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ORIGINAL RESEARCH

Synergistic effects of neuroendoscopic minimally invasive surgery with mannitol and furosemide in managing hypertensive intracerebral hemorrhage

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Abstract

This study aimed to assess the therapeutic efficacy of neuroendoscopic minimally invasive surgery combined with mannitol and furosemide for treating hypertensive intracerebral hemorrhage. We retrospectively analyzed clinical data from 200 patients with hypertensive intracerebral hemorrhage treated at our hospital between July 2020 and July 2022. The patients were categorized into either the experimental group (undergoing neuroendoscopic minimally invasive surgery combined with mannitol and furosemide) or the control group (undergoing neuroendoscopic minimally invasive surgery alone). Then, we compared the efficacy and impact on patients between the two groups. After treatment, the experimental group exhibited a smaller edema area compared to the control group and a reduced hematoma volume ($p < 0.001$). The total effective rate was significantly higher in the experimental group compared to the control group ($p < 0.05$). At 7 days post-treatment, patients in the experimental group demonstrated a significantly lower National Institutes of Health Stroke Scale (NIHSS) score compared to the control group ($p < 0.001$). Additionally, 3 and 7 days after treatment, levels of lipid peroxidation (LPO), neuron-specific enolase (NSE), and S-100β were significantly lower in the experimental group compared to the control group ($p < 0.001$). Similarly, carotid total blood flow volume (Q) and blood flow velocity (V) were significantly higher in the experimental group at 3 and 7 days post-treatment, with lower peripheral resistance (R) compared to the control group ($p < 0.001$). The incidence rate of complications was significantly lower in the experimental group compared to the control group ($p < 0.05$). The integration of neuroendoscopic minimally invasive surgery with mannitol and furosemide administration demonstrates potential in alleviating brain edema, reducing related cytokine levels, facilitating neurological function recovery, and improving cerebral hemodynamic parameters in hypertensive intracerebral hemorrhage patients. These findings merit clinical promotion and application.

Keywords

Neuroendoscopic minimally invasive surgery; Mannitol; Furosemide; Hypertensive intracerebral hemorrhage

1. Introduction

Hypertensive intracerebral hemorrhage (HICH), a severe complication of hypertension, results from the dysfunction of small cerebral arteries and predominantly affects middle-aged and elderly individuals, posing significant risks to their health and survival [1]. This condition often occurs due to sudden increases in blood pressure triggered by activities such as strenuous exercise, exhaustion, or emotional stress in hypertensive patients. These surges can result in local brain damage, rupture of cerebral vessels, elevated intracranial pressure, and compromised cerebral blood flow, leading to severe consequences like paralysis, aphasia, and central nervous system failure [2, 3]. With its high mortality rate and rapid progression, HICH presents considerable challenges in treatment [4]. Pharmacotherapy in clinical practice aims to reduce intracranial pressure and alleviate edema [5]. However, the efficacy of drugs varies significantly among different agents. Mannitol, known for its potent diuretic effect, can help alleviate intracranial hypertension [6], while furosemide is used to manage brain edema. Conventional drugs primarily target intracranial pressure and hypertension control but may not adequately address symptoms such as elevated intracranial pressure, mass effect, and herniation following hematoma formation. In contrast, surgical intervention, particularly hematoma evacuation under direct visualization, can substantially decrease intracranial

pressure and reduce the risk associated with toxic byproducts of hematomas, thus preserving brain tissue [7]. Surgical techniques for hematoma removal range from traditional craniotomy, which is invasive and associated with significant tissue damage and lengthy recovery, to neuroendoscopic minimally invasive surgery, which is characterized by reduced trauma, enhanced safety, and more favorable outcomes [8]. However, research on the integration of surgical and pharmacological treatments for HICH is limited. Therefore, this study retrospectively analyzes clinical data from 200 patients treated for hypertensive cerebral hemorrhage at our institution between July 2020 and July 2022 to investigate the combined impact of neuroendoscopic minimally invasive surgery with mannitol and furosemide therapy on this life-threatening condition.

2. Materials and methods

2.1 General information

We conducted a retrospective analysis of clinical data from 200 patients diagnosed with hypertensive intracerebral hemorrhage who received treatment at the First Affiliated Hospital of Shihezi University between July 2020 and July 2022. Patients were stratified into two groups based on their treatment method: the experimental group (combination therapy) and the control group (neuroendoscopic minimally invasive surgery alone). Table 1 outlines the baseline characteristics of both groups, demonstrating statistically comparable parameters ($p > 0.05$). The hematoma locations in patients are detailed in Table 2.

The inclusion criteria for this study were as follows: (1) Patients diagnosed with hypertensive intracerebral hemorrhage; (2) Confirmation of cerebral hemorrhage through Computer tomography (CT) scan; (3) Admission to the hospital and initiation of treatment within 24 hours of symptom onset; (4) Age less than 80 years old; (5) Glasgow Coma Scale (GCS) score ranging between 6 and 13 points; (6) Hematoma volume ranging from 30 to 60 mL; (7) Absence of hemorrhage rupture into the brain ventricle.

The exclusion criteria were: (1) Abnormal coagulation function; (2) Patients with significant organ failure or impairment; (3) Severe systemic diseases or malignant tumors; (4) Patients with cognitive impairment or mental disorders; (5) History of previous cerebral hemorrhage, cerebrovascular malformations, aneurysms or other lesions; (6) Tumor stroke or patients with hemorrhagic stroke complicated by cerebral infarction.

2.2 Treatments

Preoperatively, all patients in both groups underwent thrombolytic therapy. Urokinase was intravenously administered at dosages ranging from 40,000 to 60,000 units per day, dissolved in 20 to 40 mL of saline. This dosage could be administered as a single dose or divided into 2 to 3 doses over a standard treatment period of 7 to 10 days, with adjustments made based on the individual's clinical response.

Anticoagulants such as heparin sodium injection were utilized to reduce the risk of venous thrombosis and pulmonary embolism in patients. Administration was recommended once the hematoma had stabilized, typically 1 to 4 days after onset. The suggested dosage for intravenous infusion ranged between 20,000 and 40,000 International Units (IU) daily, diluted in 1000 mL of sodium chloride injection for continuous infusion. An initial bolus of 5000 IU was given intravenously before starting the infusion.

For hematoma evacuation, the control group underwent neuroendoscopic minimally invasive surgery. Cerebral hematoma location and morphology were assessed by conducting head CT scans. A straight incision, approximately 6 cm in length, was made closest to the hematoma site through the skin, fol-

TABLE 1. Comparison of the baseline characteristics of the two groups ($\bar{x} \pm s$).

Variables	Experimental group (n = 100)	Control group (n = 100)	χ^2/t	p
Gender (male/female)	65/35	62/38	0.194	0.659
Age (yr)	62.30 ± 6.12	61.95 ± 6.44	0.394	0.694
Midline shift distance (mm)	4.01 ± 1.09	4.10 ± 1.05	0.595	0.553
GCS	9.15 ± 2.06	9.34 ± 2.13	0.641	0.522
Diastolic pressure (mmHg)	95.61 ± 6.30	96.34 ± 5.98	0.840	0.402
Systolic pressure (mmHg)	145.30 ± 15.20	144.32 ± 14.60	0.465	0.643
History of diabetes	23	27	0.427	0.514
History of hyperlipidemia	28	26	0.102	0.750
Smoking history	30	32	0.094	0.760

GCS: Glasgow Coma Scale.

TABLE 2. Location of hematoma in the two groups (n (%)).

Group	n	Hematoma position				
		Deep thalamus	Putamen	Internal capsule-Lobar	Cerebellum	Brainstem
Experimental group	100	36 (36.00)	3 (3.00)	47 (47.00)	8 (8.00)	6 (6.00)
Control group	100	39 (39.00)	6 (6.00)	46 (46.00)	5 (5.00)	4 (4.00)

lowed by the creation of a 3 cm bone window using a milling cutter. The dura mater was then opened, and the hematoma was localized with ultrasound guidance. Subsequently, a transparent endoscope sheath was guided along the pathway to the hematoma. Using a 30° viewing angle Aesculap neuroendoscope, a drainage tube was attached, and negative pressure suction was used to aspirate the hematoma. Electrocoagulation was conducted to control arterial hemorrhage and venous bleeding was managed with hemostatic agents. Upon completion of the hematoma evacuation, the dura mater was sutured, the bone flap was repositioned, and the skull incision was closed. Postoperative assessment included a cranial CT scan conducted 4–6 hours after the procedure to evaluate hematoma removal, regulate blood pressure, and prevent complications.

In addition to the control group's protocol, the experimental group underwent adjuvant pharmacotherapy post-surgery, which included a 250 mL 20% mannitol intravenous (IV) infusion administered every 8 hours and a 20 mg intravenous bolus of furosemide given every 12 hours for two weeks. Renal function tests were conducted post-treatment. Single-photon emission computed tomography (SPECT) was conducted to monitor changes in edema and hematoma volume before and after intervention.

2.3 Observation indicators

(1) Cerebral edema in both groups was compared using SPECT before and two weeks after treatment to assess changes in edema area and hematoma volume. (2) Neurological function was evaluated using the National Institutes of Health Stroke Scale (NIHSS) on day 1 before treatment and day 7 after treatment. This scale comprises 11 items, with a higher score indicating more severe neurological deficits. (3) Serum indicators were measured by collecting fasting venous blood samples (approximately 5 mL) on day 1 before treatment, day 3, and day 7 after treatment. Enzyme-linked immunosorbent assay (ELISA) was used to measure lipid peroxidation (LPO), neuron-specific enolase (NSE), and S-100β protein levels. (4) Cerebral hemodynamic parameters, including the blood flow volume (Q), blood flow velocity (V), and peripheral vascular resistance (R) of the carotid artery, were assessed using a color Doppler ultrasound diagnostic instrument on day 1 before treatment, day 3, and day 7 after treatment. (5) Clinical efficacy was evaluated using the NIHSS scores. Full recovery was defined as achieving a level 0 disability, with an NIHSS score reduction of more than 90%. Markedly effective treatment was indicated by disability levels IIII and an NIHSS score reduction between 45% and 90%. Effective treatment was characterized by disability levels IIII and an NIHSS score reduction ranging from 18% to 45%. Ineffective treatment was identified by disability levels greater than III, with an NIHSS score reduction of 18% or less. The total effective rate was calculated as follows: Total effective rate = (full recovery + markedly effective + effective)/total number of cases $\times$ 100%. (6) Postoperative complications, including rebleeding, intracranial infection and death, were monitored.

2.4 Statistical methods

The data was analyzed using the SPSS v18.0 (IBM, Armonk, NY, USA) statistical software, and quantitative data was described as ($\bar{x} \pm s$). The comparison was carried out using *t*-tests for continuous data, while count data were described in percentage (%) and compared using χ^2 tests. Statistical significance was set at $p < 0.05$.

3. Results

3.1 Comparison of cerebral edema

After treatment, the experimental group exhibited a smaller area of edema and a reduced hematoma volume compared to the control group ($p < 0.05$) (Table 3).

3.2 Comparison of treatment efficacy

The total effective rate in the experimental group was significantly higher than that in the control group ($p < 0.05$). The detailed comparison is shown in Table 4.

3.3 Comparison of neurological function scores

On day 7 after treatment, the NIHSS scores of patients in the experimental group were significantly lower than those in the control group ($p < 0.05$), as shown in Table 5.

3.4 Serum indicators

On day 3 and day 7 after treatment, the levels of LPO, NSE and S-100β in the experimental group were significantly lower than those in the control group ($p < 0.05$) (Table 6).

3.5 Cerebral hemodynamic parameters

On day 3 and day 7 after treatment, the levels of Q and V in the experimental group were found to be significantly higher than those in the control group, while the level of R in the experimental group was significantly lower than that in the control group ($p < 0.05$). Further details are shown in Table 7.

3.6 Complications

Further analysis showed that the incidence of complications in the experimental group was significantly lower than that in the control group ($p < 0.05$) (Table 8).

4. Discussion

HICH represents a significant clinical emergency characterized by high mortality and morbidity. This condition often leads to complications, including cerebral ischemia, brain edema and neuronal death [9]. It predominantly affects middle-aged and elderly males. The pathophysiology of HICH involves sustained hypertension causing microscopic arterial changes, resulting in weakened vessel walls that are prone to necrosis and rupture upon acute pressure surges from factors such as emotional stress, overwork or intense mental effort [10]. The occurrence of a hemorrhage exacerbates intracranial pressure, impairs cerebral circulation, and

TABLE 3. Comparison of brain edema between the two groups ($\bar{x} \pm s$).

Group	n	Edema area (cm^2)		Hematoma volume (mL)	
		Before treatment	After two weeks of treatment	Before treatment	After two weeks of treatment
Experimental group	100	5.50 ± 0.73	2.59 ± 0.58	38.20 ± 8.34	13.98 ± 2.61
Control group	100	5.63 ± 0.82	3.35 ± 0.71	37.68 ± 9.12	18.36 ± 3.34
t	-	1.184	8.290	0.421	10.330
p	-	0.238	<0.001	0.674	<0.001

TABLE 4. Comparison of therapeutic effects between the two groups of patients (n (%)).

Group	n	Full recovery	Markedly effective	Effective	Ineffective	Total effective rate
Experimental group	100	22 (22.00)	26 (26.00)	46 (46.00)	6 (6.00)	94 (94.00)
Control group	100	20 (20.00)	22 (22.00)	40 (40.00)	18 (18.00)	82 (82.00)
χ^2						6.818
p						0.009

TABLE 5. Comparison of NIHSS scores between the two groups of patients ($\bar{x} \pm s$, score).

Group	n	1 day before treatment	7 days after treatment
Experimental group	100	27.35 ± 4.18	10.43 ± 1.93
Control group	100	26.69 ± 3.96	15.34 ± 2.01
t	-	1.146	58.351
p	-	0.253	<0.001

TABLE 6. Comparison of serological index levels between the two groups of patients ($\bar{x} \pm s$).

Group	n	LPO (μmol/L)			NSE (μg/L)		
		1 day before treatment	3 days after treatment	7 days after treatment	1 day before treatment	3 days after treatment	7 days after treatment
Experimental group	100	35.67 ± 5.40	30.25 ± 3.73	26.43 ± 3.40	19.51 ± 3.10	15.61 ± 2.75	10.12 ± 2.19
Control group	100	36.02 ± 5.25	33.48 ± 3.92	31.50 ± 4.01	19.73 ± 3.18	17.78 ± 2.79	14.52 ± 3.39
t	-	0.465	5.969	9.644	0.495	5.539	10.902
p	-	0.643	<0.001	<0.001	0.621	<0.001	<0.001
Group	n	S-100β (ng/mL)					
		1 day before treatment		3 days after treatment		7 days after treatment	
Experimental group	100	204.35 ± 20.04		95.14 ± 10.29		24.31 ± 2.73	
Control group	100	205.07 ± 19.84		121.04 ± 12.53		35.18 ± 3.44	
t	-	0.255		15.974		24.752	
p	-	0.799		<0.001		<0.001	

LPO: lipid peroxidation; NSE: neuron-specific enolase.

TABLE 7. Comparison of cerebral hemodynamic parameter levels between the two groups of patients ($\bar{x} \pm s$).

Group	n	Q (cm/m^2)			V (m/s)		
		1 day before treatment	3 days after treatment	7 days after treatment	1 day before treatment	3 days after treatment	7 days after treatment
Experimental group	100	9.87 ± 2.53	13.37 ± 2.95	16.02 ± 3.26	6.86 ± 2.20	9.35 ± 2.75	11.03 ± 3.14
Control group	100	9.92 ± 2.32	11.35 ± 2.75	13.27 ± 2.85	6.94 ± 2.17	7.52 ± 2.50	8.82 ± 2.74
t	-	0.146	5.009	6.351	0.259	4.924	5.303
p	-	0.884	<0.001	<0.001	0.796	<0.001	<0.001
Group	n	R (Pa·s/mL)					
		1 day before treatment		3 days after treatment		7 days after treatment	
Experimental group	100	1726.45 ± 298.18		1450.38 ± 237.88		1386.45 ± 208.66	
Control group	100	1710.65 ± 304.11		1609.50 ± 262.18		1506.76 ± 219.53	
t	-	0.371		4.495		3.972	
p	-	0.711		<0.001		<0.001	

Q: blood flow volume; V: blood flow velocity; R: and peripheral vascular resistance.

TABLE 8. Complications in both groups (n (%)).

Group	n	Hemorrhage	Intracranial infection	Death	Total
Experimental group	100	0	1 (1.00)	1 (1.00)	2 (2.00)
Control group	100	3 (3.00)	4 (4.00)	2 (2.00)	9 (9.00)
χ^2					4.714
p					0.030

induces neurological dysfunction, typically presenting with vomiting, nausea, dizziness, headache, coma and hemiplegia [11]. Brain edema is particularly detrimental, significantly influencing patient prognosis by compounding secondary damage post-HICH [12]. Addressing cerebral edema and reducing intracranial pressure are crucial for effective HICH management, aiding neural recovery, decreasing complication rates, and enhancing overall outcomes [13].

Surgical intervention is widely employed in clinical practice to evacuate hematomas, alleviate mass effect, and prevent secondary injury from toxic hematoma byproducts [14, 15]. Neuroendoscopic minimally invasive surgery has gained popularity due to its reduced invasiveness and lower complication rates, emerging as a prominent treatment modality. However, postoperative management plays a crucial role in avoiding adverse outcomes, underscoring the importance of selecting appropriate osmotherapy agents [16]. Mannitol, an osmotic diuretic, rapidly elevates plasma osmolality, drawing interstitial fluid into the vascular compartment, thereby promoting dehydration and potentially improving cerebral perfusion. Furosemide, a loop diuretic, inhibits sodium and water reabsorption in the renal tubules, thus controlling cerebral edema [17]. Our study findings demonstrate that the experimental group experienced a reduction in both edema extent and hematoma volume compared to the control group, suggesting that a combination of minimally invasive surgery with mannitol and furosemide can effectively reduce edema and hematoma size.

Mannitol's efficacy as an edema treatment stems from its ability to increase plasma osmotic pressure without undergoing metabolism in the body, facilitating efficient extracellular and cerebrospinal fluid excretion, thereby alleviating edema symptoms [18]. Additionally, it exhibits diuretic properties, enhancing blood volume, glomerular filtration rate, and prostaglandin production, collectively expediting fluid excretion and reducing intracranial pressure [19]. Furosemide functions by inhibiting the uptake of sodium, potassium, and chloride ions, leading to diuresis and amelioration of cerebral edema, in addition to reducing cerebrospinal fluid production and, consequently, intracranial pressure [20]. Ultimately, our research confirms that integrating surgical procedures with pharmacological therapy significantly reduces postoperative hematoma and edema. The results indicate that the experimental group demonstrates a higher total efficacy rate and markedly reduced NIHSS scores after 7 days of treatment compared to controls. This underscores the effectiveness of neuroendoscopic surgery coupled with mannitol and furosemide in HICH treatment, leading to improved clinical outcomes. Neuroendoscopic surgery benefits from enhanced visualization of the operative field through direct lighting and precise ultrasound-guided hematoma local-

ization, ensuring efficient removal and better clearance rates [21]. Additionally, mannitol, an established osmotic diuretic, draws water from edematous brain tissue into the vascular system for renal excretion. This action effectively reduces intracranial pressure, mitigates cerebral edema, and prevents secondary damage following HICH. Consequently, the synergistic effect of combining surgical intervention with mannitol administration appears to enhance patient outcomes.

After treatment, the levels of LPO, NSE and S-100β in the experimental group were found to be significantly lower than those in the control group, indicating that the dual treatment modality effectively mitigates damage to the intracranial nervous system. NSE and S-100β proteins serve as established indicators of neuronal injury; NSE is a cytoplasmic glycolytic enzyme released by damaged neuroendocrine cells, while S-100β is a glial-derived calcium-binding protein. Under physiological conditions, these proteins are present at low concentrations within cells, but their levels surge in response to neuronal injury [22]. LPO plays a crucial role in regulating the equilibrium between oxygen-free radical activity and lipid peroxidation processes. Disruption of this balance, as seen during inflammatory responses, leads to elevated LPO, triggering a cascade of oxidative stress that impairs neural structures and tissues. Brain edema is a key factor in the secondary damage caused by HICH. In clinical settings, mannitol serves as a frontline diuretic post-surgery to promote dehydration and alleviate brain swelling, thus reducing intracranial pressure and enhancing plasma osmolarity. It is metabolized *via* the kidneys, facilitating the clearance of waste substances. Furosemide, on the other hand, inhibits sodium uptake into compromised brain tissue, diminishes cerebrospinal fluid production, and through its diuretic effect, concentrates blood proteins, acting as an osmotic dehydrating agent. The combination use of mannitol and furosemide not only better regulates serum biomarker levels but also aids in reducing intracranial pressure, averting various postoperative complications, and bolstering neurological function. After treatment, the Q and V values in the experimental group were significantly higher than those in the control group, while the R value was notably lower than in the control group. These findings suggest that adjuvant therapy with mannitol and furosemide enhances cerebral circulation in patients. Furosemide contributes to this improvement by inhibiting the breakdown of prostaglandins, elevating levels of prostaglandin E2, inducing vasodilation, and specifically augmenting renal blood flow, leading to lowered renal vascular resistance and heightened perfusion in the kidney's deep cortex. This effect facilitates more rapid elimination of toxins and supports systemic recovery. Accordingly, integrating surgical intervention with pharmacotherapy appears to optimize cerebral hemodynamic parameters. However, the limited sample size of this study may introduce biases in the outcomes. Future research with expanded sample sizes and multicenter contributions could enhance result validity.

5. Conclusions

In conclusion, the combination of neuroendoscopic minimally invasive surgery with mannitol and furosemide therapy demonstrated promising benefits in managing HICH by effectively enhancing neurological function, reducing NIHSS scores and promoting cerebral blood flow, thereby warranting broader clinical application.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

HX and JTD—designed the study and carried them out. HX, JTD, GGW, SLW, HHD and YJH—supervised the data collection. HX, JTD, GGW, SLW and HHD—analyzed the data. HX, JTD, GGW and SLW—interpreted the data, prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Science and Technology Ethics Committee of the First Affiliated Hospital of Shihezi University (Approval no. KJX2022-084-01). Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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