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Recombinant erythropoietin protective and related effects on brain injury in premature infants

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Abstract. – OBJECTIVE: The aim of this study was to investigate the protective effect of recombinant erythropoietin at different doses on brain injury in premature infants and the related effects on blood routine, liver function, intellectual development, mental development index (MDI), psychomotor development index (PDI), etc.

PATIENTS AND METHODS: A total of 120 premature infants were divided into four groups, including experimental group A (n=30), experimental group B (n=30), experimental group C (n=30) and control group (n=30). The experimental group was treated with different doses of recombinant erythropoietin for brain injury protection of premature infants, while the control group with conventional methods.

RESULTS: There was no statistical significance in all test indicators of the four groups of patients before the intervention. After the intervention experiment, the S-100B index was $p<0.05$, and the erythropoietin (EPO) index was $p<0.05$. In the comparison of IL-6 indicators, the indicators of the experimental group were reduced after the comparison experiment, and there were significant differences, $p<0.05$. In neonatal behavior evaluation, there was a statistical difference between groups A and B and the control group ($p<0.05$), and no statistical significance was shown between group C and the control group ($p>0.05$). In the intelligence test comparison, the F value of the experimental group was 3.113 three months after treatment. After six months, the F value was 3.654. After nine months, the F value was 3.392 with $p<0.05$. In the comparison of blood routine indicators, the p-values of four indicators between groups were more than 0.05. In the comparison of liver function indexes, the indexes of groups A, B, and C were significantly changed before and after treatment, and the data after treatment were significantly different from those before treatment, $p<0.05$. In the comparison of development, there were no significant differences observed in the p-values of the two indicators of vigorous exercise and language in the experimental group.

CONCLUSIONS: Recombinant erythropoietin has a protective effect on infants with brain injury and can improve the intellectual development of premature infants, but has no significant effect on blood routine indicators. It can effectively improve the MDI, PDI, and related cytokines of premature infants, and has certain significance for the treatment of brain injury.

Key Words:

Inflammatory factors, Intelligence evaluation, Blood routine index, Preterm infant protection, Brain injury treatment.

Introduction

With the improvement and advancement of medical technology and neonatal treatment, the survival rate of premature infants (PI) has improved significantly. However, the incidence of brain injury in PI (BIPI), especially premature brain injury (PBI), is still high, which seriously affects the growth and development of children and leads to complications such as intellectual disability, motor dysfunction, sensory impairment, and brings huge life pressure to children and their families[1-3]. Thus, investigating the pathogenesis, prevention, and treatment of BIPI holds significant clinical importance. At present, the main mechanisms of brain injury in premature infants include hypoxia-ischemia, infection, inflammation, free radicals, and other factors, which can lead to cell growth disorders, apoptosis, autophagy, and other adverse processes, and ultimately lead to brain nerve cell injury or death[4,5].

Recombinant Erythropoietin (rEPO) is a recombinant human erythropoietin that has been approved for clinical treatment in China. It has achieved remarkable clinical efficacy in the treatment of anemia and ischemic disease and has

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been widely used. At the same time, studies[4-6] have shown that rEPO has multiple protective effects, such as reducing nerve cell death, promoting nerve cell repair and regeneration, anti-oxidation, anti-inflammatory, etc., and also, they have shown good clinical application prospects in cerebral ischemic diseases, brain injury, and neurodegenerative diseases.

Although the protective effect of recombinant erythropoietin in BIPI has received extensive attention from researchers around the world, it still faces some problems and challenges in the actual clinical application process, such as the specification of the scope of application, the optimization of dose and course of treatment, the control of drug and the treatment evaluation effect[7-9].

In addition, this study provides a useful reference for clinical practice through the multi-dimensional study of rEPO on PI brain injury. Although there are limitations in studying the protective impact of rEPO on BIPI, a better understanding of its mechanism is gradually emerging. Further research into its effective usage, dosage, and treatment duration is showing promise for developing effective and safer treatment strategies for BIPI. These recommendations could improve patient outcomes and quality of life while providing essential data for clinical practice. Therefore, this study analyzed the protective effect and related influencing factors of recombinant erythropoietin on brain injury in premature infants under different doses through experiments, control, clinical observation, and other methods to provide a new theoretical basis and practical guidance for BIPI prevention and treatment.

Patients and Methods

General Information

In this study, 120 premature infants admitted to the intensive care unit of a general hospital from February 2021 to March 2022 were selected, including group A 30 cases, group B 30 cases, group C 30 cases, and control group 30 cases. PI in the experimental group were treated with recombinant erythropoietin, while the control group with routine nursing. Inclusion criteria: (1) diagnosed as premature infants, and the gestational age (GA) was less than 32 weeks and greater than 28 weeks; (2) premature infants need to be hospitalized in an intensive care unit after birth; (3) infants who visited the hospital aged 24 hours at most; (4) premature infants and their families agreed the study; (5) birth weight less than 2,500 g. Exclusion criteria: (1) premature infants with other serious reproductive system diseases and serious infections; (2) children with severe congenital heart disease and genetic metabolic disease; (3) premature infants with severe cardiac, hepatic, and renal dysfunction; (4) the legal guardian of the minor patient did not provide sufficient informed consent. After the inclusion criteria screening, PI 120 cases were divided into four groups, with 30 cases in each group. The dose, route, and treatment time of recombinant erythropoietin follows the standards of clinical guidelines and relevant regulations in China. During the experiment, the ethical principles were followed, and the interests and rights of the tested children were guaranteed. Before the study commences, the parents of the children will receive a detailed explanation about the purpose, methods, potential effects, and possible side effects of the study. This will enable the parents to make an informed decision and give their consent. In the research process, the operating procedures of medical institutions were strictly observed to ensure the safety of patients on the premise of ensuring the treatment effect.

Research Methods

The research and treatment steps of the experimental group were as follows. The study subjects were premature infants (28 weeks to 32 weeks gestational age), with clear diagnosis and meeting the inclusion criteria. PI in the experimental group were given different doses of recombinant erythropoietin immediately after admission. The dosage of group A was 1,000 u/kg for 3 consecutive days; group B was treated with 750 u/kg for 3 consecutive days; the dosage of group C was 500 U/kg for 3 consecutive days. During the treatment, the vital signs, blood routine, erythrocyte sedimentation rate, blood biochemistry, coagulation function, etc. of premature infants were monitored regularly to observe whether other related complications occurred, and the corresponding life nursing was provided for premature infants to ensure that they passed the treatment period smoothly. The preterm infants in the experimental group underwent head magnetic resonance imaging (MRI) or ultrasound and other related examinations at the time of discharge to evaluate the integrity of the head structure and nerve injury.

At 3, 6, and 9 months after birth, the neurodevelopmental status of the study subjects was evaluated, including behavioral observation, gross motor, fine motor, cognitive ability, etc.

The study treatment steps of the control group were as follows. The study subjects were premature infants (28 weeks to 32 weeks gestational age), with a clear diagnosis and meeting the basic inclusion criteria. The control group of premature infants did not use recombinant erythropoietin and received routine nursing. During the treatment, the erythrocyte sedimentation rate, etc. of premature infants was also monitored regularly to observe whether other related complications occurred and provide corresponding life nursing for premature infants. The preterm infants in the control group underwent head MRI or ultrasound and other related examinations at discharge to evaluate the integrity of the head structure and nerve injury. At 3, 6, and 9 months after birth, the same method evaluated the neurodevelopmental status of the study subjects, including behavioral observation, gross motor, fine motor, cognitive ability, etc. All children received detailed history collection, physical examination, biochemistry, blood routine, imaging examination, and other related examinations. The experimental group was treated with recombinant erythropoietin, while the other received routine nursing. The neurodevelopmental status of premature infants after admission was taken as the main observation index for data collection, and the score was scored after 7 days of treatment, and the score value was recorded and analyzed. The medical equipment of this study mainly includes recombinant erythropoietin for injection, a blood cell analyzer, a blood oxygen saturation monitor, an electrocardiogram (ECG) monitor, an intracranial pressure monitor, electroencephalograph, magnetic resonance MRI equipment, etc. The sources of medical equipment were strictly verified, and functional tests were carried out before the study to ensure the accuracy of the equipment.

Table I shows the self-built assessment of brain injury symptoms in premature infants based on the internationally recognized neonatal neurological assessment tool. The symptoms of brain injury include dystonia, developmental delay, behavioral problems, and epilepsy. The signs of brain injury can be scored according to a scale of 1-10. 1-3 points are mild brain injury, 4-6 points are moderate brain damage, 7-9 points are severe brain injury, and 10 points are extreme brain injury.

Efficacy Evaluation Criteria

The experimental group was divided into an experimental group and a control group. The experimental group and the control group were followed up in the first quarter, half a year, and three quarters after treatment, respectively. The evaluation indexes of the therapeutic effect mainly include the evaluation index of intellectual development and liver function to evaluate the degree of brain injury. The evaluation included imaging examinations before treatment, one quarter, six months, and three quarters after treatment. Secondly, neurodevelopment assessment of patients before and after treatment was performed using professional assessment scales such as MDI and PDI. Meanwhile, relevant indicators such as daily activity ability and language ability of patients were recorded to calculate the neurodevelopment assessment index. Based on the above evaluation criteria, this study evaluated the protective effect of recombinant erythropoietin on brain injury in premature infants, providing a reference for subsequent clinical and scientific research work.

Table I. Signs and symptoms of BIPI.

Symptoms of brain injury	Detailed description	
Dystonia	Hypertonia or hypotonia, muscle weakness, etc.	
Developmental delay	Height, weight growth is slow, development lag	
Behavior problem	Hyperactivity, emotional installation, etc.	
Epilepsy	Seizures and related symptoms occur	
Signs of brain injury	**Score**	**Physical sign description**
1	1-3	Mild brain damage
2	4-6	Moderate brain damage
3	7-9	Severe brain damage
4	10	Extreme brain damage

Brain injury in premature infants (BIPI).

Table II. Comparison of patients' physical data.

Item	Number of cases	Male	Female	Gestational age	Body weight
Group A	25	13	12	31.03 ± 1.20	1,730.60 ±1 05.06
Group B	25	11	14	30.67 ± 1.00	1,745.09 ± 97.43
Group C	25	12	13	31.10 ± 1.07	1,684.57 ± 139.46
Control group	25	15	10	30.57 ± 1.16	1,744.33 ± 60.24
p	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

All $p > 0.05$, including 75 in the experimental group and 25 in the control group, show no statistical difference in general information.

Statistical Analysis

SPSS 25.0 statistical analysis software was used for analysis (IBM Corp., Armonk, NY, USA). Among them, when the distribution interval suitable for measurement data conforms to the normal distribution, the data are expressed in mean ± standard deviation through *t*-test. When the distribution interval of measurement data does not conform to a normal distribution, the data set and discrete state are expressed by a quartile generalized estimation equation. For intra-group and inter-group comparisons, *t*-test and one-way ANOVA were respectively chosen. The statistical significance of the data is determined by the test criteria, $p<0.05$ indicates statistical significance, while $p<0.01$ indicates high statistical significance.

Results

General Information Comparison

120 PI with brain injury were selected according to the inclusion criteria, including experimental group A (n=30), experimental group B (n=30), experimental group C (n=30), and control group (n=30). 104 patients successfully completed the late follow-up, 8 lost follow-up, and 3 launched the experiment during the experiment. Finally, it was determined that there was group A (n=25), experimental group B (n=25), experimental group C (n=25), and control group (n=25). The physiological data of patients before treatment are shown in Table II.

Cell Correlation Analysis of Patients After Treatment

The scores of relevant cell mediators of patients were compared. S-100B was brain calcium protein and EPO was erythropoietin. The specific results are shown in Table III. Table III shows the indexes comparison between different experimental groups and the control group. The *p*-value of the S-100B index in groups A, B, and C after treatment is lower than 0.05, and the *p*-value of the EPO index after treatment is lower than 0.05.

Interleukins Comparison

Interleukin indexes of group A and group B were compared before and after treatment (Figure 1).

Table III. Comparison of cell-related mediators.

Item	Number of cases	S-100B (ng/l)		EPO (iu/l)	
		Before treatment	After treatment	Before treatment	After treatment
Group A	25	247.18 ± 73.14	208.62 ± 69.16	4.21 ± 1.25	9.05 ± 2.15
Group B	25	245.32 ± 72.05	218.22 ± 68.91	3.73 ± 2.11	8.37 ± 2.50
Group C	25	248.52 ± 71.50	239.90 ± 53.63	3.67 ± 2.27	5.43 ± 2.25
Control group	25	246.62 ± 76.56	254.92 ± 66.19	3.85 ± 2.18	3.51 ± 2.23
F	/	0.114	4.524	0.062	48.301
p	/	> 0.05	< 0.05	> 0.05	< 0.05

All $p > 0.05$, including 75 in the experimental group and 25 in the control group, show no statistical difference in general information.

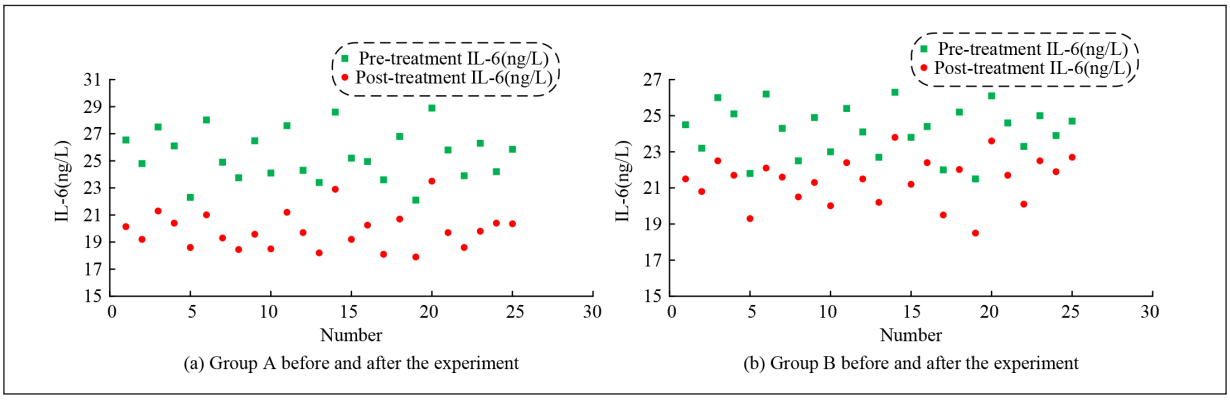

Figure 1. Comparison of interleukin index.

In the comparison of IL-6 indicators in Figure 1, the indicators of groups A and B were reduced after the comparative experiment, and there were significant differences ($p<0.05$).

Comparison of Intelligence Test of Patients After Treatment

The intelligence tests of children in different experimental groups and control groups were compared, and the mental development index (MDI) was selected for the comparison scale (Table IV).

Table IV shows the significant comparison of post-treatment MDI. F value was 3.113, $p<0.05$, after 3 months, the F was 3.654 ($p<0.05$), and after 9 months, the F was 3.792, ($p<0.05$).

Comparison of Psychomotor Development Index of Patients After Treatment

The psychomotor development index (PDI) was selected according to the psychomotor test of children in different experimental groups and control groups (Table V).

Table IV. MDI comparison after treatment.

Item	Number of cases	Half months MDI	1 months MDI	3 months MDI	6 months MDI	9 months MDI
Group A	25	84.01 ± 5.32	84.24 ± 4.31	85.67 ± 5.68	87.34 ± 4.85	89.34 ± 4.43
Group B	25	83.21 ± 3.56	83.44 ± 2.87	84.53 ± 3.90	86.48 ± 3.54	89.83 ± 3.69
Group C	25	81.22 ± 3.25	82.37 ± 3.47	82.86 ± 3.69	84.94 ± 3.53	88.50 ± 3.34
Control group	25	79.03 ± 3.87	79.98 ± 3.28	80.19 ± 3.94	83.37 ± 3.70	86.84 ± 3.46
F	/	2.975	3.021	3.113	3.654	3.792
p	/	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

Mental development index (MDI).

Table V. PDI comparison after treatment.

Item	Number of cases	Half months MDI	1 months MDI	3 months PDI	6 months PDI	9 months PDI
Group A	25	84.77 ± 3.28	85.33 ± 3.29	87.92 ± 5.40	89.87 ± 4.61	93.29 ± 4.36
Group B	25	83.09 ± 1.92	84.57 ± 2.04	86.88 ± 3.76	88.63 ± 3.54	92.20 ± 3.73
Group C	25	82.34 ± 2.96	83.66 ± 3.19	85.31 ± 3.40	87.19 ± 3.52	90.81 ± 3.20
Control group	25	80.07 ± 3.50	81.21 ± 3.67	83.63 ± 3.94	85.58 ± 3.76	90.21 ± 3.08
F	/	2.837	2.913	3.042	3.282	3.301
p	/	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

Mental development index (MDI), psychomotor development index (PDI).

Table VI. Blood routine comparison in different groups before and after treatment.

Item	WBC ($\times 10^9$/l)	RBC ($\times 10^{12}$/l)	HB (g/l)	PLT ($\times 10^9$/l)
A before treatment	12.54 ± 5.81	4.59 ± 0.83	143.74 ± 13.29	236.82 ± 68.04
A after treatment	11.49 ± 4.24	4.85 ± 0.45	155.53 ± 12.66	260.70 ± 63.02
B before treatment	14.45 ± 5.60	4.51 ± 0.60	143.37 ± 19.97	244.87 ± 60.23
B after treatment	11.74 ± 4.72	4.80 ± 0.51	152.96 ± 14.23	268.09 ± 49.51
C before treatment	13.84 ± 5.51	4.52 ± 0.40	143.17 ± 16.18	233.52 ± 44.79
C after treatment	11.56 ± 4.70	5.01 ± 0.55	148.09 ± 12.97	251.11 ± 42.19
CG before treatment	13.10 ± 4.19	4.31 ± 0.54	141.69 ± 14.85	240.09 ± 62.87
CG after treatment	13.35 ± 4.57	4.49 ± 0.52	142.16 ± 17.47	238.02 ± 54.75
p	> 0.05	> 0.05	> 0.05	> 0.05

White blood cells (WBC), red blood cells (RBC), hemoglobin (Hb), platelets (PLT).

Table V shows the PDI comparison results at different doses. The F value reached 3.042 after 3 months ago, 3.282 after half a year of treatment, and 3.301 after nine months of treatment, all *p*-values were within 0.05.

Blood Routine Indexes Comparison

Before and after treatment, the blood routine data of premature infants in different experimental groups and control groups were compared (Table VI).

Table VI shows the comparison of blood routine between the experimental group and the control group at different doses. The *p*-values of four indicators were more than 0.05, and the difference was not statistically significant.

Comparison of Liver Function Indexes

Before and after treatment, the liver function indexes of preterm infants in different experimental groups and control groups were compared. The indexes were Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Blood Urea Nitrogen (BUN), Creatinine (Cr), as shown (Table VII).

Table VII shows a liver function comparison, in which the indicators of groups A, B, and C were changed before and after treatment, and the data after treatment were different from data before treatment, and the *p*-value was greater than 0.05.

Comparison of Developmental Scale Scores After the Comparative Experiment

For the development evaluation, the Gesell development scale was selected. The comparative experimental results are shown (Table VIII).

Table VIII shows a development evaluation comparison. Among them, there is no significant difference in *p*-value in vigorous exercise and language, but there is a very significant difference in adaptability, subtle movements, and social behavior.

Comparison of Neuron-Specific Enolase (NSE) Decline

All the experiments were combined and compared with the decrease of NSE. The comparative experimental results are shown (Figure 2).

Table VII. Blood routine comparison in different groups before and after treatment.

Item	Alt (μ/L)	Ast (μ/L)	Bun (mmol/l)	Cr (μMol/l)	*p*
A before treatment	14.35 ± 6.97	36.05 ± 9.36	4.33 ± 1.76	58.03 ± 14.05	> 0.05
A after treatment	11.99 ± 5.46	31.71 ± 10.07	3.53 ± 1.31	53.27 ± 11.18	> 0.05
B before treatment	15.34 ± 8.09	37.70 ± 11.86	3.89 ± 1.30	61.28 ± 20.02	> 0.05
B after treatment	12.57 ± 4.44	33.09 ± 6.78	3.31 ± 1.22	56.99 ± 13.41	> 0.05
C before treatment	12.74 ± 4.69	37.36 ± 9.17	3.84 ± 1.37	59.97 ± 16.89	> 0.05
C after treatment	10.83 ± 3.80	32.62 ± 7.69	3.35 ± 1.42	54.36 ± 17.39	> 0.05
CG before treatment	13.14 ± 5.64	35.88 ± 9.45	3.81 ± 1.37	55.20 ± 12.50	> 0.05
CG after treatment	13.27 ± 6.49	35.79 ± 9.14	3.90 ± 1.44	56.27 ± 15.71	> 0.05

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine (Cr).

Table VIII. Developmental scale score.

Item	Number of cases	Strepitous exercise	Adaptability	Subtle movement	Social behavior	Language
Group A	25	87.00 ± 11.50	101.50 ± 25.00	94.50 ± 9.00	88.50 ± 9.50	92.50 ± 13.00
Group B	25	89.00 ± 12.00	104.50 ± 28.00	92.00 ± 11.00	86.50 ± 11.00	90.50 ± 14.00
Group C	25	88.00 ± 11.00	103.00 ± 27.00	93.00 ± 12.00	87.00 ± 13.00	92.00 ± 16.00
Control group	25	86.63 ± 10.27	94.51 ± 11.05	83.63 ± 10.45	81.66 ± 10.09	88.63 ± 11.08
t	/	2.131	4.623	5.347	5.724	2.361
p	/	> 0.05	< 0.01	< 0.01	< 0.01	> 0.05

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine (Cr).

Figure 2 shows the NSE decline comparison. Among them, the control group decreased slightly, while the experimental group decreased significantly, the *p*-value was lower than 0.05 after 3 months, and lower than 0.01 after half a year.

Discussion

The results of this study show that recombinant erythropoietin in different doses protects BIPI and improves the physiological and psychological conditions of patients and the recovery process. First of all, the physiological indexes such as hemodynamic stability, oxygenation function, and white blood cell count of the patients with brain injury in premature infants treated with recombinant erythropoietin were significantly improved. The improvement of these physiological indicators helps to stabilize the vital signs of patients with premature infants and helps to reduce the occurrence of complications. When comparing the relevant cell mediators of patients, it can be seen from S-100B and EPO that after receiving different doses of recombinant erythropoietin treatment, the level of S-100B was significantly reduced, while the other was increased. Meanwhile, the EPO levels of patients in each group increased to varying degrees after treatment, and the increasing amplitude of groups A, B, and C was higher. This result indicates that recombinant

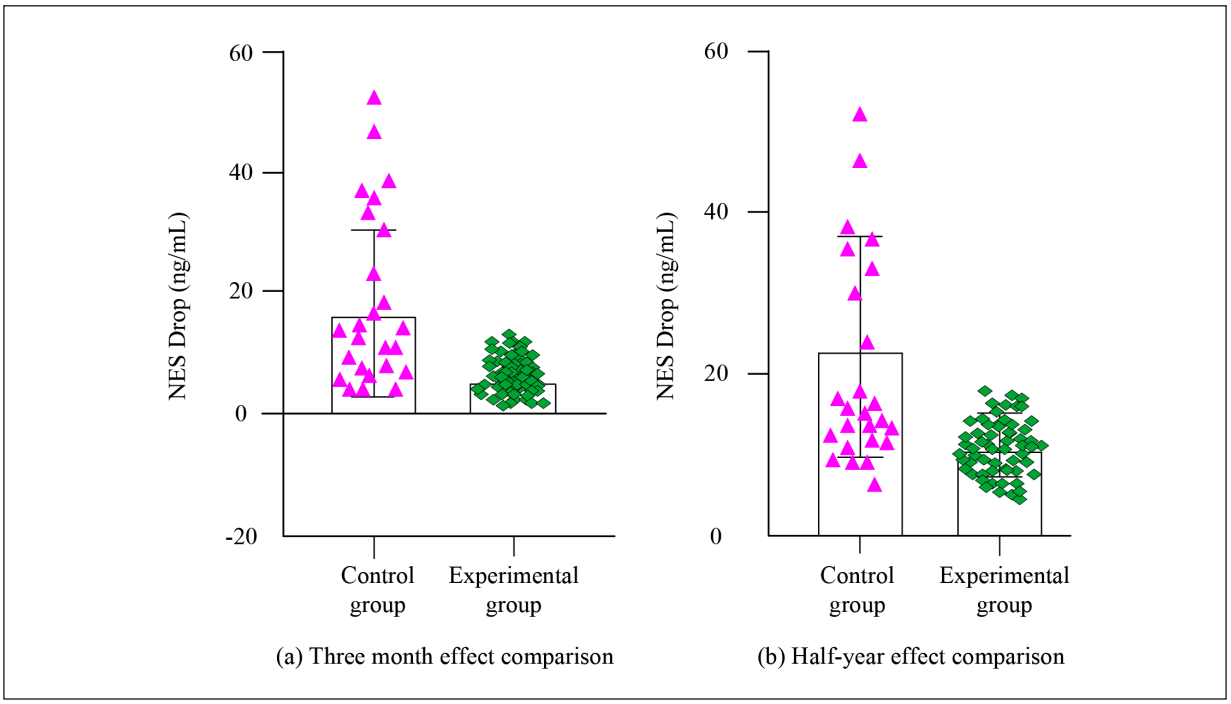

Figure 2. NSE Comparison of decline.

erythropoietin treatment has a protective effect on BIPI. In the comparison of interleukins, the indexes of the high-dose recombinant erythropoietin experimental group and medium-dose recombinant erythropoietin experimental group were reduced after treatment, and there was a significant difference. It can be seen that recombinant erythropoietin can effectively improve the brain injury disease of premature infants. Some studies reported that in premature infants, brain injury has no significant correlation with gestational age and mode of delivery[10-12].

In terms of functional recovery, we found that PI in the recombinant erythropoietin treatment group was better in neurodevelopment, cognitive function, emotional stability, etc. These results further confirmed that recombinant erythropoietin significantly protected brain injury in premature infants. Follow-up showed that the effects of recombinant erythropoietin treatment on cognitive function, exercise ability, and social behavior of premature infants were long-term and sustained. After the intelligence test of the children in different experimental groups and the control group, the MDI of the experimental group was higher in March, June, and September, and gradually increased as time went on. The experimental group received recombinant erythropoietin treatment of preterm infants in the level of intellectual development is better than the control group, preterm infants' brain injury has a protective effect, and this protective effect may contribute to the children's neurodevelopment and intellectual performance. In addition, with the passage of time, the MDI index of children in the experimental group showed an upward trend, and its role in protecting against brain injury in premature infants was persistent[13-15]. It can be seen that recombinant erythropoietin is of positive significance for the treatment of BIPI, and is helpful for the intellectual development and life quality of children. Several studies[16-18] also explored that cells can effectively protect and treat brain injury in premature infants, and recombinant erythropoietin showed neuroprotective potential in preclinical studies.

In terms of the safety of recombinant erythropoietin, the application of recombinant erythropoietin in patients with brain injury in premature infants has good safety. We closely observed and monitored the children in the recombinant erythropoietin experimental group, and no obvious adverse drug reactions or complications were found. At the same time, the hemoglobin levels were monitored. In the comparison of blood routine indicators before and after treatment, no difference showed in changes in white blood cells (WBC), red blood cells (RBC), hemoglobin (Hb), and platelets (PLT) values between the experimental and the control group (p-values of all indicators were greater than 0.05), indicating that recombinant erythropoietin treatment has little effect on blood routine indicators of children. This result has a good reference significance for the application of rhEPO in the treatment of premature infants in practice, suggesting the safety of rhEPO. Although results showed that rhEPO has little effect on blood routine indicators, this does not rule out its protective effect on brain injury in premature infants. As the previous data analysis shows, rhEPO treatment is beneficial in improving the brain structure and functional recovery of premature infants and can improve the level of intellectual development. The blood routine indicators did not change significantly, which may be due to the weak connection between the relevant biological effects caused by rhEPO treatment and blood routine indicators, so it did not affect the data performance of blood routine indicators. RhEPO treatment has a protective effect on BIPI and can be used as an effective treatment method. It has little effect on blood routine indicators of premature infants and has good safety. However, in the application of recombinant erythropoietin in BIPI treatment, attention should be paid to the drug dosage, treatment course, and other related issues to ensure the best treatment effect and safety[19-21].

Although recombinant erythropoietin has a protective effect on brain injury in premature infants, shortages still exist. Nevertheless, results provide strong evidence support for recombinant erythropoietin application in BIPI treatment and provide a new idea for improving the clinical treatment strategy of brain injury in premature infants[22-24].

Limitations

In future practice, recombinant erythropoietin is expected to become an effective and safe treatment, further improve BIPI prognosis, and help patients achieve better quality of life and physical and mental health. Although this study has certain limitations, recombinant erythropoietin has great clinical application prospects in BIPI treatment, and further large sample, multi-cen-

ter clinical studies are needed to verify its effectiveness and safety. Although this study has reached certain conclusions, there are still some limitations. First, the study sample size is relatively small, which may affect the stability and reliability of the results. Second, this study only focused on the observation and analysis of brain injury in preterm infants and failed to comprehensively examine other potential effects that the use of recombinant erythropoietin may cause. Moreover, the experiment and control group were closely observed throughout the study, but single or double blindness was not achieved, which may lead to evaluation bias. Finally, the study failed to conduct long-term follow-up and observation on the dose and duration of recombinant erythropoietin. Therefore, although this study provides some clues for the effective treatment of brain injury in preterm infants, larger, multi-center clinical studies are needed to verify its effectiveness and safety.

Conclusions

In summary, this study found that recombinant erythropoietin has a significant protective effect on brain injury in premature infants, which can significantly improve the physiological indicators, the degree of brain structural abnormalities, and the functional recovery of patients in the early stage after treatment. In addition, recombinant erythropoietin has good safety in BIPI treatment.

Conflict of Interest

The authors declare that they have no conflict of interests.

Ethics Approval

The ethical approval for this study was obtained from the Handan Central Hospital of Hebei Province (No. ZXYYLL-005). All the experiments of this study were conducted in accordance with the relevant guidelines and regulations or in accordance with the Declaration of Helsinki.

Informed Consent

Written informed consent was obtained from the patients' parents.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

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Authors' Contribution

LM, XS, SHZ, XOW, NL, and XHL did the screening and data extraction, did the analysis, designed and conceived the study, analyzed, wrote and drafted the manuscript, and provided feedback; all the authors approved the final version of the article to be published.

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