

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

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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.⁷ 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.⁸ 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.^{9–11} Previous study reported that the addition of MHT could significantly improve the efficacy of MIS in treating HICH.¹² 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,¹³ 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 I^2 index were used to assess the heterogeneity.¹⁴ If the corresponding P -value was more than 0.10 and I^2 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.¹⁵

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.^{16–43} 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.

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)
Chen ¹⁶	96	29/67	56.3 (6.4)	NA	NA	33.2 vs 31.5 (CSS)
Chen ¹⁷	89	34/55	56.15 (8.0)	NA	5≤GCS	38.1 vs 36.8 (CSS)
Wang ¹⁸	60	23/37	52.7 (10.82)	6.96 (0.84)	GCS≤8	42.2 vs 42.1 (ESS)
Yu et al ¹⁹	112	53/59	59.80 (4.13)	NA	NA	43.4 vs 42.4 (ESS)
Peng and Zhou ²⁰	48	18/30	57.24 (11.24)	8.55 (2.14)	NA	35.0 vs 34.9 (CSS)
Chen et al ²¹	100	39/41	53.65 (10.12)	5.3 (0.8)	NA	35.1 vs 33.6 (CSS)
Liu ²²	80	19/61	59.3 (3.5)	NA	NA	NA
Jia and Ding ²³	140	42/98	65.31 (6.75)	3.1 (0.59)	NA	28.5 vs 28.9 (CSS)
Yang ²⁴	80	31/49	55.18 (10.84)	NA	NA	18.8 vs 18.7 (NIHSS)
Ou ²⁵	98	39/59	66.15 (7.6)	NA	NA	36.8 vs 37.6 (CSS)
Zhao et al ²⁶	98	34/62	65.09 (5.31)	NA	NA	NA (CSS)
He ²⁷	76	29/47	58.3 (17.5)	NA	NA	NA (CSS)
Shen ²⁸	80	43/37	56.65 (7.4)	NA	3≤GCS≤12	38.4 vs 38.0 (CSS)
Lin ²⁹	86	37/49	60.65 (10.67)	NA	NA	NA
Xu ³⁰	60	23/37	56.3 (1.6)	NA	NA	NA
Ye ³¹	98	30/68	58.7 (9.6)	NA	NA	48.9 vs 51.3 (ESS)
Bei and Zhao ³²	48	22/26	53.2 (6.5)	NA	NA	27.9 vs 28.1 (CSS)
Zhang and Xie ³³	120	43/77	55.28 (11.24)	6.87 (0.37)	GCS≤8	33.5 vs 32.7 (CSS)
Xie ³⁴	80	34/46	56.4 (6.4)	NA	3<GCS≤8	44.3 vs 43.4 (ESS)
Zhang ³⁵	51	19/32	57.7 (5.6)	NA	GCS≤8	38.6 vs 36.0 (CSS)
Zhou and Chen ³⁶	40	18/22	57.2 (11.2)	8.56 (2.14)	NA	35.0 vs 34.9 (CSS)
Ning et al ³⁷	304	132/172	64.1 (7.54)	NA	3<GCS≤8	34.1 vs 33.5 (CSS)
Bai ³⁸	86	36/50	50.03 (10.31)	NA	GCS≤8	NA
Chen et al ³⁹	134	51/83	57.48 (18.75)	7.09 (8.05)	GCS≤8	NA (CSS)
Zhang and Feng ⁴⁰	152	55/97	65.44 (4.38)	3.16 (0.57)	GCS≤8	27.6 vs 28.5 (CSS)
Yao ⁴¹	79	35/44	73.7 (6.83)	NA	5≤GCS≤8	13.8 vs 13.6 (NIHSS)
Zuo ⁴²	53	19/34	66.7 (NA)	NA	GCS≤8	NA
Yang et al ⁴³	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.

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 2 Characteristic of included controlled trials

Study	MIS		HT			Random
	CT location	Puncture needle	Device	BT (°C)	Duration (days)	
Chen ¹⁶	Yes	YL-I	YZK-I086	32–35	3–5	Yes
Chen ¹⁷	Yes	YL-I	Ice hat	33–35	3–5	Yes
Wang ¹⁸	Yes	YL-I	HGT-200Ö	33–34	3–5	Yes
Yu et al ¹⁹	Yes	YL-I	HGT-200II	33–34	2–7	Yes
Peng and Zhou ²⁰	Yes	NA	CB	33–35	3–5	Yes
Chen et al ²¹	Yes	NA	CB	33–35	3–5	Yes
Liu ²²	Yes	NA	CB	32–35	3–5	Yes
Jia and Ding ²³	Yes	YL-I	YZK-I066	33–35	2–3	Yes
Yang ²⁴	Yes	YL-I	CB	33–35	3–5	Yes
Ou ²⁵	Yes	YL-I	YZK-I086	32–35	NA	Yes
Zhao et al ²⁶	Yes	NA	CB	33–35	3–7	Yes
He ²⁷	Yes	YL-I	HDB-0I	33–35	3–5	Yes
Shen ²⁸	Yes	NA	CB	32–35	2–5	Yes
Lin ²⁹	Yes	NA	CB	33–35	2–5	Yes
Xu ³⁰	Yes	NA	CB	33–35	2–5	Yes
Ye ³¹	Yes	YL-I	CB	33–35	2–5	Yes
Bei and Zhao ³²	Yes	YL-I	CB	33–35	3–5	Yes
Zhang and Xie ³³	Yes	YL-I	HGT-200Ö	33–34	3–5	Yes
Xie ³⁴	Yes	YL-I	CB	33–35	3–5	Yes
Zhang ³⁵	Yes	NA	NA	32–35	NA	Yes
Zhou and Chen ³⁶	Yes	YL-I	CB	33–35	3–5	Yes
Ning et al ³⁷	Yes	YL-I	CB	33–35	3–5	Yes
Bai ³⁸	Yes	YL-I	CB	33–35	2–5	Yes
Chen et al ³⁹	Yes	YL-I	CB	33–35	3–5	Yes
Zhang and Feng ⁴⁰	Yes	YL-I	YZK-I066	33–35	NA	Yes
Yao ⁴¹	Yes	YL-I	CB	33–35	3–5	Yes
Zuo ⁴²	Yes	YL-I	CB	33–35	3–7	Yes
Yang et al ⁴³	Yes	YL-I	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.

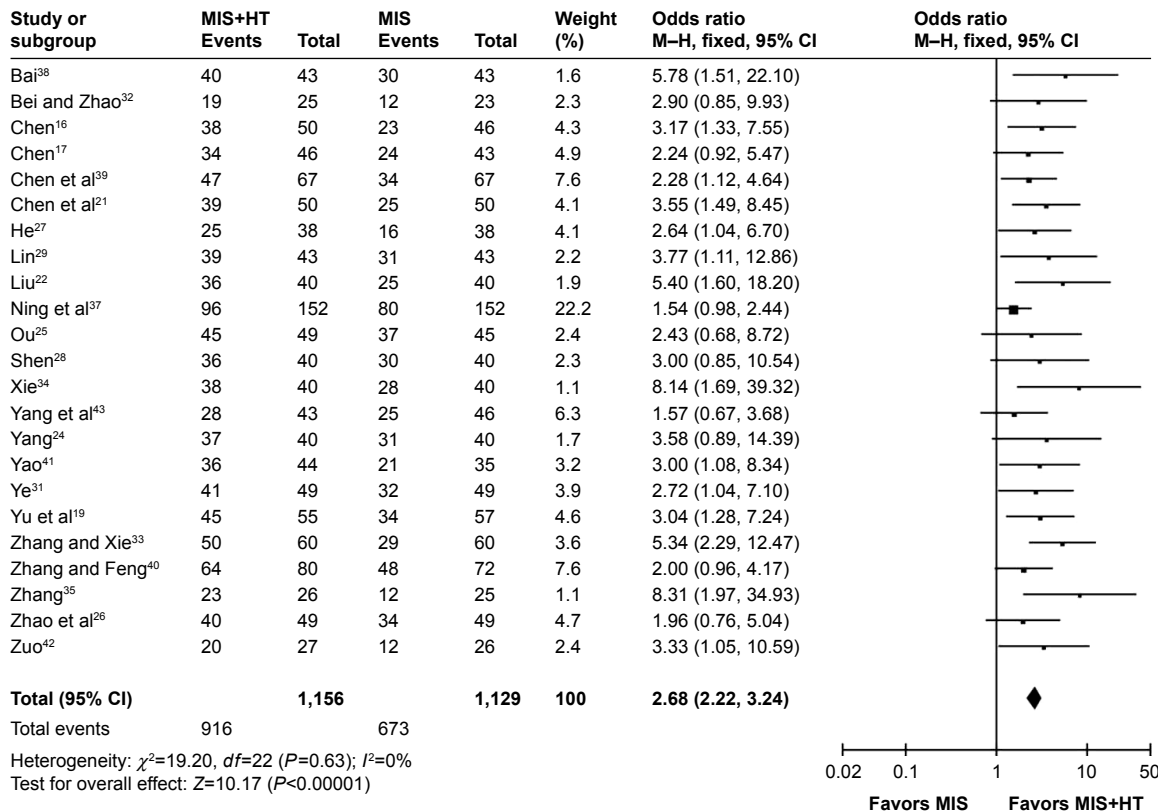


Figure 1 Response rate of 23 trials.

Abbreviations: MIS, minimally invasive surgery; M-H, Mantel-Haenszel; HT, hypothermia therapy; CI, confidence interval; *df*, degrees of freedom.

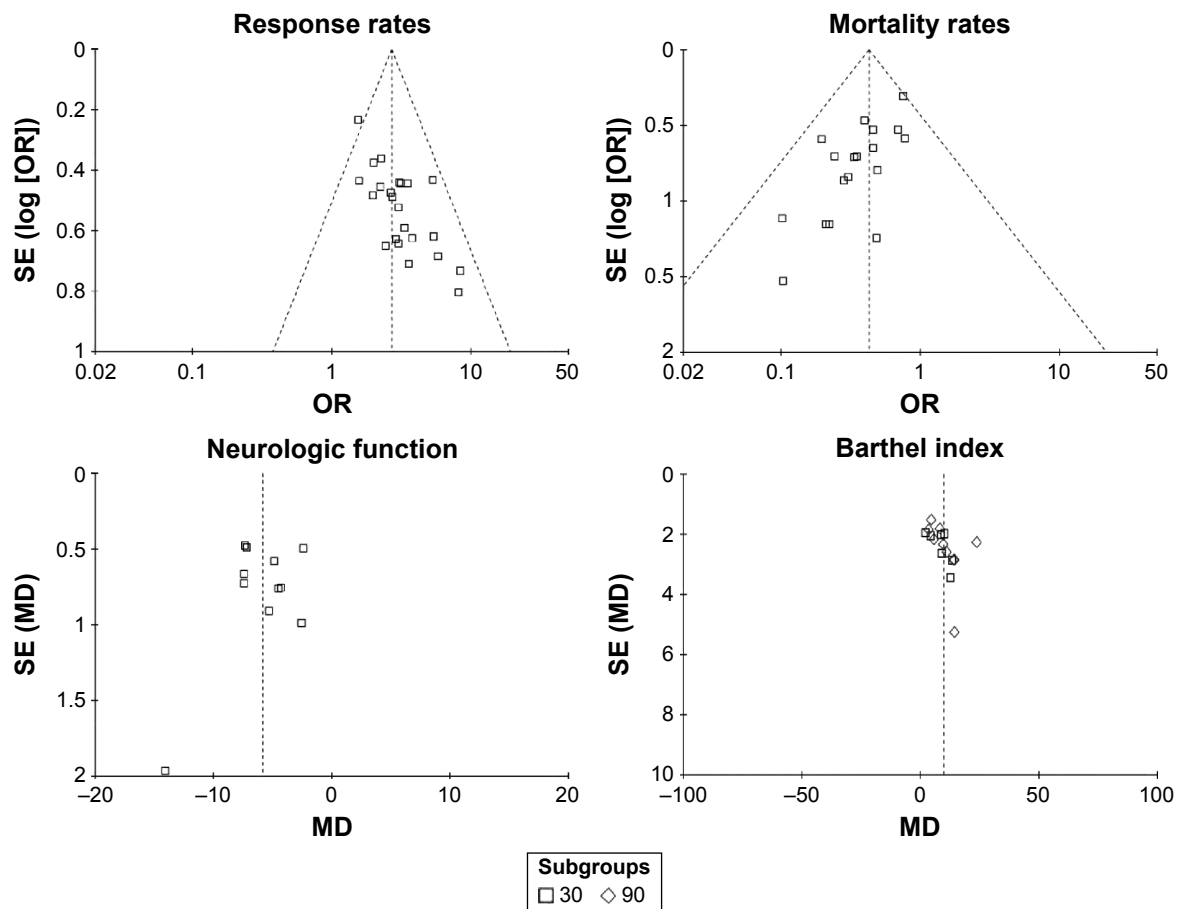


Figure 2 Funnel plots showing no publication bias.

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.

Study or subgroup	MIS+HT Events	Total	MIS Events	Total	Weight (%)	Odds ratio M-H, fixed, 95% CI	Odds ratio M-H, fixed, 95% CI
Bei and Zhao ³²	3	25	5	23	3.1	0.49 (0.10, 2.34)	
Chen ¹⁶	7	50	12	46	7.3	0.46 (0.16, 1.30)	
Chen ¹⁷	8	46	10	43	5.8	0.69 (0.25, 1.97)	
Chen et al ³⁹	8	67	17	67	10.1	0.40 (0.16, 1.00)	
Chen et al ²¹	4	50	8	50	5.0	0.46 (0.13, 1.63)	
Liu ²²	3	40	10	40	6.3	0.24 (0.06, 0.96)	
Ning et al ³⁷	22	152	28	152	16.2	0.75 (0.41, 1.38)	
Shen ²⁸	1	40	2	40	1.3	0.49 (0.04, 5.60)	
Wang ¹⁸	2	30	6	30	3.8	0.29 (0.05, 1.55)	
Xu ³⁰	1	30	4	30	2.6	0.22 (0.02, 2.14)	
Yang et al ⁴³	6	43	8	46	4.5	0.77 (0.24, 2.44)	
Yao ⁴¹	0	44	3	35	2.6	0.10 (0.01, 2.09)	
Ye ³¹	3	49	8	49	5.1	0.33 (0.08, 1.34)	
Yu et al ¹⁹	3	55	8	57	5.0	0.35 (0.09, 1.41)	
Zhang and Xie ³³	4	60	16	60	10.1	0.20 (0.06, 0.63)	
Zhang ³⁵	1	26	7	25	4.6	0.10 (0.01, 0.91)	
Zhao et al ²⁶	2	49	6	49	3.9	0.30 (0.06, 1.59)	
Zuo ⁴²	1	27	4	26	2.7	0.21 (0.02, 2.03)	
Total (95% CI)		883		868	100	0.43 (0.32, 0.57)	
Total events	79		162				
Heterogeneity: $\chi^2=11.30$, $df=17$ ($P=0.84$); $I^2=0\%$							
Test for overall effect: $Z=5.79$ ($P<0.00001$)							

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.

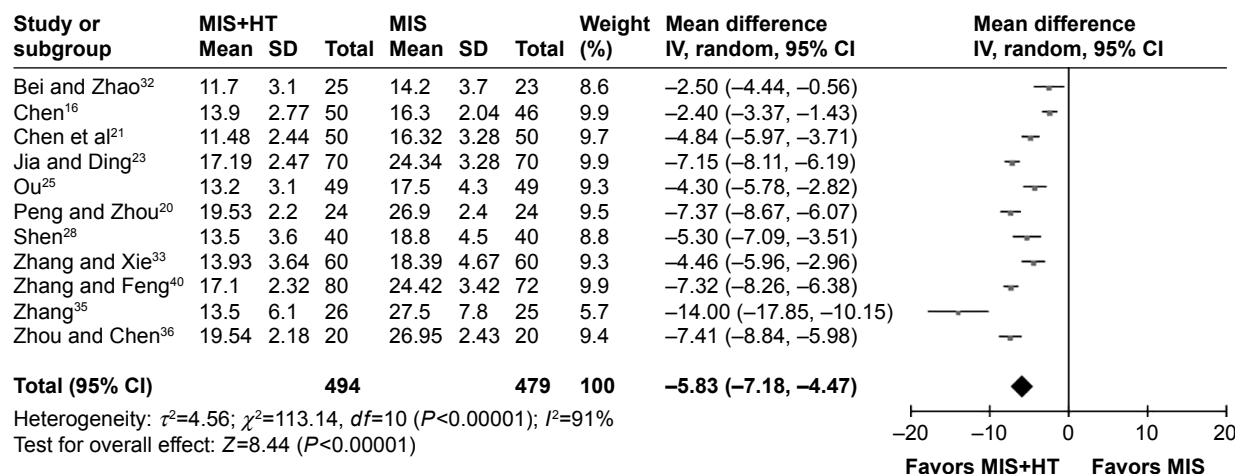


Figure 4 Neurologic function of 11 trials.

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.

existed. Then, the random-effects model was used. The pooled WMD was 8.17 with 95% CI=5.16–11.19. Ten studies assessed ADL three months after treatment (Figure 5B). Heterogeneity ($I^2=87\%$, $P<0.00001$) existed. Then, the random-effects model was used. The pooled WMD was 10.75 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

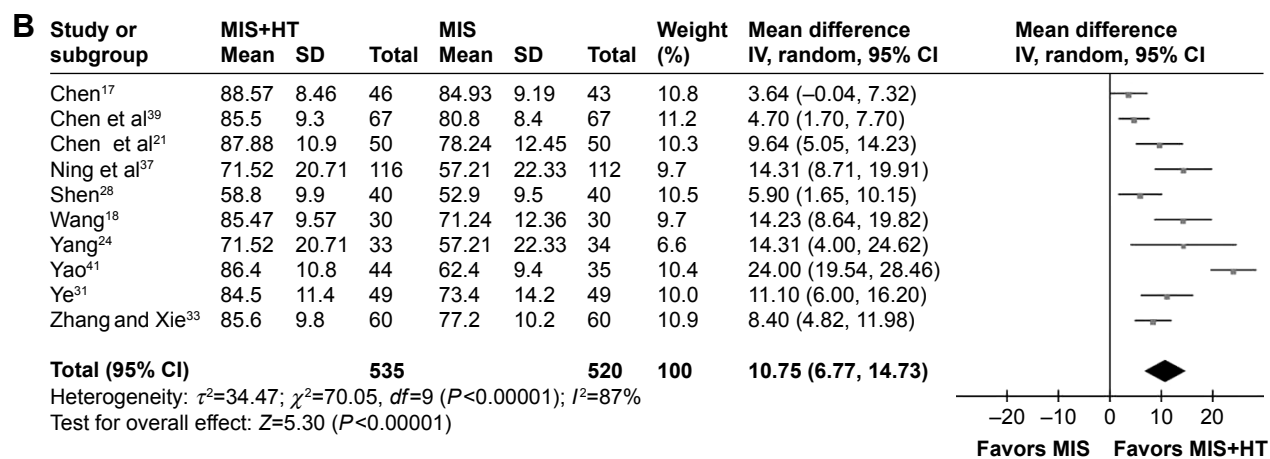
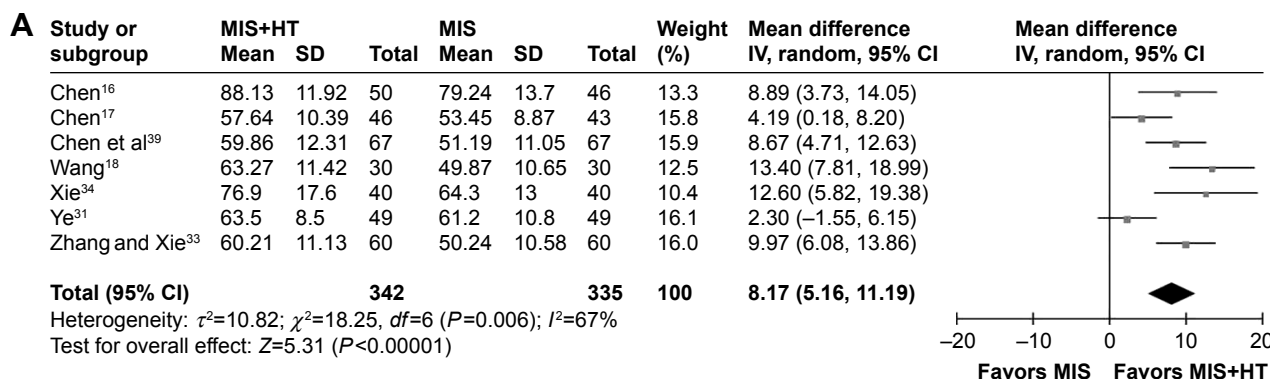


Figure 5 Barthel index: (A) one month after treatment and (B) three months after treatment.

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.⁴⁴ Additionally, there was one trial without the needed data,⁴⁵ and despite our best efforts, we could not obtain them. However, this trial concluded that the MIS+LMHT could be good at protecting nerve cell and promoting neurofunctional rehabilitation. 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.⁴⁶ 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.⁴⁷ 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.^{40,48}

Previous studies on ischemic and hemorrhagic stroke subtypes showed that the mild hypothermia (body temperature reduced by 3°C–5°C) was neuroprotective.^{49,50} But one point should be noticed in clinical practice: systemic mild

hypothermia is difficult to perform because of its possible side effects.^{10,11} Alternatively, local mild hypothermia could quickly obtain the target temperature and overcome the potential side effects.⁵¹ 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.⁵² 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.^{53,54}

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.

Acknowledgments

This work was supported by the medical research subjects from Health and Family Planning Commission of Chongqing (No 20142008) and State Key Clinical Specialties, Department of Neurology, First Affiliated Hospital of Chongqing Medical University.

Disclosure

The authors report no conflicts of interest in this work.

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