

# Clinical efficacy of mouse nerve growth factor plus nimodipine in neonatal intracranial hemorrhage and its effect on plasma PAF, CNP, MMP-2, and neurological function

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**Abstract.** – **OBJECTIVE:** To investigate the clinical efficacy of combination of mouse nerve growth factor (NGF) and nimodipine in the treatment of neonatal intracranial hemorrhage (NICH) and its effect on plasma platelet-activating factor (PAF), C-type natriuretic peptide (CNP), matrix metalloproteinase-2 (MMP-2), and neurological function.

**PATIENTS AND METHODS:** A total of 90 infants with severe ICH admitted to our hospital from December 2016 to December 2018 were enrolled for retrospective study. According to different treatment schemes, they were assigned into 2 groups: group A (n=40) treated with mouse NGF plus nimodipine; group B (n=50) treated with nimodipine. The recovery time, serum indexes (PAF, MMP-2, CNP), neurological function (neonatal behavioral neurological assessment (NBNA) score), complications, and total effective rate of patients were recorded, and the satisfaction degree of family members was statistically analyzed.

**RESULTS:** Patients in group A showed shorter recovery time, down-regulated PAF and MMP-2, evidently up-regulated CNP, and significantly increased NBNA score after one/two weeks of treatment, as well as fewer complications, higher total effective rate and higher satisfaction of family members.

**CONCLUSIONS:** To sum up, the combination of mouse NGF and nimodipine achieves good clinical efficacy in NICH, which down-regulates plasma PAF and MMP-2, up-regulates CNP, and improves neurological function. Therefore, it is suitable for clinical promotion.

*Key Words:*

Mouse nerve growth factor, Nimodipine, Neonatal intracranial hemorrhage, PAF, CNP, MMP-2, NBNA score.

## Introduction

Neonatal intracranial hemorrhage (NICH), a rare clinical disease detrimental to central nervous system<sup>1-3</sup>, is the leading cause of neonatal morbidity and mortality, with a mortality rate of approximately 50% to 70%<sup>4,5</sup>. NICH mainly refers to subdural hemorrhage (SDH), subarachnoid hemorrhage (SAH), intraparenchymal hemorrhage (IPH) and intraventricular hemorrhage (IVH) in full-term newborns, which have the clinical features of apnea, bradycardia, and epileptic seizures<sup>6,7</sup>. The options for treating NICH are numerous and varied. In this study, we introduce one of them, that is, mouse nerve growth factor (NGF) combined with nimodipine therapy.

NGF is one of the most important growth factors in the nervous system and plays a vital role in inflammatory hyperalgesia<sup>8</sup>. Mouse NGF, homologous to human NGF, is widely used in the treatment of tumours and diseases of central nervous system and peripheral system, especially in the repair of peripheral nerve injury and craniocerebral injury. It could also improve the motor and cognitive functions of newborns<sup>9-12</sup>. Nimodipine is often adopted in brain diseases because it is beneficial to increasing cerebral blood flow<sup>13-15</sup>. However, there are few related reports on the effect of the combination of mouse NGF and nimodipine on NICH. Therefore, this study is designed to explore this effect via indicators of clinical efficacy, plasma PAF, CNP, MMP-2, and neurological function.

## Patients and Methods

### General Data

A total of 90 newborns with severe ICH treated in our hospital from January 2015 to July 2019 were enrolled for this retrospective study. According to different treatment schemes, they were allocated into group A (n=40) and group B (n=50). Inclusion criteria: newborns with a gestational age of more than 37 weeks, as well as those who were treated for the first time; their family members were informed of this study and signed the consent form. Exclusion criteria: newborns with intrauterine infection, sepsis, congenital malformation, congenital endocrine and metabolic abnormalities, central nervous system diseases, or drug allergy. The investigation was approved by Hospital Ethics Committee.

### Treatment Methods

**Group A:** Received mouse NGF combined with nimodipine therapy. Newborns were given basic comprehensive treatment, including oxygen inhalation, blood glucose monitoring, rehydration, anticonvulsant, intracranial hypotension, and correction of electrolyte or acidolysis balance. Meanwhile, vital signs such as heart rate and blood pressure were monitored. In addition, mouse NGF was injected (Xiamen Sinobioway Biomedicine Co., Ltd., SFDA Approval No. S20060052, 18 µg/piece). Treatment: Mouse NGF was dissolved with 2 mL sodium chloride injection or sterile water and intramuscularly injected (18 µg daily, once a day). Simultaneously, nimodipine tablets (Mudanjiang Lingtai Pharmaceutical Co., Ltd., SFDA Approval No. H23022380) were orally taken at a dose of 0.5-1.0 mg/(kg.time), once every 8 hours and 20 days as a course.

**Group B:** Nimodipine therapy. Newborns were given basic comprehensive treatment, including oxygen inhalation, blood glucose monitoring, rehydration, anticonvulsant, intracranial hypotension, and correction of electrolyte or acidolysis balance. Nimodipine tablets (Lingtai Pharmaceutical Co., Ltd., Mudanjiang, Heilongjiang, China; National Pharmaceutical Standards: H23022380) were given orally, at a dose of 0.5-1.0 mg / (kg • time), once every 8 h for 20 days. Meanwhile, vital signs such as heart rate and blood pressure were monitored.

## Analysis Indicators

### Recovery Time

The recovery time of muscle tension, convulsion, consciousness and reflex were compared between the two groups.

### Serum Indexes

Five mL of blood was taken at 8:00 a.m. before treatment and one week and two weeks after treatment. After standing for 2 hours, the blood was centrifuged (1500 × g) at 4°C for 10 min. The upper serum was collected and stored at -80°C. Platelet-activating factor (PAF), matrix metalloproteinase -2 (MMP-2) levels were quantified with enzyme-linked immunosorbent assay (ELISA). MMP-2 ELISA kit was purchased from Quanzhou Ruixin Biotechnology Co., Ltd., and PAF ELISA kit was from Shanghai Gelatins Bio-engineering Co., Ltd. C-type natriuretic polypeptide (CNP) was measured by radioimmunoassay (RIA), and the CNP RIA kit was purchased from Shanghai HZ Industrial Co., Ltd.

### Neurological Function

The nervous system was scored with neonatal behavioral neurological assessment (NBNA)<sup>16</sup>, mainly including general reaction, passive muscle tension, active muscle tension, primitive reflexion and behavioral competence. A score greater than 37 indicated injured nerves, and a score less than 37 indicated normal nerves.

### Complications

The occurrence of intracranial hypertension, apnea, convulsion and hydrocephalus in the two groups was statistically analyzed.

### Total Effective Rate

The effective rate was statistically analyzed. The standard is as follows: Markedly effective: After 5 days of treatment, neonates showed normal consciousness, muscle tension and respiration, restored Moro and grasp reflex, no vomiting after breast feeding, as well as those whose ischemic symptoms basically disappeared by CT reexamination one month after birth. Effective: After 5 days of treatment, neonates showed normal consciousness, partially recovered muscle tension, relieved respiration, and restored Moro and grasp reflex under the guidance, as well as slightly widened anterior median fissure by CT reexamination one month after birth. Ineffective: Neonates showed no improvement in the above

symptoms or those who gave up treatment or died. Total effective rate = markedly effective rate + effective rate.

**Family Satisfaction**

The self-made treatment satisfaction questionnaire was used to test and compare the satisfaction of the family members between the two groups, and the test items and evaluation criteria were self-made. The questionnaire had been validated. The families of children in the two groups were aware of the treatment process. With a total score of 100 points, 100-90 points indicated satisfactory, 70-90 points indicated basically satisfactory, and less than 70 points indicated unsatisfactory.

**Statistical Analysis**

SPSS 19.0 (Asia Analytics Formerly SPSS China) was used for statistical analysis of integrated data. The counting data such as total effective rate, complication rate, satisfaction degree, part of general data, were analyzed with  $\chi^2$ -test. The measurement data including recovery time, serum indexes and neurological function were expressed as mean±standard deviation ( $\bar{x} \pm SD$ ) and analyzed by *t*-test. Values of  $p < 0.05$  were considered statistically significant.

**Results**

**General Data**

There was no significant difference between the two groups in general data of sex, gestational age, body weight, delivery, and CT results ( $p > 0.05$ ; Table I).

**Recovery Time**

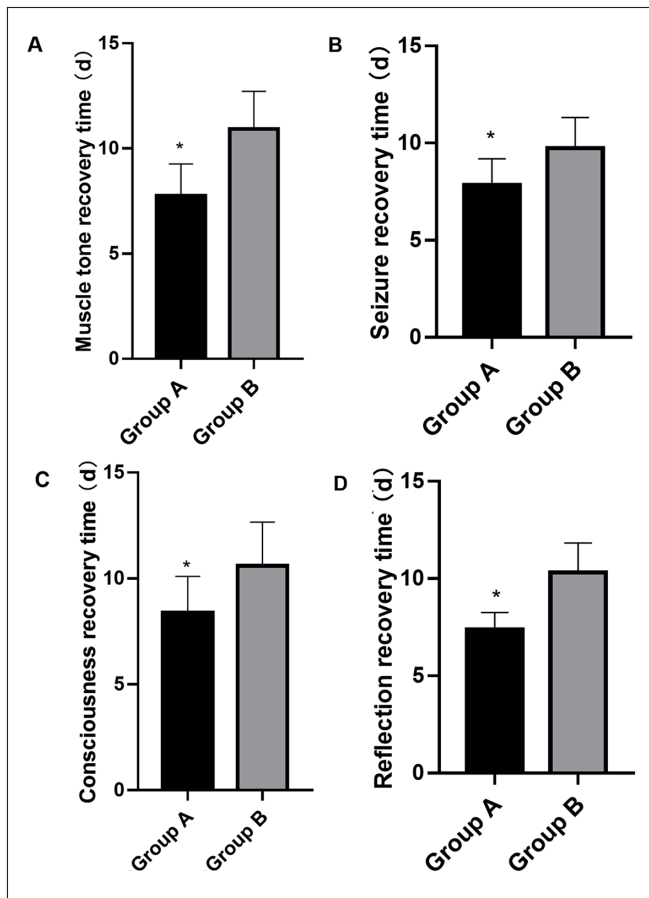
The recovery time of muscle tension, convulsion, consciousness, and reflex in group A was (7.76±1.51) d, (7.83±1.36) d, (8.38±1.72) d, and (7.37±0.88), respectively, and that in group B was (10.93±1.79) d, (9.74±1.58) d, (10.59±2.07) d, and (10.32±1.51) d. The recovery time in group A was significantly shorter than that in group B ( $p < 0.05$ ; Figure 1).

**Serum Indexes**

In group A, the levels of PAF before treatment and 1 week and 2 weeks after treatment were (11.58±2.76) µg/L, (7.79±0.93) µg/L and (4.78±0.67) µg/L, respectively. In group B, the levels were (11.62±2.65) µg/L, (9.13±1.85) µg/L, and (6.91±0.95) µg/L, respectively. In group A, the levels of MMP-2 before treatment and 1 week and 2 weeks after treatment were (297.82±26.74) µg/L, (131.11±14.13) µg/L, and (72.67±9.54) µg/L, respectively. In group B, the levels were (294.54±30.98) µg/L, (165.76±19.18) µg/L, and (102.75±13.21) µg/L, respectively. The CNP level in group A before treatment was (23.85±3.58) µg/L, and the levels 1 week and 2 weeks after treatment were (35.32±6.67) µg/L and (47.67±5.87) µg/L respectively. The levels in group B were (22.95±4.33) µg/L, (31.53±4.01) µg/L, and (40.28±6.11) µg/L respectively. PAF and MMP-2 in the two groups decreased and CNP increased 1 week and 2 weeks after treatment. PAF and MMP-2 in group A were significantly lower than those in group B, while CNP in group A was significantly higher than that in group B ( $p < 0.05$ ; Figure 2).

**Table I.** General data.

Group	Group A (n = 40)	Group B (n = 50)	t/ $\chi^2$	p
Sex			0.02	0.887
Male	17 (42.50)	22 (44.00)		
Female	23 (57.50)	28 (56.00)		
Gestational age (weeks)	34.92 ± 4.13	35.13 ± 3.87	0.25	0.805
Average body weight (Kg)	3.04 ± 0.85	3.17 ± 0.81	0.74	0.461
Delivery			0.01	0.993
Vaginal delivery	18 (45.00)	22 (44.00)		
Cesarean section	12 (30.00)	15 (30.00)		
Precipitate labour	10 (25.00)	13 (26.00)		
CT results			2.13	0.547
Subarachnoid hemorrhage	23 (57.50)	26 (52.00)		
Subdural hemorrhage	7 (17.50)	11 (22.00)		
Intraparenchymal hemorrhage	6 (15.00)	11 (22.00)		
Intraventricular hemorrhage	4 (10.00)	2 (2.50)		

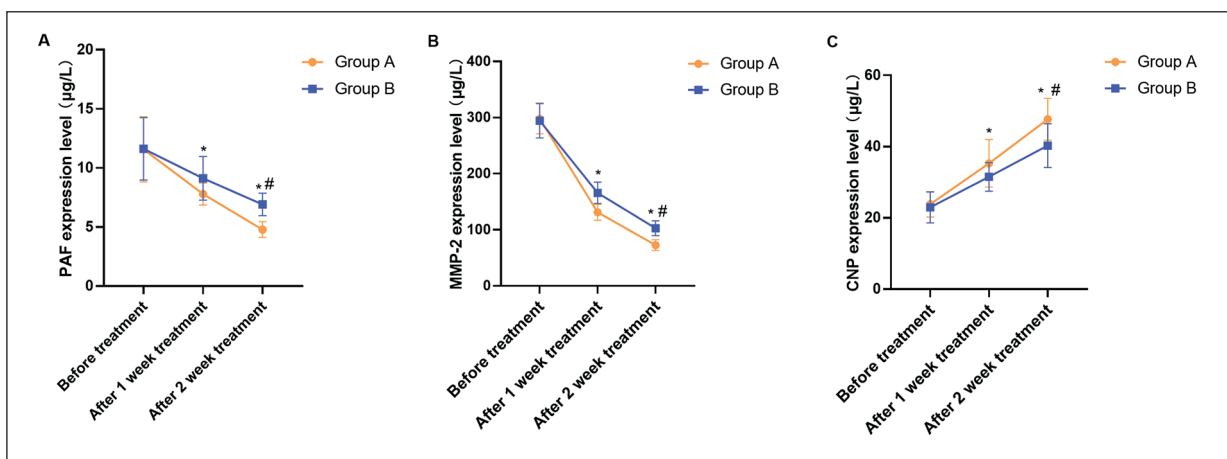


**Figure 1.** Recovery time. **A**, The recovery time of muscle tension in group A was significantly shorter than that in group B ( $p < 0.05$ ). **B**, The recovery time of convulsion in group A was significantly shorter than that in group B ( $p < 0.05$ ). **C**, The recovery time of consciousness in group A was significantly shorter than that in group B ( $p < 0.05$ ). **D**, The recovery time of reflex in group A was significantly shorter than that in group B ( $p < 0.05$ ). Note: \* $p < 0.05$  vs. group B.

### Neurological Function

The NBNA score in group A was  $(22.02 \pm 3.56)$  before treatment, and was  $(34.74 \pm 3.19)$ ,  $(42.25 \pm 4.32)$  1 week and 2 weeks after treatment,

respectively. Meanwhile, the scores in group B were  $(21.88 \pm 3.75)$ ,  $(27.68 \pm 2.78)$ , and  $(36.95 \pm 3.66)$ , respectively. Newborns in both groups got higher NBNA scores one week and two weeks after



**Figure 2.** Serum indexes. **A**, PAF decreased in the two groups 1 week and 2 weeks after treatment, and group A was significantly lower than group B ( $p < 0.05$ ). **B**, MMP-2 decreased in the two groups 1 week and 2 weeks after treatment, and group A was significantly lower than group B ( $p < 0.05$ ). **C**, CNP increased in the two groups 1 week and 2 weeks after treatment, and group A was significantly higher than group B ( $p < 0.05$ ). Note: \* $p < 0.05$  vs. before treatment, # $p < 0.05$  vs. after 1 week of treatment.

**Table II.** NBNA score.

Period of time	Group A (n = 40)	Group B (n = 50)	t	p
Before treatment	22.02 ± 3.56	21.88 ± 3.75	0.18	0.858
Treatment for 1 week	34.74 ± 3.19	27.68 ± 2.78	11.21	< 0.001
Treatment for 2 weeks	42.25 ± 4.32	36.95 ± 3.66	6.30	< 0.001

**Table III.** Incidence of complications (%).

	Group A (n = 40)	Group B (n = 50)	t	p
Intracranial hypertension	1 (2.50)	4 (8.00)	–	–
Apnea	0 (0.00)	2 (4.00)	–	–
Convulsion	3 (7.50)	5 (10.00)	–	–
Hydrocephalus	0 (0.00)	4 (8.00)	–	–
Incidence of complications (%)	4 (10.00)	15 (30.00)	5.34	0.021

treatment, and the score group A was higher than that in group B ( $p < 0.05$ ; Table II).

**Complications**

In group A, intracranial hypertension was found in 1 case (2.50%), convulsion in 3 cases (7.50%), no apnea and hydrocephalus, with an incidence rate of 10.00%. In group B, intracranial hypertension was found in 4 cases (8.00%), apnea in 2 cases (4.00%), convulsion in 5 cases (10.00%), hydrocephalus in 4 cases (8.00%). Therefore, the prevalence of complications in group A was much lower than that in group B ( $p < 0.05$ ; Table III).

**Total Effective Rate**

In group A, there were 31 markedly effective cases (77.50%), 6 effective cases (15.00%), and 3 ineffective cases (7.50%), with a total effective rate of 92.50%. While in group B, the treatment

was markedly effective in 22 cases (44.00%), effective in 16 cases (32.00%), and ineffective in 12 cases (24.00%). Therefore, the total effective rate in group A was much higher than that in group B ( $p < 0.05$ ; Table IV).

**Family Satisfaction**

The satisfaction degree of family members in group A was much higher than that in group B (95.00% vs. 76%) ( $p < 0.05$ ; Table V).

**Discussion**

Mouse NGF and nimodipine are both drugs for brain damage and nerve defect<sup>17-19</sup>. However, the effects of them on NICH, either alone or in combination, are poorly explored, so this study was designed to explore this.

**Table IV.** Total effective rate (%).

	Group A (n = 40)	Group B (n = 50)	t	p
Markedly effective	31 (77.50)	22 (44.00)	–	–
Effective	6 (15.00)	16 (32.00)	–	–
Ineffective	3 (7.50)	12 (24.00)	–	–
Total effective rate	37 (92.50)	38 (76.00)	4.36	0.037

**Table V.** Satisfaction of family members (%).

	Group A (n = 40)	Group B (n = 50)	t	p
Satisfactory	28 (70.00)	22 (44.00)	–	–
basically satisfactory	8 (25.00)	16 (32.00)	–	–
Unsatisfactory	4 (5.00)	12 (24.00)	–	–
Degree of satisfaction	36 (95.00)	38 (76.00)	4.36	0.037



First, we found that the recovery time of muscle tension, convulsion, consciousness and reflex in group A treated with mouse NGF combined with nimodipine was shorter than that in group B treated with nimodipine. Second, we revealed that the NBNA scores of the neurological function in group A were higher than those in group B one week and two weeks after treatment. Mouse NGF, a neurotrophic factor, has been proved to have excellent effects in enhancing neurotransmitter activity and boosting regeneration of damaged nerve fibers<sup>20</sup>. In an animal experiment, it could improve the motor dysfunction of rat limbs caused by peripheral neuropathy. It could also promote the recovery of damaged neurological function and reduce neurodegeneration by inhibiting myelin swelling<sup>21</sup>. A study on the effect of nimodipine on primary microglia in mice demonstrated that nimodipine has a great influence on the inflammation of brain cells and the metabolism of mitochondrial energy, especially on inhibiting neuroinflammation<sup>22,23</sup>. Combining these cases with our findings, we draw a conclusion that both mouse NGF and nimodipine contribute to the improvement of neurological function recovery, and their combination can accelerate the recovery. Moreover, the faster recovery of neurological function leads to better improvement of muscle tension, convulsion, consciousness and reflex recovery.

Analysis on serum indexes showed that 1 and 2 weeks after treatment, PAF and MMP-2 decreased and CNP increased in both groups. PAF and MMP-2 in group A were lower than those in group B, while CNP was higher than that in group B. In the end, we found that the prevalence of complications in group A was lower than that in group B, while the total effective rate and family satisfaction were higher than those in group B. PAF is a bioactive phospholipid that can be released to the injured site in the early stage of inflammatory reaction<sup>24</sup>. MMP-2 and CNP are also important factors in brain inflammation. MMP-2 induces the deterioration of brain inflammation, and the over-expression of CNP plays an anti-inflammatory role<sup>25,26</sup>. Therefore, it is concluded that the anti-inflammatory effect of mouse NGF and nimodipine leads to faster decrease in PAF and MMP-2 and increase in CNP, and alleviated inflammation, which further results in better restore of neurological function, fewer complications, shorter recovery time, as well as higher total effective rate and family satisfaction.

However, there are still several limitations in our study. First, as a retrospective study related to ICH, the levels of inflammatory factors have not been analyzed. Second, the role of relevant molecular pathways in NICH has not been explored in detail. We will address these limitations in future experiments.

## Conclusions

To sum up, the combination of mouse NGF and nimodipine achieves good clinical efficacy in NICH, which down-regulates plasma PAF and MMP-2, up-regulates CNP, and improves neurological function. Therefore, it is suitable for clinical promotion.

## Conflict of Interest

The Authors declare that they have no conflict of interests.

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