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Original Research Article

Evaluation of the clinical effect of kangaroo-style intervention mode on neonatal cerebral palsy treated with mouse nerve growth factor

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Abstract

Purpose: *To investigate the effect of application of kangaroo-style intervention mode on neonatal cerebral palsy treated with mouse nerve growth factor.*
Methods: *In this retrospective study, 153 newborns with cerebral palsy on admission to Wuhan Maternal and Child Healthcare Hospital, China between January 2016 and January 2020 were assigned to control group (n = 81) and study group (n = 72), based on differences in intervention schemes used. The control and study groups received mouse nerve growth factor and routine intervention, while study group received additional treatment with kangaroo-style intervention mode. After treatment, neonatal neurological function, intellectual development, intelligence development quotient, and growth and development indices were compared between the two groups.*
Results: *Scores on neurological function, mental development index and psychomotor development index, as well as intelligence development quotient were significantly higher in the study group than in the control group ($p < 0.05$). There were no significant differences in growth and development indices between the two groups ($p > 0.05$).*
Conclusion: *Kangaroo-style intervention mode effectively improves neurological function, and promotes intellectual development in cerebral palsy newborns treated with mouse nerve growth factor. However, it had no significant effect on neonatal physical development.*

Keywords: *Kangaroo-style intervention, Cerebral palsy, Mouse nerve growth factor, Newborns*

INTRODUCTION

Neonatal cerebral palsy refers to non-progressive brain damage and developmental defects that occur in the early stages of brain development, from the prenatal period to within one month after birth, due to various factors. The incidence of this disease in China is 1.8 - 4.0 % [1]. Neonatal cerebral palsy manifests mainly as physical and central movement disorders, mental retardation, epilepsy, disorders of perception, language, mind and behaviors, as well as delayed motor development [2]. Due to its complex etiology, this disease is not attributable to a single pathogenic factor. It develops as a result of congenital (genetic and chromosomal) factors, or other influences, e.g., adverse stimulation. Unfortunately, at present, there is no effective and radical drug for treatment of the disease.

Mouse nerve growth factor is a bioactive protein which is widely used for neural protection and nutrition. It is an important component of the neural microenvironment, and it increases the viability and regeneration of nerve cells [3]. Mouse nerve growth factor accelerates cell membrane recovery and increases the catalytic effects of various enzymes [4]. It repairs injured brain cells, but it causes irritation and allergic reactions. Due to inability to fully adapt to the external environment after birth, coupled with the side effects of neuroactive medications, some newborns may be prone to various physiological stress reactions which are detrimental to neonatal neurological recovery, growth and development.

Kangaroo-style intervention is a clinical nursing approach that utilizes multiple sensory stimuli provided through skin-to-skin contact between mothers and infants, thereby stimulating the development of central nervous system and brain function [5]. The application of kangaroo-style intervention mode in combination with mouse nerve growth factor in the treatment of neonatal cerebral palsy is expected to reduce drug stimulation, promote rehabilitation of brain function and improve behavioral and nerve developments in newborns. The present study was done to investigate the effectiveness of kangaroo-style intervention mode, so as to provide reference data for improving neural development in newborns with cerebral palsy.

METHODS

General data

The clinical data for 153 newborns with cerebral palsy in Wuhan Maternal and Child Healthcare Hospital, China from January 2016 to January 2020 were retrospectively analyzed. These patients were assigned to study group (n = 72) and control group (n = 81), on the basis of treatment used. Control group which was treated with routine intervention had 41 males and 40 females aged 12.01 ± 3.35 days, while study group which received kangaroo-style intervention mode in addition to routine intervention, comprised 36 males and 36 females aged 11.92 ± 3.26 days. In terms of disease types, the control cohort comprised 29 neonates with spastic type, 27 neonates with mixed type and 25 cases of other types. In study group, there were 21 cases of spastic type, 26 cases of mixed type, and 25 neonates with other types. With respect to the degrees of physical involvement, the presentations in control group were 39 monoplegia, 41 diplegia and 1 triplegia, while 35 monoplegia, 36 diplegia and triplegia were seen in study group. There were no significant differences in the general data between the two groups ($p > 0.05$).

Inclusion criteria

The included neonatal patients were those who met the diagnostic criteria of neonatal cerebral palsy as stipulated in *Guidelines for Cerebral Palsy and Revision of Definition, Classification and Diagnostic Criteria* (2014 edition) [6], and full-term neonates without intrauterine infection.

Exclusion criteria

Newborns with epilepsy or other neurological diseases, Down syndrome and severe water and electrolyte disorders, severe damage in vital organs such as heart, liver, and kidney, and congenital malformations or other congenital diseases, were excluded.

This study conformed with the principles contained in the 2013 Declaration of Helsinki [7]. The study was approved by the ethics committee of Wuhan Children's Hospital, Tongji Medical College Huazhong University of Science & Technology, with approval no. 2023R040-E01. The families of the newborns presented signed informed consent after fully being aware of the purpose, significance, content and confidentiality of the study.

Treatments

The two groups of newborns were treated with mouse nerve growth factor (Staidson (Beijing) Biopharmaceuticals Co. Ltd.; specification: 30 μg; NMPA approval no. S20060023). Before treatment, 30 μg of the drug was dissolved in 2 mL of sterile physiological saline (sterile sodium chloride injection water) and injected intramuscularly. The drug was administered daily for 3 - 6 weeks which constituted one course of treatment.

Neonates in control group received routine intervention during the treatment period. The routine intervention was given as follows: specialized nurses performed cutaneous sensory stimulation by touching the neonate skin on the cheeks, chest, abdomen, palms, soles and back. This was done for 10 min, 2 - 3 times a day. This was followed by visual stimulation in which nursing staff shook red, yellow and green balls 20 cm away from the newborn. Moreover, the newborns were given visual contact and gustatory and olfactory stimulations during breastfeeding, changing of diapers and intravenous puncture. This was followed by exercise rehabilitation training which comprised head training (triangle cushion method and holding ball method), limb and rolling training (trunk rotation, whole-body stretching and hand-foot coordination); sitting posture training (sitting balance and sitting position conversion), crawling training (interactive movement of limbs and balanced reaction exercise), and standing training (helping newborns to stand or guiding them to stand independently, and posture conversion). Each training was performed for 1 h, once daily for 3 months.

In addition to routine intervention, study group received kangaroo-style intervention mode in a special independent ward with constant room temperature and no convective wind. Used diapers were replaced with clean ones in advance so as to reduce the area wrapped by diapers, thereby increasing neonate-mother skin contact. After learning unified operations and passing the examination, mothers of the newborns implemented kangaroo-style intervention. Each mother sat on a chair with a backrest, adjusted herself to a comfortable sitting posture and opened her blouse. Then, the nursing staff placed the newborn wearing only diapers on the naked chest of its mother. For maximum skin contact, the mother held the neck of newborn lightly with her left hand and placed the newborn in a prone position with her right hand. At the same time, the mother was guided to hold the neck and back of the newborn with one hand, lift the mandible gently, tilt the head to one side, and support and hold the buttocks with the other arm. The back of the newborn was covered with a preheated blanket or quilt. Nursing staff carefully monitored ECG using a disposable pulse oxygen probe to prevent the development of blood oxygen intolerance, hypothermia, cyanosis, bradycardia and other abnormalities in the neonates.

Evaluation of parameters/indices

Neurological function score

Neonatal neurobehavioral assessment rating scale (NBNA) [8] was used to evaluate neurological function of newborns in both groups before and after intervention. The scale comprised 5 dimensions viz: behavioral ability, passive muscle tension, active muscle tension, primitive reflex, and general reaction, with a total of 20 items. Each item was scored 0, 1 or 2 points according to the scoring criteria, with the full score of 40 points. The sum of scores in all items was the total score. Total NBNA score ≥ 35 points indicated normal neurological function, while lower scores indicated abnormality.

Intellectual development

Mental development index (MDI) [9] and psychomotor development index (PDI) [10] were used to evaluate the intellectual development of newborns in both groups. The MDI comprised cognition, language and social functions, with a total of 163 items, while PDI had 81 sub-items under gross movements (lifting of the head, climbing, walking, sitting and standing) and fine movements (fingering and grasping). The final scores on both scales were transformed into a 100-point system, and a standard score with a standard deviation of 16 was adopted.

Intelligence development quotient

Developmental quotient (DQ) [11] was used to evaluate the mental development of newborns. It consisted of gross movements, fine movements, adaptability, language and social behaviors. Each dimension had 10 sub-items and score range of 0-20 points. The higher the score, the higher the neonatal mental level.

Growth and development index

The growth and development in both groups before and after intervention were compared, and the observed indices were composed of weight, height and growth of head circumference.

Statistical analysis

The data obtained in this study were processed with SPSS26.0 software, while GraphPad Prism 7 was used for plotting graphs. Enumeration data are presented as numbers and percentages (n (%)) and were compared using chi-squared (χ^2) test. Measurement data are presented as mean ± standard deviation (SD), and comparison between the two groups was done with Student's *t*-test. Statistical significance was assumed *at* $p < 0.05$.

RESULTS

Neurological function scores

Table 1 shows that pre-treatment neurological function scores were comparable. However, significantly higher post-treatment neurological function scores were seen in the study cohort, relative to the control cohort.

Table 1: Comparison of neurological function scores in both groups

Index	Before intervention		t	*P*-value	After intervention		t	*P*-value
	Control (n=81)	***Study (n=72)***			***Control (n=81)***	***Study (n=72)***		
Behavior ability	8.96±1.38	8.81±1.66	0.720	0.474	10.19±1.46	10.81±1.21	2.543	0.013
Passive muscle tension	7.11±1.48	7.22±1.31	0.649	0.518	8.01±1.36	8.88±1.89	3.456	0.001
Active muscle tension	5.11±1.47	5.10±1.39	0.171	0.865	6.43±1.63	7.01±1.45	2.776	0.007
Primitive reflex	5.04±1.46	5.06±1.51	0.173	0.863	5.96±1.52	6.54±1.70	2.165	0.034
General reaction	4.37±1.10	4.53±1.15	1.062	0.292	5.90±1.53	6.48±1.10	3.062	0.003

Intellectual development

Figures 1 A and C show that before treatment, the MDI scores of control group and study group were 55.35 ± 3.63 points and 56.06 ± 3.97 points, respectively, while the PDI scores were 47.77 ± 4.32 points and 47.64 ± 4.59 points, respectively. There were significant differences in intellectual development scores between the two groups ($p > 0.05$). As shown in Figures 1 B and D, the post-treatment MDI and PDI scores were significantly higher in study group than control group (MDI: 64.22 ± 3.31 vs 62.20 ± 3.58; PDI: 56.93 ± 3.62 vs 54.48 ± 3.74; $p < 0.05$).

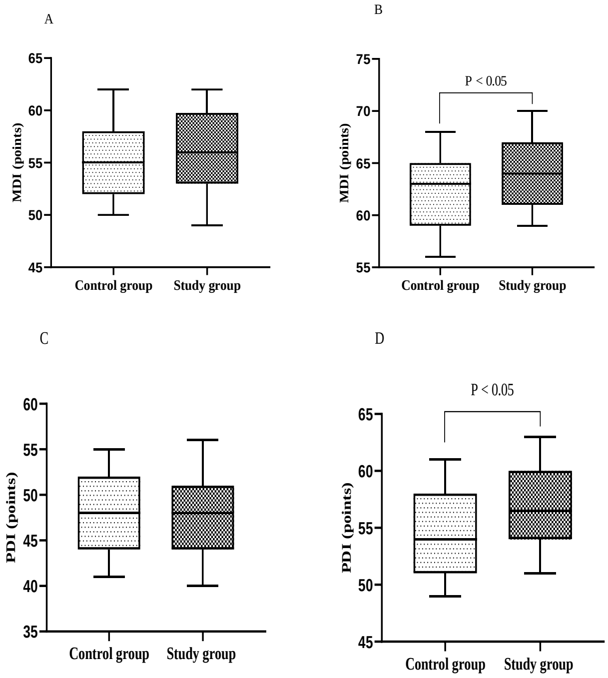

Figure 1: Scores on intellectual development in the 2 groups

Intelligence development quotient

After treatment, the study cohort had a significantly higher intelligence development quotient than the control cohort. These data are shown in Table 2.

Growth and development indices

Before and after treatment, there were no significant differences in growth and development indices between the two groups, as shown in Table 3.

Table 2: Comparison of intelligence development quotient between the two groups (points)

Group	Gross movements	Fine movements	Adaptability	Language	Social behaviors
Control (n=81)	9.62±2.26	8.23±1.54	7.25±2.12	10.09±1.35	9.04±1.39
Study (n=72)	10.83±1.97	9.60±1.85	8.21±1.74	10.96±1.36	10.03±1.29
t	3.507	5.047	3.619	3.874	4.024
P-value	0.001	<0.001	0.001	<0.001	<0.001

Table 3: Pre- and post-treatment values of growth and development indices in both groups

Parameter	Before treatment		t	*P*-value	After intervention		t	*P*-value
	Control (n=81)	***Study (n=72)***			***Control (n=81)***	***Study (n=72)***		
Weight (kg)	4.08±0.53	4.01±0.55	0.643	0.552	4.36±0.53	4.34±0.49	0.041	0.967
Height (cm)	56.25±2.77	56.85±2.59	0.299	0.766	59.85±3.11	59.90±2.74	0.596	0.553
HC (cm)	41.57±1.85	41.55±1.96	0.457	0.649	41.97±1.64	41.98±1.63	0.418	0.677

***Note**:* HC: head circumference

DISCUSSION

Neonatal cerebral palsy, a group of syndromes caused by non-progressive damage to the brain neurons in developing fetuses, is characterized by central motor and postural developmental disorders and limited activity [12]. Newborns may have symptoms such as crying and anorexia in the early stage, and they may show symptoms of physical weakness, reduced spontaneous movement, delayed growth and poor food intake in the later stage [13]. With growth, the occurrence of intellectual and developmental disorders leads to negative emotions such as stubbornness, willfulness, solitude and self-injury, and behavioral disorders such as increased muscle tension, movement disorders and abnormal posture. A clinical study has found promising recovery rates for neonatal brain structure and function, while early effective treatment significantly enhanced the repair of damaged brain tissue and nerve function in newborns with cerebral palsy [14]. Due to the numerous causes and complex etiology of neonatal cerebral palsy, the current clinical treatment methods are mainly neurotrophy and rehabilitative exercises.

The active ingredient of mouse nerve growth factor, a neurotrophic protective agent with biological activity, is a nerve growth factor extracted and purified from mouse submandibular glands [15]. Results from histopathological examination have shown that mouse nerve growth factor reduces the incidence of myelin sheath swelling of animal tibial nerves and decreases the number of degenerative tibial nerve fibers, thereby enhancing the recovery of injured nerves [16]. In the early stage of embryonic development, the content of central nervous growth factor determines the density of cholinergic nerves. In the cerebellum and hypothalamus without cholinergic innervation, the content of nerve growth factor is high, indicating that in addition to cholinergic nerves, nerve growth factor also has nutritional effects on other types of neurons [17]. Therefore, in newborns with cerebral palsy, the mouse nerve growth factor nourishes brain neurons, inhibits apoptosis of cells, and reduces or prevents the occurrence of secondary pathological damage. Nevertheless, allergic reactions occur after the injection of mouse nerve growth factor, a macromolecular protein produced through modern biotechnology. Moreover, newborns experience obvious local pain after intramuscular injection of mouse growth factor due to its irritation. This routine intervention mode is aimed at enhancing the recovery of neonatal limb function in all affected neonatal populations. After the newborn is separated from its mother, there are increases in secretion of cortical hormones and catecholamines. Besides, drug intervention easily results in stimulation of physiological emergency which is detrimental to the development and repair of neonatal brain nerves.

Kangaroo-style intervention mode (also called skin contact nursing) has been applied in neonatal asphyxia, neonatal respiratory distress syndrome, neonatal jaundice and other diseases, and it refers to the skin contact of newborns with their mothers for some time [18]. This nursing mode was developed as an early neonatal treatment method in the early 1980s. Previous studies were aimed at improving the mother-infant relationship by observing the effects on physiological conditions such as respiration, circulation, body temperature, energy metabolism and sleep. Nowadays, the beneficial effect of kangaroo-style intervention mode on neonatal neural development has been recognized [19].

The skin is the most expansive and most crucial sensory system in man, and in kangaroo-style intervention, mother and infant have long-term and large-area skin contact. The contact excites the central nervous system, stimulates the transmission of neurobehavioral information and the formation of nerve cells, and promotes the development of the nervous system through transmitting information related to the senses of position, balance, vision and hearing, under the influence of the receptors on the skin.

In the present investigation, scores on neurological function and intellectual development in study group were significantly higher than those in control group. The reason for this is that the kangaroo-style intervention mode conciliates neonatal negative physiology, reduces the secretion of glucagon and cortisol, increases the volume of specific cerebral areas and the connections in damaged brain, thereby positively affecting the structure of brain cells and promoting neural development [20]. This study investigated the effect of kangaroo-style intervention mode on neurological, intellectual and physical developments in neonatal cerebral palsy treated with mouse nerve growth factor through a retrospective method. The findings in this study provide useful data for improving neurodevelopmental prognosis in newborns with cerebral palsy.

Limitations of the study

There are some shortcomings in this study that need to be addressed in the future. This study was limited by study time, funds and other conditions. Moreover, all the neonates studied were from the same hospital. Therefore, there is need to carry out subsequent studies with large samples, and in multiple centers. Moreover, there was no investigation on the long-term effect of treatment on neural development.

CONCLUSION

Kangaroo-style intervention mode effectively improves neurological and intellectual development as well as intelligence development quotient in cerebral palsy neonates treated with mouse nerve growth factor but it had no significant effect on their physical development. There is a need to extend observation time in order to investigate the long-term effect of this mode of treatment.

DECLARATIONS

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None provided.

Ethical approval

The study was approved by the Ethics Committee of Wuhan Children's Hospital, Tongji Medical College Huazhong University of Science & Technology (approval no. 2023R040-E01).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Hui Yang and Dan Sun conceived and designed the study, and drafted the manuscript. Hui Yang, Dan Sun and Chunling Gao collected, analyzed and interpreted the experimental data. Dan Sun and Chunling Gao revised the manuscript for important intellectual content. All authors read and approved the final draft of the manuscript for publication.

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REFERENCES

1. *Correr MT, Pfeifer LI. Cultural adaptation and reliability assessment of the Hammersmith neonatal neurological examination for Brazilian newborns at risk of cerebral palsy. Arq Neuropsiquiatr 2023; 81: 47-54.*
2. *Olusanya BO, Smythe T, Ogbo FA, Nair MKC, Scher M, Davis AC. Global prevalence of developmental disabilities in children and adolescents: A systematic umbrella review. Front Public Health 2023; 11: 1122009.*
3. *Yokozeki Y, Uchida K, Kawakubo A, Nakawaki M, Okubo T, Miyagi M, Inoue G, Itakura M, Sekiguchi H, Takaso M. TGF-β regulates nerve growth factor expression in a mouse intervertebral disc injury model. BMC Musculoskelet Disord 2021; 22: 634.*
4. *Sylvester CM, Myers MJ, Perino MT, Kaplan S, Kenley JK, Smyser TA, Warner BB, Barch DM, Pine DS, Luby JL, et al. Neonatal brain response to deviant auditory stimuli and relation to maternal trait anxiety. Am J Psychiatry 2021; 178: 771-778.*
5. *Gebuza G, Kaźmierczak M, Leńska K. The effects of kangaroo mother care and music listening on physiological parameters, oxygen saturation, crying, awake state and sleep in infants in NICU. J Matern Fetal Neonatal Med 2022; 35: 3659-3669.*
6. *Mlodawski J, Mlodawska M, Pazera G, Michalski W, Domanski T, Dolecka-Slusarczyk M, Gluszek S, Rokita W. Cerebral palsy and obstetric-neonatological interventions. Ginekol Pol 2019; 90: 722-727.*
7. *World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310(20): 2191-2194.*
8. *McNamara L, Morgan C, Novak I. Interventions for motor disorders in high-risk neonates. Clin Perinatol 2023; 50: 121-155.*
9. *Gill VR, Liley HG, Erdei C, Sen S, Davidge R, Wright AL, Bora S. Improving the uptake of Kangaroo Mother Care in neonatal units: A narrative review and conceptual framework. Acta Paediatr 2021; 110: 1407-1416.*
10. *El Rafei R, Maier RF, Jarreau PH, Norman M, Barros H, Van Reempts P, Van Heijst A, Pedersen P, Cuttini M,*

Johnson S, et al. Postnatal growth restriction and neurodevelopment at 5 years of age: a European extremely preterm birth cohort study. Arch Dis Child Fetal Neonatal Ed 2023;

11. Palaskar P, Ramekar SD, Sant N, Malani RJ. Ideal mode of auditory stimulation in preterm neonates in neonatal intensive care unit: A systematic review. Cureus 2023; 15: e34496.
12. Almutairi AB, AlAbdullkarim AE, Al-Shatti AA. Establishing a cerebral palsy registry in Kuwait: An exploratory study. J Taibah Univ Med Sci 2023; 18: 947-953.
13. Diallo A, Darre P, Metowogo K, Lawson-evi P, Selva D, Potchoo Y, Creppy E, Ramanathan M. Fetal toxicity and cytotoxicity of Lannea kerstingii Engl and Krause stem bark (Anacardiaceae). Trop J Pharm Res 2016; 15: 253-258.
14. Zhang M, Zheng H, Zhang X, Tian X, Xu S, Liu Y, Jiang S, Liu X, Shi R, Gong K, et al. Involvement of nerve growth factor in mouse hippocampal neuronal cell line (HT22) differentiation and underlying role of DNA methyltransferases. J Toxicol Environ Health A 2018; 81: 1116-1122.
15. Yang X, Mou D, Yu Q, Zhang J, Xiong Y, Zhang Z, Xing S. Nerve growth factor promotes osteogenic differentiation of MC3T3-E1 cells via BMP-2/Smads pathway. Ann Anat 2022; 239: 151819.
16. Xiao S, Zhang F, Zheng Y, Liu Z, Wang D, Wei Z, Deng C. Synergistic effect of nano fat and mouse nerve-growth factor for the promotion of sensory recovery in anterolateral thigh free flaps. Stem Cells Transl Med 2021; 10: 181-189.
17. Sun H, Yang X, Zheng M, Liu J, Guo Z, Shi L, Xie B, Zhang Y, Wang X, Wang L. Nerve growth factor protects against cadmium-induced hypertension in mice via vascular remodeling. Trop J Pharm Res 2021; 20: 1419-1424.
18. El-Farrash RA, Shinkar DM, Ragab DA, Salem RM, Saad WE, Farag AS, Salama DH, Sakr MF. Longer duration of kangaroo care improves neurobehavioral performance and feeding in preterm infants: a randomized controlled trial. Pediatr Res 2020; 87: 683-688.
19. Cristóbal Cañadas D, Bonillo Perales A, Galera Martínez R, Casado-Belmonte MDP, Parrón Carreño T. Effects of Kangaroo Mother Care in the NICU on the physiological stress parameters of premature infants: A meta-analysis of RCTs. Int J Environ Res Public Health 2022; 19: 583.
20. Landry MA, Kumaran K, Tyebkhan JM, Levesque V, Spinella M. Mindful Kangaroo Care: Mindfulness intervention for mothers during skin-to-skin care: a randomized control pilot study. BMC Pregnancy Childbirth 2022; 22: 35.