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Original Article

Effects of mild hypothermia therapy combined with minimally invasive debridement in patients with hypertensive intracranial hemorrhage: a randomized controlled study

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Abstract: Objective: To investigate the clinical effect of mild hypothermia therapy (MHT) combined with minimally invasive debridement (MID) in patients with severe hypertensive intracranial hemorrhage (HICH). Methods: A total of 120 patients with severe HICH who received clinical intervention in our hospital were enrolled as study subjects. In this randomized, controlled, double-blind trial, they were divided into a study group (SG, n=70) and a control group (CNG, n=50). The CNG was treated with MID, and the SG was treated with MID combined with MHT. The general surgical indices, short-term postoperative outcomes, postoperative neurological and recovery in activities of daily living, and complications were compared between the two groups. Patients' Glasgow prognosis (Glasgow Outcome Scale, GOS) scores at 1 year after surgery were analyzed. Results: The operative time, intraoperative blood loss and intensive care unit (ICU) admission were shorter/lower in the SG than in the CNG (P<0.05). The SG had higher hematoma clearance rate at 1 d and 3 d postoperatively, and lower residual hematoma volume at 3 d and 7 d postoperatively than the CNG (P<0.05). Patients in the SG had higher Barthel scores and lower National Institutes of Health Stroke Scale (NIHSS) scores than the CNG at 1-12 months after intervention (P<0.05). The incidence of complications in the SG was lower than that in the CNG (P<0.05). The percentage of GOS grade IV and V was significantly higher in the SG than in the CNG 1 year after surgery (P<0.05). Conclusion: The combination of MID and MHT in patients with severe HICH has better clinical results in the short and long term, and improves the postoperative outcomes and quality of life. It can also reduce the incidence of perioperative complications.

Keywords: Severe hypertensive intracranial hemorrhage, mild hypothermia therapy, minimally invasive debridement, controlled study

Introduction

Hypertensive intracerebral hemorrhage (HICH) is one of the most severe complications of hypertension and one of the main disabling conditions [1]. HICH is mostly caused by long-term hypertension and intracranial atherosclerosis, resulting in intraparenchymal hemorrhage caused by rupture of small intracranial arteries in patients [2]. HICH does not have symptoms in the early stage, and most patients have sudden onset of severe headache, irritability and vomiting during strenuous exercise or emotional state, progressing to drowsiness, coma and even death within minutes or hours [3]. Epidemiological data have shown that HICH mainly affects population aged 50-68 years, its 30 d mortality rate can reach 32%-50%, and even if survived, about 70% of patients will still have dysfunction, and only 28%-35% will have independent living skills [4, 5].

HICH has the characteristics of rapid onset, rapid development, poor prognosis, high mortality and high disability. The clinical treatment of this disease focuses on early and rapid elimination of intracranial hematoma, reduction of intracranial pressure and active control of

clinical symptoms [6]. Traditional craniotomy to clear the hematoma often has a long operative time, and patient's normal brain tissue is also damaged during the surgery, leading to a poor prognosis. With the development of minimally invasive surgery, small bone window craniotomy has become one of the mainstream surgical methods for HICH [7]. It has been noted that small bone window craniotomy can remove the patient's intracranial hematoma through small bone window and facilitate hemostasis, with little damage to the patient's normal brain tissue [8]. Mild hypothermia therapy (MHT) is also a popular clinical research direction that has been validated in areas such as severe craniocerebral injury and cardiac ischemia-reperfusion [9]. The results of a prospective clinical multicenter controlled study of 428 patients with severe HICH showed that MHT significantly improved neurological function in patients with craniocerebral injury, without significant side effects [10].

This study aimed to investigate the feasibility of combining MHT with minimally invasive debridement (MID) in patients with severe HICH, thus to provide a clinical reference for improving the prognosis of these patients.

Materials and methods

Baseline data

A total of 120 patients with severe HICH who received clinical interventions during January 2017 and January 2020 were enrolled in the study, and were randomized into a study group (SG, n=70) and a control group (CNG, n=50) according to the principle of a randomized, controlled, double-blind trial.

Inclusion criteria: (1) patients met the diagnostic criteria for severe HICH [11] and were diagnosed by cranial imaging; (2) those with a clear previous history of hypertension or with higher blood pressure on admission; (3) ≤48 h from onset to admission; (4) bleeding ≥30 mL; (5) surgical treatment within 72 h of onset; (6) those with complete data; (7) the study was approved by the Ethics Committee of Huzhou Central Hospital, Affiliated Hospital of Huzhou Normal University; and (8) the patients' family members signed the informed consent.

Exclusion criteria: (1) non-hypertensive cerebral hemorrhage caused by intracranial tumor, trauma, infarction, *etc*.; (2) patients with coagulation dysfunction; (3) patients with brain herniation or signs of brain death found on examination; (4) patients with systemic chronic infection; (5) patients with concomitant malignancy; (6) patients with serious organic disease; and (7) patients with mental disorders.

Elimination criteria: (1) those who were lost to follow up; (2) those who voluntarily requested to withdraw during the study.

Intervention methods

Patients in the CNG received MID alone. Preoperative imaging was performed to determine the site and amount of bleeding, followed by local infiltration anesthesia. After the cranial drill penetrates the dura, the drainage tube is placed into the hematoma cavity for aspiration and coagulation and drainage, flushed with adrenaline and normal saline, and finally urokinase is injected into the hematoma cavity.

Patients in the SG were treated with MID combined with MHT, with their body temperature controlled at 34-35°C by intelligent MHT apparatus. The patients were injected with chlorpromazine 30 min before cooling, and the temperature was set to 10-15°C after the patient's body temperature was lowered to the surgical requirement. After completion of MID, temperature was increased 1°C every 4 h, and MHT should last for 5 days.

Outcome measurement

Surgical indicators: The surgical indicators such as hospitalization cost, operative time, intraoperative blood loss, and the length of intensive care unit (ICU) stay were recorded, and statistical analysis was conducted on the differences of the above indicators between the two groups.

Comparison of short-term clinical efficacy: Neurological deficits in both groups were assessed at 7 d postoperatively using the National Institutes of Health Stroke Scale (NIHSS) [12]. Patients' short-term effectiveness was calculated as NIHSS reduction rate = (pre-intervention NIHSS score-post-intervention NIHSS score)/pre-intervention NIHSS score × 100%, with a NIHSS reduction rate of 90%-100% being considered as cure, 45%-89% as significant improvement, 18%-44% as improvement,

Table 1. Comparison of baseline data ($\bar{x}$±s) [n (%)]

General data		Study group (n=70)	Control group (n=50)	t/χ^2	*P*
Gender	Male	40	28	0.016	0.901
	Female	30	22		
Average age (years)		54.49±2.32	54.52±2.21	0.071	0.944
Average weight (kg)		70.11±2.21	69.98±2.32	0.311	0.756
Average duration of illness (h)		3.29±1.43	3.31±1.39	0.076	0.94
Hematoma volume (mL)		45.11±3.21	45.21±2.98	0.173	0.863
GOS score		10.29±2.11	10.31±2.09	0.051	0.959
Bleeding site	Frontal lobe	14	11	0.334	0.545
	Parietal lobe	26	15		
	Temporal lobe	14	12		
	Occipital lobe	16	12		

0%-17% as no change, and an increase of 18% and above as progression. The effective rate = (cure + significant improvement + improvement)/total cases. The hematoma clearance rate at 1 d and 3 d postoperatively, the amount of residual hematoma at 3 d postoperatively, and the amount of perihematoma edema at 7 d postoperatively were compared between the two groups.

Changes in neurological function and mobility: Neurological function and activities of daily living (ADL) were assessed before intervention and at 1, 3, 6 and 12 months after intervention, respectively. The Barthel scale [13] was used to assess the ability to perform ADL, which included 10 items such as dressing, grooming, eating, toileting, *etc*. The scale ranges 0-100 points, with a higher score representing a higher ADL.

Evaluation of perioperative complications and long-term outcomes: The incidence of perioperative complications such as rebleeding, intracranial infection, gastrointestinal bleeding, and renal failure was recorded, while patients in both groups were followed up for 1 year, and the long-term prognosis of both groups was evaluated using the Glasgow Outcome Scale (GOS), which can be differentiated into levels 1-5 [14], where level 1 represents death and level 5 represents a normal life with minor physical or mental deficits.

Statistical methods

SPSS22.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data collected from the study. Measurement data were expressed as mean ± SD. The *t*-test was used for the data meeting normal distribution or with even variance while approximate *t*-test was applied for data with uneven variance, and chi-square test was used for the difference in count data between groups. $P<0.05$ indicated significant difference, and Graphpad prism 8.3 [15] was used as the graphing tool.

Results

Comparison of clinical data

This study included 120 patients, including 68 males and 52 females, aged 50-68 years, with the mean age of (54.50±2.33) years. There was no significant difference between the two groups in terms of gender, average age, average weight, average duration of illness, GOS score, and bleeding site ($P>0.05$), suggesting that the two groups were comparable (**Table 1**).

Comparison of surgical indicators

The SG exhibited significantly shorter operative time, less intraoperative blood loss, shorter length of ICU stay of the patients, and higher hospitalization cost than the CNG, and the differences of the above indices between the groups were statistically significant ($P<0.05$) (**Figure 1**).

Comparison of short-term clinical efficacy

The SG had 9 cases of cure, 35 cases of significant improvement, and 14 cases of improvement, while the CNG had 4 cases of cure, 15 cases of significant improvement, and 10 cases

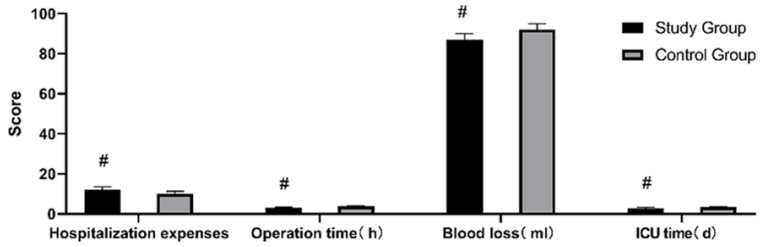

Figure 1. Comparison of general surgical indicators between the two groups. #*P*<0.05 vs. the control group.

of improvement. The total short-term effective rate was 82.86% in the SG, which was higher than 58.00% in the CNG (*P*<0.05) (**Table 2**). The hematoma clearance rate of the SG was significantly higher than that of the CNG at 1 d and 3 d after surgery, while the hematoma residual volume at 3 d after surgery and the edema volume around the hematoma at 7 d after surgery were significantly lower than those of the CNG (*P*<0.05) (**Figure 2**).

Changes in neurological function and mobility

Before intervention, there was no significant difference in NIHSS and Barthel scores between the two groups (*P*>0.05). NIHSS scores were decreased while Barthel scale scores were increased in both groups after intervention. At 1, 3, 6 and 12 months after intervention, patients in the SG had lower NIHSS scores and higher Barthel scores than the CNG (*P*<0.05) (**Figure 3**).

Perioperative complications and long-term outcomes

The patients in the SG had 1 case of gastrointestinal bleeding, with a total complication rate of 1.43%, while the patients in the CNG had 1 case of rebleeding, 1 case of intracranial infection, 2 cases of gastrointestinal bleeding and 1 case of renal failure, with a total complication rate of 10.00% (*P*<0.05) (**Table 3**). Patients in the two groups were followed up for a period of 1 year, and the GOS scale was used to evaluate the long term efficacy. The results showed that the percentage of patients in the SG in grades IV and V at 1 year after surgery was 50.00% and 14.29%, while the percentage in the CNG in grades IV and V at 1 year after surgery was 32.00% and 2.00%. The percentage of GOS grades IV and V in the SG was higher than that in the CNG (*P*<0.05) (**Table 4**).

Discussion

HICH is the parenchymal hemorrhage, a severe complication, caused by persistent hypertension [16]. Clinical practice has found that patients with HICH tend to have a poor prognosis and high mortality. To date, there has been no significant progress in improving the functional outcomes of patients with HICH [17]. Some studies have suggested that even though the surgical treatment can rapidly remove the hematoma and eliminate the damage to brain tissues by harmful substances released from hematoma dissipation, it remains unknown whether the trauma caused by surgery will cause secondary injury to patients [18, 19]. A large number of clinical studies have pointed out that minimally invasive surgery has better effects on HICH and is outstanding in reducing patient's mortality compared with conservative treatment as well as traditional open surgery [20-22].

In this study, we analyzed the effect of MID and MHT on patients with severe HICH by setting up different subgroups, and the results showed that patients in the SG had more significant advantages in surgical indicators, and their operative time, intraoperative blood loss, and length of ICU stay were lower than those in the CNG. This indicated that the combined intervention minimized the trauma caused by surgery and accelerated the postoperative regression of patients. It has been shown that patients with HICH often have impaired consciousness and neurological impairment when they are admitted to hospital, and the hematoma caused by intracranial hemorrhage can compress deep brain structures, leading to endocrine dysfunction and abnormal circulatory and respiratory functions, and the clinical treatment option should be performed to relieve the compression of the hematoma on the brain tissue and reduce the intracranial pressure as early as possible [23]. The shorter operative time and length of ICU stay in the SG indicated that the combined intervention was less traumatic for the patients, which undoubtedly laid a good foundation for their postoperative

Table 2. Comparison of the effectiveness of clinical interventions [n (%)]

Group	Case	Cure	Significant improvement	Improvement	No change	Progression	Total effective rate
Study group	70	9 (12.86)	35 (50.00)	14 (20.00)	6 (8.57)	6 (8.57)	58 (82.86)
Control group	50	4 (8.00)	15 (30.00)	10 (20.00)	14 (28.00)	7 (14.00)	29 (58.00)
χ^2	-	-	-	-	-	-	9.039
P	-	-	-	-	-	-	0.003

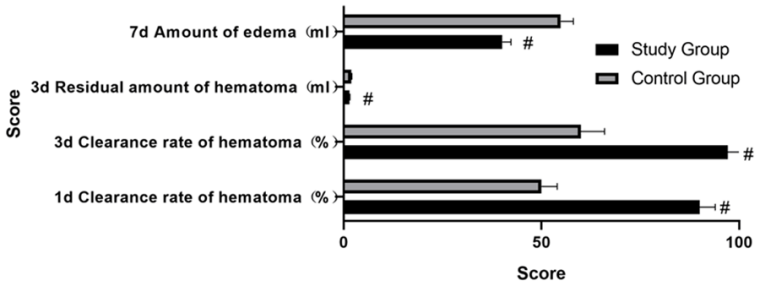

Figure 2. Comparison of short-term clinical efficacy between the two groups. #*P*<0.05 vs. the control group.

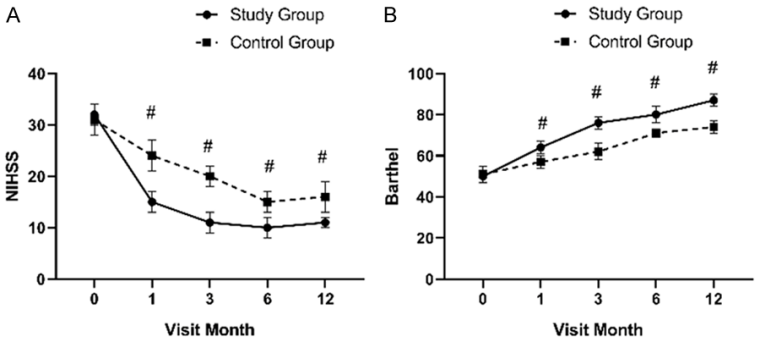

Figure 3. Changes in neurological function and mobility before and after intervention. #*P*<0.05 vs. the control group.

recovery and better short-term clinical outcomes. The total short-term effective rate was 82.86% in the SG, significantly higher than 58.00% in the CNG, similar to the results of other studies. A controlled study of 86 patients with HICH showed that the treatment effective rate of the observation group with MID + MHT was 95.35%, which was higher than 81.40% of the CNG, may be caused by longer waiting time before admission, leading to more significant brain damage [24]. It was speculated that MHT played the role of regulating cerebral blood flow, reducing cerebral metabolic rate of oxygen, and improving cellular energy metabolism, and that intraoperative MHT could reduce brain cell death and facilitate postoperative neurological recovery, which was evidenced by the fact that the NIHSS scores of patients in the SG were lower than those of the CNG at 1, 3, 6, and 12 months after surgery, and the Barthel index scores were higher than those of the CNG.

This study also showed that the percentage of GOS grades IV and V in the SG was significantly higher than that in the CNG at 1 year postoperatively, suggesting that the long-term effect of the combined intervention was positive. A study of 90 patients with HICH found that the total effective rate after intervention was 64.44% in the CNG who underwent MID, which was lower than 84.44% in the observation group treated with MID + MHT, while the percentage of GOS score grade V at 12 months after surgery was 42.86% in the observation group, which was higher than 20.69% in the CNG, which was similar to the results of this study [25]. The underlying reason may be that brain tissues are often in an inflammatory state after craniocerebral injury and secrete a large number of inflammatory factors, which have a killing effect on healthy nerve cells. MHT has the effect of inhibiting the release of endogenous harmful factors and reducing brain damage. Combined with MID, it can not only rapidly eliminate the hematoma, but also improve stress response, contributing to short-term as well as long-term clinical outcomes of patients [26], which is also reflected by the results that the complication rate of the SG was lower than that of the CNG.

In conclusion, MDT combined with MHT in patients with severe HICH has good clinical efficacy in the short-term and long term, which can help accelerate the postoperative regression,

Table 3. Comparison of the complication rate [n (%)]

Group	Case	Re-bleeding	Intracranial infection	Gastrointestinal bleeding	Renal failure	Total incidence rate
Study group	70	0 (0.00)	0 (0.00)	1 (1.43)	0 (0.00)	1 (1.43)
Control group	50	1 (2.00)	1 (2.00)	2 (4.00)	1 (2.00)	5 (10.00)
χ^2	-	-	-	-	-	4.511
P	-	-	-	-	-	0.034

Table 4. Comparison of clinical outcomes at 1 year after surgery [n (%)]

Group	Case	Grade I	Grade II	Grade III	Grade IV	Grade V
Study group	70	0 (0.00)	5 (7.14)	20 (28.57)	35 (50.00)	10 (14.29)
Control group	50	1 (2.00)	11 (22.00)	21 (42.00)	16 (32.00)	1 (2.00)
χ^2	-	1.412	5.571	2.338	3.867	5.287
P	-	0.235	0.018	0.126	0.049	0.021

improve their postoperative neurological function and quality of life, and also reduce the incidence of perioperative complications. The deficiency of this study is that only patients with HICH were included, and the effectiveness of the intervention in patients with, for example, cerebral infarction and normal blood pressure need further investigation.

Disclosure of conflict of interest

None.

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