Early physical intervention of premature infants to reduce incidence of cerebral palsy: a multicenter clinical investigation

National Cooperative Group for Lowering Incidence of Cerebral Palsy of Premature Infants through Early Intervention

Beijing, China

Original article

Background: **Preterm infants are more likely to suffer from cerebral palsy than term infants. The aim of this study was to evaluate the effect of early physiotherapy on the incidence of cerebral palsy in premature infants.**

Methods: **A total of 2684 infants born at less than 37-week gestation, excluding those with congenital deformity and hereditary metabolic diseases, and treated at 29 collaborative units in China from March 2001 to December 2004 were included in this study. The premature infants were classified into 2 groups: intervention group (1390 infants) whose family members actively participated in the early intervention after the initiation of this investigation; routine group (1294 infants) including the premature infants born within 1 year before this investigation, and the premature infants born after the investigation and who did not receive early intervention because of lack of support from family members. The infants of the intervention group received massage, exercise and motor training on the basis of early education at home after discharge from hospitals. All infants with abnormal motor manifestations were given appropriate rehabilitation training. The infants in the routine care group received only conventional baby care.**

Results: **In the 2 groups, no significant differences were found in complications of pregnant mothers, average gestational age and birth weight, proportion of small for gestational age (SGA) and appropriate gestational age (AGA), proportion of single and multiple births, fetal stress, postnatal asphyxia, Apgar Score, incidence of neonatal hypoxic ischemic encephalopathy (HIE) and intracranial hemorrhage ($P > 0.05$). The findings indicate that the two groups were comparable. At 1 year of age, cerebral palsy occurred in 13 (9.4‰) of the intervention group vs 46 (35.5‰) of the routine care group ($P < 0.001$).**

Conclusions: **The instructions for the parents to carry out physical intervention for their premature infants can reduce the incidence of cerebral palsy.**

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Key words: **premature infants; early physical intervention; cerebral palsy**

Introduction

In recent years, the survival rates of seriously sick newborn infants including premature infants and low birth weight infants have been increasing, but the incidence of cerebral palsy has not been decreasing, but rather increasing.[1,2] An investigation of over 30 000 children 1-6 years of age conducted in 1997 in 7 provinces in China showed an incidence of 1.59‰ for cerebral palsy. In premature infants, the incidence of cerebral palsy was 29.12‰, 25.16 times higher than that in full-term infants.[3-8] Each year, about 20 million infants are born in China. With the incidence of premature infants as 5%, about 1 million premature infants are born anually, thus giving an increase of 29 000 cerebral palsy infants each year in China. The rehabilitative expense for cerebral palsy infants is as high as 5000-10 000 RMB a month. Unfortunately, older patients with cerebral palsy can not be cured, but improved life quality is possible. Cerebral palsy is a great burden, mentally and financially, to the individual, family and society. Therefore, early intervention in the high-risk group, premature infants, and lowering the incidence of cerebral palsy are of great importance in improving the long-term prognosis of premature infants and raising the quality of the population. For this reason, we conducted this investigation from March 1, 2001 to the end of December 2004. Preliminary results were significant,[9] and

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the present study further confirmed the success in the study of larger samples.

Methods

Infants

A total of 2684 cases of surviving premature infants, gestational age under 37 weeks, excluding those with congenital deformity and hereditary metabolic diseases, born or treated at 29 collaborative units from March 1, 2001 to the end of December 2004 were included in this study. They were classified into 2 groups: routine care (routine group) and early physical intervention (intervention group). The routine group included premature infants born within 1 year before the initiation of this investigation and those born after the initiation of the investigation who did not receive early intervention because of lack of support from their family members; the intervention group included all premature infants who received early intervention after the beginning of the investigation.

Methods

Intervention group

Before discharge of premature infants from hospitals, the pediatrician briefed the parents on the objective and contents of early intervention, obtained their consent, gave them a letter, explained to them the methods and materials of physical intervention, and filled in the registration form. After discharge, the pediatrician explained to the parents the importance of early intervention, the rules of motor and intellectual development, the relevant information on feeding, nursing care, prevention and treatment of common diseases of infants and young children. If facilities were available, cranial B ultrasonography was carried out within 7 days of birth. Cranial CT and/or MRI (corrected age 1-3 months), examination of brain stem auditory evoked potentials (ABR) and EEG were required if necessary. Neonatal behavioral neurological assessment (NBNA) was made 3-5 days after the corrected age of 40 weeks. Premature infants were fed mother milk or special milk powder, at least until birth weight reached 2000 g. Two weeks to 1 month after birth, iron preparations were given when necessary, while vitamin D was given to prevent rickets. Once a month before the corrected age of 6 months and twice a month after 6 months, infants returned for examination of growth and development, nutritional status and motor neurological function. Beginning from 1-2 weeks after discharge with early comprehensive education of premature infants, including cognition, language, emotion and communication ability, etc,[10] stress was put on motor training such as total body massage and passive exercise twice a day for 5-15 minutes each time; afterwards, active motor training was carried out according to the rules of motor development of infants including head erection in prone position, pulling to sitting position, turning over, crawl-ing, standing and walking under the *Guidance of Scientific Health Training of Infants* (disc).[11-17] If motor development was retarded or abnormal posture appeared, appropriate rehabilitative training was emphasized.

Routine group

The infants of this group received similar feeding, nursing care and health guidance as in the intervention group. The infants classified 1 year before the initiation of the investigation, neuron-motor and intelligence were examined at 1 year of age, and in those classified according to their parents who had negative response to early intervention for their infants, neuron-motor function was examined at 6, 9 or 12 months. All infants were subjected to intelligence test at 1 year of age.

If neuron-motor function found nothing abnormal and mental development index was <70, the infant was followed up until he or she could walk with normal posture to exclude non-spastic or mild cerebral palsy.

Evaluation of results

Neuron-motor function was examined with the Amiol-Tison Method.[18,19]

Intellectual development test of infants and young children was done with the standardized Bayley Scales used in China.[20]

Cerebral palsy was diagnosed according to *Practical Pediatrics* (7th Edition).[21]

The severity of cerebral palsy was classified at 1 year of age (Table 1).

Table 1. The severity of cerebral palsy at 1 year of age

Severity	Gross movement	Fine movement	Mental development index (MDI)
Mild	Crawl Walk with help but posture abnormal	Grasp object with thumb & other fingers, can not with thumb & forefinger	>70
Moderate	Sit but posture abnormal Fail to crawl Fail to walk with help	Grasp large object Can not grasp object with thumb & other fingers	50-70
Severe	Fail to sit Fail to crawl	See object but fail to move it	<50

*: If 3 items are not in parallel, gross movement is emphasized.

Diagnosis of cerebral palsy was made by the local pediatric neurologist or cerebral palsy rehabilitation specialist, who did not know to which group the infant belongs. If necessary, the diagnosis was confirmed by the specialists of a supervising group. If the mental development index was < 70 shown by the intellectual test, neurological examination or follow-up to 2 years was carried out to exclude cerebral palsy.

Results

Comparison of basic conditions

No significant differences were observed ($P > 0.05$) among sex ratio, gestational age, birth weight, and number of birth (Tables 2,3). In perinatal conditions (Table 3), intrauterine distress, and cord and placental abnormality including placenta previa, calcification of the placenta, cord problems were mostly cord around the neck, and a few were cord prolapse and abnormal cord blood flow. Differences in proportions of the above abnormalities in the 2 groups were not statistically significant. The incidence of post-natal asphyxia and Apgar score were also not significantly different (Table 4). Pregnancy complications were mostly pregnancy-induced hypertension. Others included diabetes mellitus, anemia, heart and kidney diseases, hepatitis A, sexually transmitted diseases, etc. The incidences were close between the two groups. Premature rupture of membranes and incidences of neonatal infections in the two groups showed no statistical difference (Table 5). Neonatal infections consisted mainly of pneumonia, 79.2% and 61.5% in the intervention and routine groups, respectively. Others were sepsis, narcotizing enterocolitis and diarrhea, etc. In the two groups, incidences and severity of neonatal hypoxic ischemic encephalopathy (HIE), intracranial hemorrhage and its degrees showed no statistical difference, excluding the incidence of neonatal HIE being higher in the intervention group than in the routine group (Table 6).

Table 2. Comparison of basic data between the 2 groups

Group	Cases	Sex ratio M/F	Gestational age (wk) (mean ± SD)	Birth weight (kg) (mean ± SD)	Single birth weight (g)			
					Cases	≥2000	<2000-1500	<1500
Intervention	1390	542/848	35.0 ± 2.0	2.2 ± 0.6	1041	739	215	87
Routine	1294	778/516	34.6 ± 2.0	2.2 ± 0.5	936	715	162	59
t (χ^2) value		$\chi^2 = 0.22$	$t = 1.03$	$t = 0.68$		$\chi^2 = 0.77$		
P value		> 0.05	> 0.05	> 0.05		< 0.05		

Table 3. Comparison of perinatal conditions between the 2 groups (%)

Group	Cases	Intrauterine distress	Cord or placental abnormality	SGA	No. of birth	
					Single	Twin & multiple
Intervention	1390	153 (12.4)	216 (15.5)	176 (12.7)	1041	349
Routine	1294	134 (11.6)	175 (13.5)	154 (11.9)	936	358
χ^2 value		0.13	2.19	2.79	2.26	

$P > 0.05$.

Table 4. Comparison of Apgar score and postnatal asphyxia between the 2 groups (mean ± SD) (%)

Group	Apgar score				Postnatal asphyxia (cases)		
	Cases	1 min	Cases	5 min	Total	Moderate	Severe
Intervention	1196	8.5 + 1.9	840	9.6 + 0.9	224 (17.2)	185 (14.2)	39 (3.0)
Routine	1168	8.6 + 1.8	1090	9.5 + 1.0	145 (16.9)	171 (14.3)	31 (2.6)
t(χ^2) value		$t = 1.27$		$t = 1.75$	$\chi^2 = 0.06$	$\chi^2 = 0.32$	

$P > 0.05$.

Table 5. Comparison of maternal pregnancy complications and premature rupture of membranes between the 2 groups (%)

Group	Cases	Maternal pregnancy complications (cases)	Premature rupture of membranes (cases)	Neonatal infections (cases)
Intervention	1390	356 (25.6)	337 (24.2)	299 (21.5)
Routine	1294	295 (22.3)	332 (25.7)	267 (20.6)
χ^2 value		2.89	0.42	0.31

$P > 0.05$.

Table 6. Comparison of HIE and intracranial hemorrhage between the 2 groups (%)

Group	Cases	HIE				Intracranial hemorrhage				
		Total cases	Mild	Moderate	Severe	Total cases	Ⅰ°	Ⅱ°	Ⅲ°	Ⅳ°
Intervention	1390	134 (9.6)	113	20	1	113 (8.1)	65	31	15	2
Routine	1294	87 (6.7)	68	17	2	113 (8.7)	63	30	19	1
χ^2 value		7.82	1.35			1.41	0.29			
P value		< 0.01	> 0.05			> 0.05	> 0.05			

Incidence of cerebral palsy

The diagnosis of cerebral palsy was made after 1 year of age in both groups. In the intervention group (13 cases), 12 were followed up for ≥2 years, and 1 was followed up for 1.5 years. In the control group (46 cases), 35 were followed up for ≥2 years, and 11 for 14-21 months.

The incidence of cerebral palsy in the routine group was 3.6 times higher than that of the intervention group. In the intervention group, 15.4% of the cases were severe, while in the routine group half of the cases were severe. The difference was of statistical significance (Table 7).

Table 7. Comparison of incidence of cerebral palsy between the 2 groups

Group	Cases	No. of CP				
		Cases	‰	Mild	Moderate	Severe
Intervention	1390	13	9.4	5	6	2
Routine	1294	46	34.0	4	19	23
χ^2 value		19.59		8.81		
P value		<0.0001		0.012		

Early abnormal neurological manifestations

In the intervention group of the non palsy infants, abnormal neurological manifestations appeared within 6 months were listed according to the frequency as follows: difficulty in erecting the head (103), dorsiflexion angle of the foot > 70 degrees (normal < 70 degrees) (44), ankle clonus (38), irritation cry (33), small angle of heel to ear (33), thumb across the palm (26), limited adductors angle (25), limited popliteal angle (17), absent pursuit of light and acoustic blink reflex (15), exaggerated knee jerk (14), low spontaneous motor activity (12), constant closure of the hands at 3-4 months (11), limited scarf sign (11), lethargic, no cry (8), and scissoring at supporting reaction (4).

Of the infants with abnormal neurological manifestation, 50 had only one, 40, 26, 12, 9, 6 and 6 cases had 2, 3, 4, 5, 6 and more than 6 items, respectively. These manifestations disappeared 3-8 months after birth.

Discussion

In this investigation, factors leading to cerebral palsy were analyzed. First, the incidence of cerebral palsy is related to the quality of early diagnosis and treatment after birth. In this investigation, the number of infants in the 2 groups from the collaborative units was quite close. Second, reports have shown that the incidence of cerebral palsy is increased with the lowering of gestation weeks. The lower the birth weight, the higher the incidence.[22] The incidence of cerebral palsy was 6.4 times higher in twins than in single birth,[3] and 6.5 times higher in small gestational age (SGA) than in appropriate gestational age (AGA).[7] In our investigation, gestational age, birth weight, proportion of single and twin babies, and incidence of SGA showed no significant difference between the two groups. The incidence of cerebral palsy of single babies, weight < 2000 g, was 70.20‰, 5 times that of babies with weight 2000-2499 g. The incidence of palsy in babies with weight <1500 g was 2-5 times higher than that of babies, weight 1500-2000 g.[21] In this research, the birth weight of babies in the intervention group was much lower than that in the routine group (Table 2); without intervention, the incidence of palsy could be higher. Third, factors causing anoxia, brain damage, intrauterine distress, Apgar score, HIE, intracranial hemorrhage, and maternal pregnancy complications were not significantly different. Fourth, it was recognized that a close relationship exists between cerebral palsy and fetal and neonatal infections.[23-25] Premature rupture of membranes was similar and the incidence of neonatal infections showed no difference. In short, the intervention and routine groups were comparable.

In our investigation, the incidence of cerebral palsy in the routine group was higher than in the intervention group, indicating that massage, exercise, motor training and early rehabilitation soon after discharge of premature infants from hospitals can lower the incidence of cerebral palsy.

Early intervention in premature infants can lower the incidence of cerebral palsy; as a result, the more immature the brain, the greater the plasticity. Congenital hemiplegia is considered a form of cerebral palsy related to vascular insults in the fetal or perinatal period.[26] The infants with the disease often show considerable reorganization or sparing of function despite the presence of extensive unilateral cortical damage. They do not show any difference in cognitive and motor function related to hemispheric damage. Multiunit electromyographic recordings and electromagnetic brain stimulation may show that the motorneuron pools of left and right hand muscles receive common synaptic imput from the abnormally branched axons provided by corticospinal fibers originating from the undamaged motor cortex. The key period of this characteristic is the first year after birth. Muller et al[27] reported a 6-year-old boy who had undergone a right hemispherectomy at age of 3.5 years. After functional recovery, the cortico motor area was reorganized. When the left hemiplegic hand moved, PET showed rCBF increased in the supplementary area, premotor area, insula and inferior frontal cortex of the left hemisphere. This finding suggests that the compensatory reallocation of motor func-

tion after contralateral hemispherectomy involves the nonrolandic brain areas rather than the primary motor cortex. We consider that intensive physical rehabilitative training will further reorganize the motor area. In the intervention group, part of the infants showed early abnormal neurological manifestations which disappeared before 1 year of age. This may be related to maturation of the nervous system, but may also be due to the compensation of cerebral function as a result of early intervention. Otherwise, cerebral palsy could occur.

Manifestations of cerebral palsy appear gradually. When classical motor dysfunction appears at 1-2 years of age and the diagnosis of cerebral palsy is fully established, it is late to start treatment. In infants and young children, motor development and development of cognition, language, behavior and emotion supplement each other and are closely related. Therefore, early rehabilitation of cerebral palsy has changed from the treatment of an individual system to a wide range of plans for early intervention together with early education, all-round guidance including motor, cognition, emotion, social communication, and self care. Regular follow-up can discover early manifestations of cerebral palsy and initiate early intensive rehabilitative training. In 1997, in the USA, an early intervention plan for children before 3 years of age was available in 50 states. This plan provided opportunities for parents to take part in early education of infants and young children, and the treatment plan of palsy was included in early education.[28-30]

In conclusion, our clinical investigation showed that guiding parents to actively participate in early intervention is very important in preventing or alleviating cerebral palsy in premature infants; the intervention measures including massage, exercise and active motor training can be carried out at home. They are helpful in strengthening the health of the baby and promoting the development of high-risk infants. Parents pay no medical expense other than regular follow-up and rehabilitative service when palsy manifestations are suspected. Therefore, this is an economic and effective technique. If widely practiced, it will play an important role in lowering the incidence of cerebral palsy and raising the quality of the population.

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