Application Research of Combined Therapy with Edaravone and Nimodipine in Endovascular Treatment for Aneurysmal Subarachnoid Hemorrhage

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To figure out the clinical value of edaravone in conjunction with nimodipine in treating aneurysmal subarachnoid hemorrhage. A total of 110 postoperative patients with aneurysmal subarachnoid hemorrhage, who received treatment at our center between May 2019 and May 2023, were categorized into an observation group (administered edaravone combined with nimodipine) and a control group (given nimodipine as a routine) based on different treatment methods. The efficacy status was the main outcome of this study, and safety was evaluated based on monitoring and recording of adverse events. Serum S-100 beta protein levels, clinical indicators of endothelin-1, middle cerebral artery blood flow velocity, as well as tumor necrosis factor-alpha, interleukin-6, and C-reactive protein levels were used as secondary outcomes. No significant difference was observed in the baseline characteristics of the two patient groups ($p>0.05$), and the occurrence of adverse events showed no significant variation between the two groups. The clinical indicators and inflammatory cytokine levels in both patient groups demonstrated substantial improvement when compared to their initial admission conditions, and the improvement was more notable in the observation group ($p<0.05$). In conclusion, the utilization of edaravone in combination with nimodipine as a treatment approach for patients following aneurysmal subarachnoid hemorrhage intervention surgery yields superior efficacy without an associated rise in adverse events. This treatment strategy possesses substantial clinical value and should be advocated for broader implementation.

Key words: Edaravone, nimodipine, subarachnoid hemorrhage, aneurysm, stroke

Subarachnoid Hemorrhage (SAH) caused by intracranial aneurysms is a highly fatal condition, accounting for 5 % of all strokes[1]. The global incidence has decreased due to smoking cessation, blood pressure control, and increased surgical rates. However, the reactive oxygen species and oxidative stress resulting from the lysis of subarachnoid blood after SAH contribute to cerebral vasospasm[2,3]. The release of oxygenated hemoglobin from the subarachnoid blood clot is believed to be a key factor triggering the generation of free radicals, such as lipid peroxides[4,5]. Existing studies indicate that the elimination of free radicals from the subarachnoid space holds promise for improving cerebral vasospasm and the prognosis of individuals with SAH[6,7]. Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one), known for its potent free radical-scavenging properties, is used in clinical practice to improve functional outcomes in patients with acute ischemic stroke. Furthermore, it has been recognized as a potential intervention for preventing and managing complications after aneurysmal SAH[8]. The purpose of the research is to evaluate the effectiveness and safety of the combined treatment strategy employing edaravone and nimodipine. By examining the clinical value of this combination in the intervention therapy for aneurysmal SAH, it seeks to provide novel insights for clinical management. This research included 110 individuals who underwent endovascular treatment for aneurysmal SAH (aSAH) at our center from May 2019 to May 2023. Its objective was to examine the effectiveness and safety of the combined treatment approach utilizing edaravone and nimodipine. The patients were

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categorized into the observation group (received edaravone combined with nimodipine) and the control group (received nimodipine alone) based on the different treatment approaches. All individuals provided written informed consent prior to participation in this study, which received approval from the review committee of our institution. The study was conducted in full compliance with the principles outlined in the Helsinki declaration. Inclusion criteria patients aged 18 y or older, of any gender; all patients confirmed to have aneurysms based on head Computed Tomography (CT) and Digital Subtraction Angiography (DSA), and underwent endovascular intervention or clipping and embolization therapy, patients and their families had a clear understanding of the study protocol and signed informed consent. Exclusion criteria individuals with SAH caused by other etiologies; patients with a history of previous stroke; patients with mental illness or any conditions that prevent them from following the study protocol and patients who are pregnant, have renal or hepatic insufficiency, or have thrombocytopenia. Both groups of patients received supportive care, including nutritional support, oxygen therapy, hemostasis, and sedation. The observation group received edaravone in conjunction with nimodipine, with nimodipine administered intravenously by infusion pump while maintaining arterial blood pressure above 80 mmHg. Edaravone was given intravenously, with a twice-daily dosage of 30 mg. The control group received nimodipine alone, administered in the same manner as the observation group. Complete resolution of symptoms and signs after treatment, absence of new infarctions on cranial CT scan, and ability to perform activities of daily living classified as excellent response; significant improvement in symptoms and signs after treatment, no new infarctions, ability to perform basic activities of daily living with mild extrapyramidal symptoms classified as effective response; and no significant improvement or worsening of symptoms and signs, presence of new infarctions on cranial CT scan classified as ineffective response. Before and after treatment, levels of Endothelin-1 (ET-1) and serum S-100β protein were measured using Enzyme-Linked Immunosorbent Assay (ELISA), while Transcranial Doppler (TCD) was utilized to assess Middle Cerebral Artery (MCA) blood flow velocity. The levels of Interleukin-6 (IL-6), C-Reactive Protein (CRP), and Tumor Necrosis Factor-Alpha (TNF-α) were measured using ELISA prior to and following the treatment. Safety evaluation was conducted based on monitoring and recording adverse events including the common terminology criteria for adverse events were utilized as the basis for grading and establishing criteria for adverse events. Data analysis was conducted using Statistical Package for the Social Sciences (SPSS) 22.0, a statistical software package. Count data were reported as number and percentage (n %), with the Chi-square (χ^2) test applied. Measurement data were presented as mean±standard deviation. For data that followed a normal distribution, the independent samples t-test was employed, while the Mann-Whitney U test was used for non-normally distributed data. Statistical significance was set at $p<0.05$. The two groups demonstrated comparable baseline characteristics, with no significant differences observed ($p<0.05$) as shown in Table 1. Upon completion of the treatment, the observation group displayed a significantly higher overall response rate of 92.73 %, surpassing the control group's rate of 78.18 % ($p<0.05$) as shown in Table 2. Prior to the commencement of treatment, no significant differences were noted in serum S-100β, MCA blood flow velocity, and ET-1 levels between the two groups. Following the intervention, significant improvements were observed in various clinical indicators for both groups. However, the group receiving edaravone combined with nimodipine showed a more pronounced improvement compared to the group receiving nimodipine alone as shown in Table 3. Before initiating the treatment, no notable differences in IL-6, CRP, and TNF-α level were observed between the two groups. Subsequent to the intervention, significant improvements were observed in various clinical indicators for both groups. However, the group receiving edaravone combined with nimodipine showed a more substantial improvement compared to the group receiving nimodipine alone as shown in Table 4. The occurrence of adverse events did not differ significantly between the two groups ($p>0.05$) as shown in Table 5. Complications resulting from cerebral vasospasm are the most significant factors determining the prognosis of patients with aSAH[9]. Oxygenated hemoglobin released from subarachnoid blood clots is considered a key substance[10]. Free radicals produced by peroxides activate intracellular signaling pathways, leading to sustained contraction of arterial smooth muscle cells. Therefore, clearing free radicals from the subarachnoid space can improve the

prognosis of individuals with aneurysmal SAH[11,12]. Our study findings highlight the significant therapeutic effects of combining edaravone and nimodipine in patients undergoing endovascular treatment for aSAH. Firstly, the effectiveness and safety of the treatment were evaluated using response rates and adverse reactions as assessment criteria. The results showed a significantly higher response rate with the combination therapy, without an increased incidence of adverse reactions. Nimodipine acts as a calcium channel blocker and easily crosses the blood-brain barrier to inhibit the entry of calcium, thereby inhibiting the contraction of vascular smooth muscle and increasing cerebral blood volume. However, monotherapy with nimodipine has its limitations and increasing the dosage can lead to significant hypotension. Therefore, when edaravone, a free radical scavenger, is combined, its ability to remove reactive oxygen species and lipid peroxides effectively improves symptoms of cerebral vasospasm and significantly enhances the therapeutic effect. The study by Zhang *et al.*[13] also reported similar findings regarding the efficacy of this combination therapy. On the other hand, clinical indicators and levels of inflammatory factors reflect the direct and quantitative assessment of the treatment process. This study shows significant changes in serum S-100β, MCA blood flow velocity, and ET-1 levels in both groups compared to baseline, with the observation group showing more significant changes than the control group. This indicates that the combination therapy of edaravone and nimodipine brings more significant improvements in these indicators. ET-1, mainly secreted by vascular endothelial cells, has a potent vasoconstrictive effect and its overproduction during brain injury exacerbates ischemia[14]. Serum S-100β protein is released in large quantities and abnormally expressed in intracranial injuries, which accelerates apoptosis of brain cells and serves as an important marker of detection[6]. These clinical indicators are essential markers for assessing relevant losses. The treatment with edaravone combined with nimodipine can significantly lower these indicator levels, which is highly favorable for the prognosis of patients. IL-6, CRP, and TNF-α levels are classical parameters for assessing inflammatory responses, reflecting the level of inflammatory reaction. Excessive inflammatory response in SAH exacerbates brain edema and damage, and timely control of inflammation greatly benefits the patient's prognosis. The significant decline in indicators in the observation group indicates better control of inflammation through combination therapy, highlighting its significant therapeutic value. The research by Liu *et al.*[15] also demonstrated the exact clinical efficacy of edaravone combined with nimodipine treatment, showing a significant reduction in intracranial pressure and levels of serum IL-6, TNF-α, and S-100β protein, improvement in level of consciousness, and enhancement of brain microcirculation and prognosis in patients. In summary, for patients after endovascular treatment for aSAH, the combination therapy of edaravone and nimodipine provides better effectiveness without increasing adverse events. It has significant clinical value and deserves to be widely applied.

TABLE 1: BASELINE CHARACTERISTICS

Group	n	Age	Gender		BMI (kg/m²)	Fisher		Hunt-Hess		
			Male	Female		1-2	3-4	1-2	3	4
Observation	55	59.3±14.2	39	16	23.06±2.80	9	46	25	18	12
Control	55	55.5±11.6	35	20	22.83±2.73	6	49	23	22	10
t/χ^2		t=1.47	χ^2=0.18		t=1.21	χ^2=0.62		χ^2=0.62		
p		0.123	0.671		0.227	0.432		0.431		

TABLE 2: TREATMENT EFFECTIVENESS (n %)

Group (n=55)	Treatment effective rate			
	Significant	Improvement	Ineffective	Overall (%)
Observation	43 (78.18)	8 (14.55)	4 (7.27)	92.73
Control	31 (56.36)	12 (21.82)	12 (21.82)	78.18
χ^2		-		5.946
P		-		0.025

TABLE 3: CHANGES IN CLINICAL INDICATORS BEFORE AND AFTER TREATMENT (x̄±s, point)

Group (n=55)	S-100ß (μg/l)		MCA blood flow velocity (cm/s)		ET-1 (pg/ml)	
	Before	After	Before	After	Before	After
Observation	0.28±0.09	0.14±0.06*	103.96±25.31	78.84±18.26*	88.03±12.30	70.23±8.46*
Control	0.25±0.06	0.20±0.04*	104.24±25.29	90.41±20.93*	88.16±12.27	74.84±8.27*
t	1.72	5.262	0.86	2.63	0.07	2.46
p	0.109	0.000	0.753	0.010	0.941	0.016

Note: (*) indicates significant difference after treatment compared with before treatment

TABLE 4: CHANGES IN INFLAMMATORY CYTOKINE LEVELS PRIOR TO AND FOLLOWING TREATMENT (x̄±s, point)

Group (n=55)	IL-6 (ng/l)		CRP (mg/l)		TNF-α (ng/l)	
	Before	After	Before	After	Before	After
Observation	12.67±3.35	8.10±2.26*	51.71±5.70	24.40±5.07*	46.62±8.00	33.89±6.31*
Control	12.47±3.53	9.53±2.48*	52.75±5.56	40.45±5.86*	46.75±7.36	40.68±8.78*
t	0.18	3.39	0.46	15.02	0.24	3.22
p	0.854	0.001	0.842	0.000	0.812	0.002

Note: (*) indicates significant difference after treatment compared with before treatment

TABLE 5: ADVERSE EVENTS

Group	n	Adverse events (n, %)					
		Fever	Hypotension	Nausea and vomiting	Rash	Rebleeding	Number of adverse reactions
Observation	55	1 (1.82 %)	1 (1.82 %)	2 (3.64 %)	1 (1.82 %)	1 (1.82 %)	5 (9.09 %)
Control	55	3 (5.45 %)	1 (1.82 %)	0 (0 %)	1 (1.82 %)	3 (5.45 %)	7 (12.73 %)
χ^2		1.04	0	2.04	0	1.04	0.374
p		0.618	1	0.495	1	0.618	0.761

Conflict of interests:

The authors declared no conflict of interests.

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