias.

Note: Subgroups represent the studies assessing ADL using Barthel index one month after treatment (30) and three months after treatment (90).

Abbreviations: SE, standard error; OR, odds ratio; MD, mean difference; ADL, activities of daily living.

Figure 3 Mortality rate of 18 trials.

Abbreviations: MIS, minimally invasive surgery; M–H, Mantel-Haenszel; HT, hypothermia therapy; CI, confidence interval; df, degrees of freedom.
 existed. Then, the random-effects model was used. The pooled WMD was 8.17 with 95% CI 6.77–14.73. No publication bias existed (Figure 2). These results indicated that the MIS+LMHT could be more effective than MIS alone in improving the ADL of patients.

Side effects

Only three studies assessed the side effects of the two treatment methods. Overall, 17 of 77 patients receiving the

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**Figure 4** Neurologic function of 11 trials.

**Abbreviations:** MIS, minimally invasive surgery; M–H, Mantel-Haenszel; HT, hypothermia therapy; SD, standard deviation; CI, confidence interval; df, degrees of freedom; IV, inverse variance.

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**Figure 5** Barthel index: (A) one month after treatment and (B) three months after treatment.

**Abbreviations:** MIS, minimally invasive surgery; M–H, Mantel-Haenszel; HT, hypothermia therapy; SD, standard deviation; CI, confidence interval; df, degrees of freedom; IV, inverse variance.
MIS+LMHT and 16 of 76 patients receiving the MIS alone experienced pneumonia. The pooled OR was 1.05 with 95% CI=0.43–2.59, which indicated that the incidence of pneumonia was similar between these two treatment methods.

Discussion
We conducted this meta-analysis of 28 randomized clinical trials to compare the efficacy of MIS+LMHT with MIS alone in the treatment of patients with HICH. The results showed that the MIS+LMHT could yield higher response rate (OR=2.68) and lower mortality rate (OR=0.43). Moreover, this treatment modality could significantly improve the neurologic function and ADL of patients. With respect to the analysis of side effects, only three studies reported the number of patients with pneumonia, which was insufficient to make a robust conclusion on the safety of the MIS+LMHT. However, these results demonstrated that the LMHT could be an effective augmentation strategy for MIS in treating patients with HICH.

In this study, almost all relevant randomized clinical trials were included, but some trials might have been missed, partly because these were published in some journals that are not indexed by international databases. Fortunately, it is likely that these trials are of low quality, and could not significantly affect the results. 

Additionally, there was one trial without the needed data, and despite our best efforts, we could not obtain them. However, this trial concluded that the MIS+LMHT could yield higher response rate and mortality rate was 2.68 and 0.43, respectively, which was in favor of the MIS+LMHT. The neurologic function and ADL were also found to be improved. Therefore, this trial would not affect our conclusion.

Under conditions of mild hypothermia, the oxygen consumption and metabolic rate in brain tissue are decreased, the production of free radicals is reduced and the synthesis of xanthine oxidase is slowed down and then the tissue damage could be alleviated. Meanwhile, the abnormal sodium–calcium exchange between cell membrane and sarcoplasmic reticulum is suppressed, which could alleviate the calcium overload. Under normal conditions, vasoactive substances, such as endothelin and vascular vasopressin, are in dynamic equilibrium to maintain the systolic and diastolic function of blood vessels. The acute period of ICH is usually accompanied by the disorder of vasoactive substances. The substantial production of endothelin and vascular vasopressin could further aggravate cerebral ischemia. Previous studies reported that the mild hypothermia could reduce the level of endothelin and vascular vasopressin.

Previous studies on ischemic and hemorrhagic stroke subtypes showed that the mild hypothermia (body temperature reduced by 3°C–5°C) was neuroprotective. But one point should be noticed in clinical practice: systemic mild hypothermia is difficult to perform because of its possible side effects. Alternatively, local mild hypothermia could quickly obtain the target temperature and overcome the potential side effects. Therefore, compared to systemic mild hypothermia, the local mild hypothermia could be more effective in treating patients with HICH.

Limitations
There were several limitations. First, all of the included studies were from the People’s Republic of China, which might limit the applicability of our findings. Second, only three studies were used to analyze the side effects; hence, future studies are needed to further assess the safety of the MIS+LMHT. Third, the target temperature and treatment time of LMHT were not consistent, but there were also the general problems for meta-studies to solve.

Conclusion
By pooling analysis of 28 randomized clinical trials, we found that the addition of LMHT could significantly improve the efficacy of MIS in the treatment of patients with HICH. The OR of response rate and mortality rate was 2.68 and 0.43, respectively, which was in favor of the MIS+LMHT. The neurologic function and ADL were also found to be improved. The clinical applicability of this modality showed greater promise and should be further explored and optimized.

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Disclosure
The authors report no conflicts of interest in this work.

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