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Original Article

Efficacy of nimodipine plus mannitol in the treatment of cerebral edema after intracerebral hemorrhage and its impact on cerebral hemodynamic parameters

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Abstract: Objective: Cerebral edema (CE) following intracerebral hemorrhage (ICH) remains a therapeutic challenge. This study aimed to evaluate the clinical effectiveness of nimodipine combined with mannitol for post-ICH CE. Methods: A total of 220 patients with post-ICH CE were retrospectively included in this study. Patients were assigned to either a control group receiving nimodipine monotherapy (n=101) or a study group receiving nimodipine plus mannitol (n=119). Therapeutic response, hematoma/edema volume, intracranial pressure (ICP), National Institutes of Health Stroke Scale (NIHSS) score, cerebral hemodynamic parameters, and adverse events were compared between the groups. Logistic regression analysis was performed to identify factors related to favorable outcomes. Results: A notably higher overall response rate was observed in the study group (86.55%) compared to the control group (69.31%) (P=0.002). Patients in the study group showed greater reductions in terms of hematoma and edema volumes, more pronounced improvements in ICP, NIHSS scores, and cerebral hemodynamics (all $P < 0.05$). Logistic regression identified combination therapy, larger initial cerebral edema volume, and higher baseline NIHSS score as factors related to favorable outcomes. No significant inter-group difference was noted in the incidence of adverse events ($P > 0.05$). Conclusion: In patients with CE secondary to ICH, nimodipine combined with mannitol is more effective than nimodipine alone in improving clinical outcomes and cerebral hemodynamics.

Keywords: Mannitol, intracerebral hemorrhage, cerebral edema, cerebral hemodynamics

Introduction

Intracerebral hemorrhage (ICH) is the leading cause of mortality among acute cerebrovascular diseases, predominantly affecting patients over 50 years of age [1, 2]. Brain tissue injury, cerebrovascular rupture, cerebral inflammation, intracranial infection, and hydrocephalus following ICH can all trigger cerebral edema (CE) [3]. Patients with CE may experience symptoms such as increased intracranial pressure (ICP) and compromised neurological function, adversely affecting patients' quality of life and prognosis [4, 5]. Prolonged CE can rapidly elevate ICP and compress normal brain tissue, further compromising patients' neurological function and their daily living abilities [6, 7].

Mannitol, a sugar alcohol, can rapidly raise plasma osmotic pressure and enhance renal blood flow, thereby increasing glomerular filtration, effectively promoting diuresis [8]. However, prolonged or excessive use of mannitol can lead to accumulation in brain tissue, potentially exacerbating CE and increasing treatment risk [9, 10]. Nimodipine, a calcium channel blocker, inhibits calcium influx into vascular smooth muscle cells, thereby reducing vasoconstriction [11]. Nimodipine easily crosses the blood-brain barrier (BBB), effectively dilating cerebral arteries, preventing and treating cerebral vasospasm caused by ICH, and mitigating ischemic damage secondary to vasospasm. Nimodipine may also improve cognitive impairment after brain injury and is applicable to ischemic cere-

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brovascular diseases, sudden deafness, migraines, and mild to moderate hypertension [12, 13].

Currently, studies on the combined use of nimodipine and mannitol in treating CE after ICH remain limited. Therefore, this study retrospectively analyzed patients receiving different therapeutic strategies to evaluate the clinical efficacy of nimodipine plus mannitol in managing post-ICH CE, providing valuable insights for optimized clinical medication.

Data and methods

Study design

This single-center, retrospective cohort study analyzed clinical records of patients with CE after ICH hospitalized at Xiangdong Hospital between January 2021 and January 2024. Patients were grouped according to the actual treatment regimen they received: those receiving nimodipine monotherapy were assigned to the control group (n=101), while those who received nimodipine combined with mannitol were assigned to the study group (n=119). The study protocol was approved by the Ethics Committee of Xiangdong Hospital, and the requirement for informed consent was waived. All relevant data were independently assessed by two blinded raters, with discrepancies resolved by a third senior adjudicator. Data analysts remained blinded to group assignment during statistical analyses.

Inclusion and exclusion criteria

Inclusion criteria: (1) Diagnosis of CE after ICH confirmed by clinical examination and imaging (CT or MRI) within 24 hours of symptom onset, with intracranial pressure exceeding normal levels; (2) Complete clinical data available; (3) No indications for surgical intervention.

Exclusion criteria: (1) Allergy to study medications; (2) Malignant tumors or immune system disorders; (3) Renal or hepatic dysfunction, or circulatory disorders; (4) Mental disorders; (5) Electrolyte disturbances upon admission or cardiovascular diseases.

Treatment methods

Patients in the control group received nimodipine (Harbin Pharmaceutical Group Sanjing Mingshui Pharmaceutical Co., Ltd, approval number: H23021402; specification: 20 mg) [14]. All patients were administered 20 mg nimodipine orally once daily for a treatment duration of 1 month.

Patients in the study group received nimodipine and mannitol (China Resources Double-Crane Pharmaceutical Co., Ltd., approval number: H11020861; specification: 250 mL:50 g) [15]. Nimodipine was administered as in the control group (20 mg orally once daily). Mannitol was administered as an intravenous infusion over 30 minutes. The concentration was standardized at 20%. The initial dose was determined by the treating neurologist based on the initial cranial CT findings: patients with severe cerebral edema (edema volume ≥ 30 mL) and/or midline shift (≥ 5 mm) received a dose of 1.5 g/kg; otherwise, a standard dose of 1.0 g/kg was administered, with a maximum single dose not exceeding 2.0 g/kg. The standard administration frequency was three times daily (at 8:00, 16:00, and 24:00), which could be reduced to twice daily if ICP remained below 20 mmHg for 24 hours or if significant neurological improvement (e.g., NIHSS score reduction ≥ 4 points) was observed. The treatment duration was 1 month.

Safety monitoring: Electrolyte and acid-base balance, as well as blood pressure, were closely monitored during the treatment. Supportive measures were promptly implemented in case of any abnormalities. Electrolyte imbalance was defined as serum potassium < 3.5 mmol/L or serum sodium < 135 mmol/L. Renal dysfunction was defined as an increase in serum creatinine ≥ 50% from the baseline value.

Outcome measures

Primary outcome measures: (1) The treatment effects of the two groups were evaluated according to the following criteria [16]: *Markedly effective*: ICP returned to normal levels, with substantial improvement in CE as confirmed by imaging; *Effective*: ICP showed a trend toward normalization, with partial improvement in CE; *Ineffective*: no improvement in ICP or CE was observed, with possible worsening, or patient mortality occurred. Overall response rate (ORR) = (Number of markedly effective cases + effective cases)/Total number of cases × 100%.

(2) Cerebral hematoma and edema volumes were measured using head CT scans conducted before and after treatment. The volumes of ICH and CE were calculated according to standardized imaging protocols.

(3) Average cerebral blood flow (CBF) and blood flow velocity (BFV) were assessed within 24 hours of admission and within 48 hours after completion of therapy using a standardized transcranial Doppler (TCD) protocol (Nicolet/VIASYS Companion III). Measurements were conducted from the bilateral middle cerebral arteries (MCA) at rest. According to institutional laboratory standards, the normal reference range for MCA mean flow velocity was defined as 40-80 cm/s. Hemodynamic abnormality was defined as values outside this range or a side-to-side difference exceeding 20%.

Secondary outcome measures: (1) To establish group comparability, baseline demographic and clinical variables were documented for each patient, including age, body mass index (BMI), sex, site of hemorrhage, time of admission, amount of bleeding, and place of residence.

(2) Adverse therapy-associated events were documented and analyzed.

(3) ICP was measured non-invasively before and after therapy.

(4) Patients' neurological deficits were assessed via the National Institutes of Health Stroke Scale (NIHSS) before and after therapy. The 13-item scale assigns higher scores to more severe neurological impairment [17].

(5) Multivariate logistic regression was performed to identify independent factors associated with favorable outcomes.

Statistical analysis

SPSS 20.0 (IBM Corp, Armonk, NY, USA) was employed for statistical analyses, and GraphPad Prism 7 (GraphPad Software, San Diego, USA) for graph plotting. Given the retrospective design, the sample size was determined by the total number of eligible patients during the study period. A post-hoc power analysis confirmed sufficient power (> 90%) to detect the observed difference in overall response rates. Categorical data were presented as [n (%)], and inter-group comparisons were conducted using the chi-square (χ^2) test. Measurement data were normally distributed and expressed as mean ± standard deviation (mean ± SD). Inter-group comparisons of measurement data were performed using independent-sample t-tests, while within-group comparisons were performed using paired t-tests. To identify independent predictors of treatment response, univariate logistic regression analyses were first performed. Variables with $P < 0.05$ were subsequently included in a multivariate logistic regression model. Forward stepwise selection based on the likelihood ratio was used to refine the final model, retaining only variables with independent predictive significance ($P < 0.05$) and clinical relevance. Consequently, some initially significant variables in univariate analysis (e.g., site of bleeding) were excluded from the final model. Multicollinearity among these candidate variables was assessed using variance inflation factors (VIFs), all of which were < 5, indicating no significant collinearity. A two-sided $P < 0.05$ was considered statistically significant.

Results

Clinical baseline data

No significant differences were observed in age, BMI, sex, hemorrhage site, time of admission, hemorrhage volume, and place of residence (all $P > 0.05$, **Table 1**).

Treatment effects

In the control group, 22 patients (21.78%) showed markedly effective outcome; 48 (47.52%) showed effective outcome, and 31 (30.69%) showed ineffective outcome, resulting in an ORR of 69.31%. In the study group, 48 (40.34%) showed markedly effective outcome; 55 (46.22%) showed effective outcome, and 16 (13.45%) showed ineffective outcome, resulting in an overall response rate of 86.55%. The study group showed a notably higher ORR than the control group (P=0.002, **Table 2**).

Cerebral hematoma and edema volumes

No notable inter-group differences were observed in cerebral hematoma volume and CE volumes prior to treatment ($P > 0.05$). However, post treatment, both groups demonstrated sig-

Table 1. Comparison of baseline characteristics between the two groups

Factors	Control group (n=101)	Study group (n=119)	χ^2/t	P
Age (year)	63.13±6.36	62.61±5.34	0.664	0.507
BMI (kg/m^2)	22.75±1.36	22.51±1.576	1.102	0.272
Sex			0.940	0.332
Male	55	57		
Female	46	62		
Hemorrhage site			1.869	0.760
Cerebral lobes	28	25		
Basal ganglia area	38	47		
Cerebellum	18	21		
Brain stem	11	18		
Others	6	8		
Time of admission	6.98±0.73	7.06±0.75	0.988	0.325
Hemorrhage volume (mL)	24.11±6.12	23.22±8.83	0.831	0.407
Place of residence			0.857	0.392
Rural areas	56	71		
Urban areas	45	48		

Note: BMI, Body mass index.

nificant reductions in cerebral hematoma volume and CE volume (P < 0.05), with the study group demonstrating notably smaller volumes than the control group (P < 0.05, **Figure 1**).

Intracranial pressure and NIHSS scores

No significant inter-group differences were observed in baseline ICP and NIHSS scores (P > 0.05). However, after treatment, both groups exhibited significant reductions in ICP and NIHSS scores (P < 0.05), with the study group showing notably lower ICP and NIHSS scores than the control group (P < 0.05, **Figure 2**).

Cerebral hemodynamic parameters

Baseline average CBF and BFV did not differ significantly between groups (P > 0.05). After treatment, the study group demonstrated significant improvements in both CBF and BFV (P < 0.05). In the control group, CBF did not show significant change (P > 0.05), while BFV increased significantly (P < 0.05). Moreover, the study group demonstrated notably higher post-treatment CBF and BFV than the control group (P < 0.05, **Figure 3**).

Adverse reactions

In the control group, 4 patients (3.96%) developed rash, 4 patients (3.96%) experienced abdominal pain, none had renal dysfunction or electrolyte imbalance, and 3 patients (2.97%) had thrombocytopenia. Overall, 11 patients (10.89%) experienced adverse reactions.

In the study group, 7 patients (5.88%) developed rash, 7 patients (5.88%) experienced abdominal pain, 3 patients (2.52%) had renal dysfunction, 2 patients (1.68%) had thrombocytopenia, and 4 patients (3.36%) had electrolyte imbalance. Overall, 23 patients (19.33%) experienced adverse reactions. No notable difference was noted in the incidence of adverse reactions between the two groups (P=0.085, **Table 3**).

Univariate analysis

A univariate analysis was performed to screen predictors of therapeutic response. Patients were stratified into responders (n=173) and non-responders (n=47) based on treatment outcomes. Univariate analysis revealed strong associations of treatment mode (P=0.002), CE volume (P=0.009), and baseline NIHSS score (P=0.001) with treatment response (**Table 4**).

Multivariate analysis

Significant variables identified in univariate analysis were included in a multivariate logistic regression model (**Table 5**). Combination therapy (adjusted OR=2.38, 95% CI: 1.10-5.15, P=0.027), larger CE volume (adjusted OR=1.16, 95% CI: 1.04-1.29, P=0.009), and higher NIHSS score (adjusted OR=1.25, 95% CI: 1.05-1.50, P=0.015) were identified as independent predictors for favorable treatment outcomes.

Discussion

ICH and consequent hematoma formation disrupt cerebral hemodynamics, precipitating persistent ischemic injury to the brain [18, 19]. Despite continuous advancements in treatment strategies, the global burden of CE remains substantial [20, 21].

In this study, nimodipine monotherapy substantially suppressed hematoma and CE volumes

Table 2. Comparison of treatment response rate between the two groups ([%])

	Markedly effective	Effective	Ineffective	Response rate
Control group (n=101)	22 (21.78%)	48 (47.52%)	31 (30.69%)	70 (69.31%)
Study group (n=119)	48 (40.34%)	55 (46.22%)	16 (13.45%)	103 (86.55%)
χ^2				9.674
P				0.002

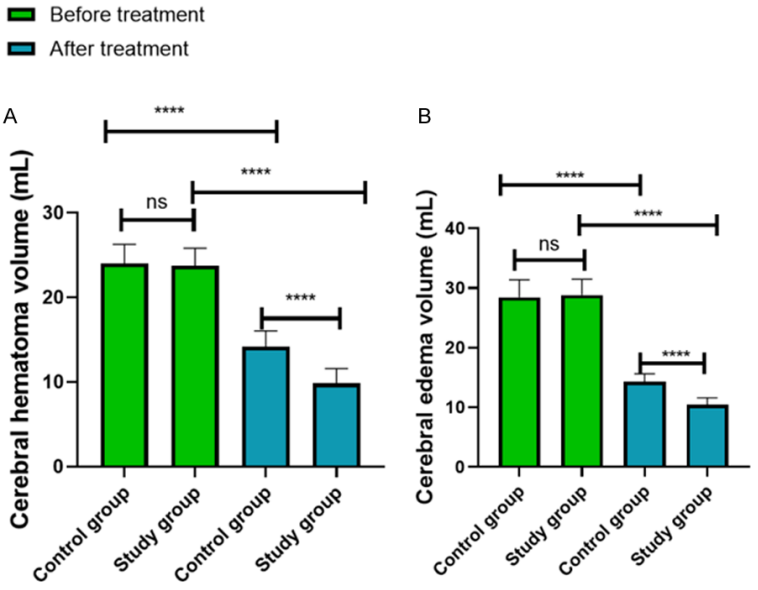

Figure 1. Comparison of intracerebral hemorrhage volume (A) and cerebral edema volume (B) between the two groups before and after treatment. Notes: ns, not significant; ****P < 0.0001.

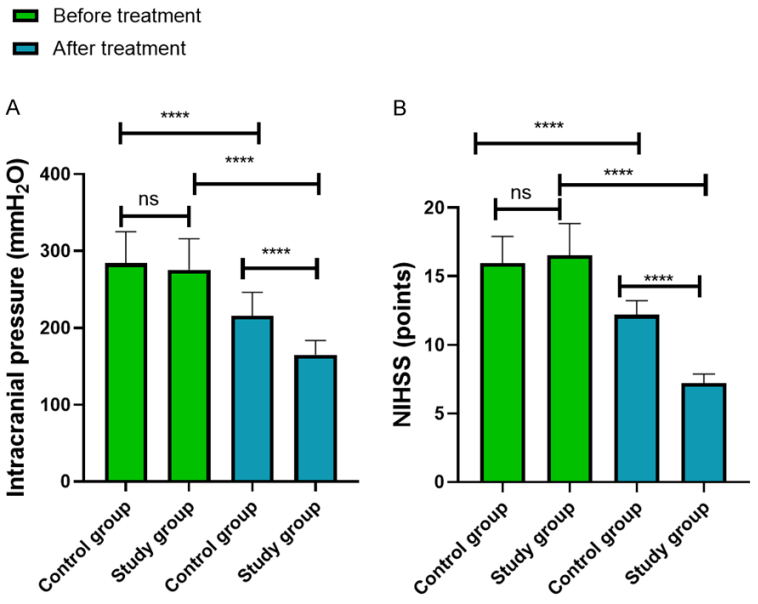

Figure 2. Comparison of intracranial pressure (A) and NIHSS scores (B) between the two groups before and after treatment. Notes: ns, not significant; ****P < 0.0001. NIHSS, National Institutes of Health Stroke Scale.

after ICH. This finding reinforces the established rationale for nimodipine in alleviating secondary brain injury by mitigating cerebral vasospasm and also suggests its potential role in improving peri-hematomal microcirculation [22]. More importantly, the combined nimodipine-mannitol regimen demonstrated superior outcomes across multiple endpoints, including hematoma resolution, edema reduction, inracranial pressure control, and NIHSS improvement, compared to monotherapy. The combination therapy group exhibited an approximately 17% higher overall response rate (86.55% vs. 69.31%). Multivariate analysis further identified combination therapy as an independent predictor of favorable outcomes. These findings are consistent with and extend previous research. Tingyan et al. demonstrated the benefits of a piracetam-mannitol regimen on neurological and endothelial function in patients with post-ICH edema, while Xiang et al. reported the efficacy of nimodipine-mannitol combination in hypertensive ICH [23, 24]. Our study provides a plausible mechanistic insight into the observed synergy, complementing prior efficacy data.

The pharmacological advantage of the nimodipine-mannitol combination likely stems from complementary actions on multiple pathways. Nimodipine may stabilize the BBB by

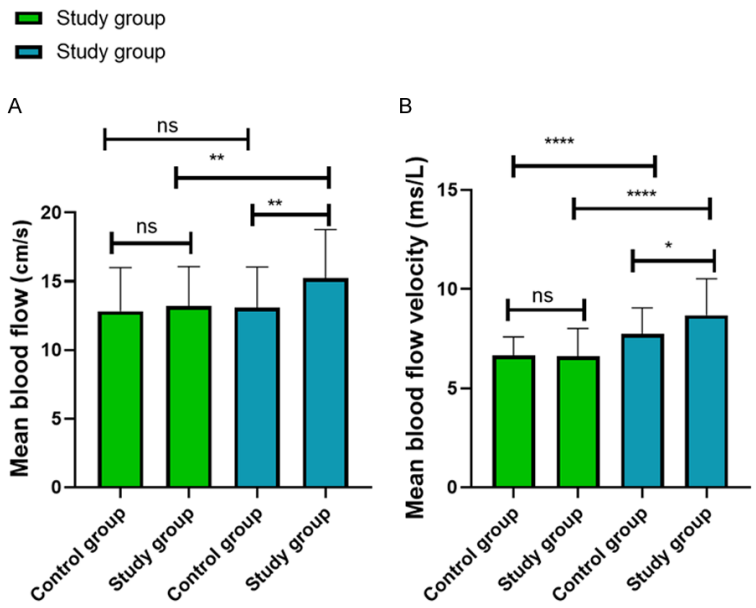

Figure 3. Comparison of average blood flow (A) and average blood flow velocity (B) between the two groups before and after treatment. Notes: ns, not significant; **P < 0.01; ****P < 0.0001.

reducing calcium-mediated endothelial injury [25], while mannitol lowers ICP and may attenuate inflammatory responses [26]. Together, these effects contribute to improved cerebral perfusion and neurological outcomes.

The significantly greater improvement in cerebral hemodynamics (CBF and BFV) observed in the combination group provides a plausible physiological explanation for the superior clinical outcomes. We hypothesize that the synergy stems from complementary mechanisms: nimodipine mitigates cerebral vasospasm, directly improving luminal diameter and downstream microcirculatory perfusion in peri-hematomal regions [24]; mannitol reduces ICP and brain parenchymal water content, potentially decreasing external compressive forces on the vasculature and improving cerebral perfusion pressure [26]. Together, these actions may create a more favorable environment for edema and hematoma resolution [25, 26].

At the molecular level, emerging evidence suggests that these beneficial effects may converge on key regulators of cell death and inflammation. For instance, caspase-8 has been identified as a critical molecular switch controlling apoptosis, necroptosis, and inflammasome activation, all of which contribute to secondary brain injury after ICH [27]. Furthermore, the ubiquitin-proteasome system, particularly its regulation of NF-κB signaling, plays a pivotal role in post-hemorrhagic neuroinflammation and BBB integrity [28]. Experimental studies have demonstrated that activating pro-survival pathways, such as ERK MAPK, can inhibit NF-κB nuclear translocation, thereby reducing cell apoptosis [29].

Therefore, it is plausible that the nimodipine-mannitol combination exerts superior effects by modulating these interconnected signaling networks, collectively alleviating cerebral edema and improving neurological outcomes. However, this study did not measure specific molecular markers (e.g., Claudin-5 for BBB integrity or IL-6/TNF-α for inflammation), and the proposed mechanisms regarding barrier stabilization and anti-inflammatory effects remain speculative, based primarily on existing literature. Similarly, the precise temporal and quantitative contribution of each drug to the observed hemodynamic improvements cannot be delineated from the current clinical data. Future prospective studies incorporating serial multimodal monitoring (e.g., combining TCD with imaging of BBB permeability and inflammatory biomarker assays) are needed to validate these mechanistic pathways and elucidate the specific roles of nimodipine and mannitol.

This study does have several limitations. First, its retrospective, single-center, and non-randomized design may have introduced unmeasured confounders, affecting the observed associations and limiting the external validity of the findings. Second, safety data were collected retrospectively, and some adverse events, such as blood pressure fluctuations, may not have been systematically captured. Prospective, randomized trials are needed to address these issues. Third, the exploratory analysis of therapeutic mechanisms was limited by the absence of direct molecular or advanced physiological data. The proposed synergistic actions on the

Table 3. Comparison of incidence of adverse reactions between the two groups (n [%])

Group	Rash	Abdominal pain	Renal function abnormalities	Thrombocytopenia	Electrolyte imbalance	Total
Control group (n=101)	4 (3.96%)	4 (3.96%)	0 (0.00%)	3 (2.97%)	0 (0.00%)	11 (10.89%)
Study group (n=119)	7 (5.88%)	7 (5.88%)	3 (2.52%)	2 (1.68%)	4 (3.36%)	23 (19.33%)
χ^2						2.976
P-value						0.085

Table 4. Univariate analysis of factors associated with treatment outcomes

Factors	Response group (n=173)	Non-response group (n=47)	χ^2/t	P
Age (year)	62.84±5.81	62.86±5.94	0.022	0.983
Sex			0.096	0.757
Male	95	27		
Female	78	20		
Hemorrhage site			/	0.026
Cerebral lobes	35	18		
Basal ganglia area	73	12		
Cerebellum	33	6		
Brain stem	23	6		
Others	9	5		
Hemorrhage volume (mL)	23.45±7.95	24.32±7.12	0.681	0.497
Cerebral hematoma volume (mL)	23.70±2.06	24.23±2.04	1.566	0.119
Cerebral edema volume (mL)	28.21±2.93	29.52±3.36	2.638	0.009
Intracranial pressure	278.38±39.96	283.00±44.78	0.686	0.494
NIHSS score	15.97±2.10	17.29±2.14	3.797	0.001
Mean blood flow	12.87±3.11	13.61±2.57	1.505	0.134
Mean blood flow velocity	6.70±1.27	6.44±0.87	1.348	0.179
Treatment mode			9.674	0.002
Monotherapy	70	31		
Combined therapy	103	16		

Table 5. Multivariate logistic regression analysis of factors associated with treatment outcomes

	B	S.E,	Wals	df	Sig.	Exp (B)	95% C.I. for EXP(B)	
							Lower limit	Upper limit
Treatment mode	0.869	0.393	4.883	1	0.027	2.384	1.103	5.150
Cerebral edema volume	0.147	0.056	6.874	1	0.009	1.159	1.038	1.294
NIHSS	0.225	0.092	5.944	1	0.015	1.252	1.045	1.500

Note: NIHSS, National Institutes of Health Stroke Scale.

BBB, inflammation, and cerebral hemodynamics require validation through targeted biomarker studies and more sophisticated perfusion imaging.

Conclusion

The nimodipine-mannitol regimen represents a more effective therapeutic strategy than nimodipine monotherapy for ICH-induced cerebral edema, improving both clinical outcomes and underlying cerebral perfusion. Its role as an independent predictor of treatment success further underscores its potential clinical utility.

Disclosure of conflict of interest

None.

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