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Original Article

Spine and head chiropractic therapy promotes neuropsychological development and decreases prevalence of cerebral palsy in premature infants

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Abstract: Objective: To Evaluate the efficacy of spine and head chiropractic therapy (SHCT) on neuropsychological development and incidence of cerebral palsy in very low birth weight premature infants. Methods: 125 infants were randomly divided into control and SHCT groups. The infants of both groups received conventional therapy, 40 minutes per session for control group and 40 minutes followed by 20 minutes of SHCT for SHCT group. The treatment lasted 3 sessions a week for 20 months. Neuropsychological development, social emotion, social skill and incidence of cerebral palsy were measured. Results: At 24 months corrected age the mental developmental quotient scores of each domain in the SHCT group were higher than those in the control group (gross motor, $P < 0.001$; fine motor, $P < 0.001$; adaptation, $P < 0.01$; social skills, $P < 0.05$, respectively). Compared with control group, the infants at 24 months corrected age in the SHCT group showed lower overt behavior, implicit behavior and dysregulation domain scores ($P < 0.01$; $P < 0.01$; $P < 0.05$, respectively), incidence of cerebral palsy ($P < 0.05$) and higher scores in realms of capabilities ($P < 0.01$). Conclusions: SHCT for very low birth weight preterm infants can promote neuropsychological development and decrease risk of cerebral palsy.

Keywords: Chiropractic therapy, neuropsychology, cerebral palsy, infant, very low birth weight

Introduction

Very low birth weight (VLBW) premature infant describes a premature baby with a birth weight below 1500 g. Organ functional development in these infants is immature. Currently, the survival rate of these infants has increased to about 70% due to the improvement of obstetric and neonatal care [1]. However, survivors often develop complications of prematurity, including intracranial hemorrhage, brain damage, patent ductus arteriosus, respiratory distress syndrome, and adverse effects that result from efforts to resuscitate and maintain life outside of the womb. Such infants have higher risks of cerebral palsy, growth retardation, chronic lung disease, as well as behavioral and emotional problems [2]. Many studies have shown that these infants have some adverse outcomes, such as cognitive delay, and neurodevelopmental abnormality [3-6].

Early intervention in VLBW premature infants can significantly decrease the incidence of cerebral palsy and hospital readmission rate, as well as improve the long-term quality of life. Wang CJ team reported that a federally enacted and state-coordinated early intervention (EI) program was important for VLBW children [7]. Dexamethasone may prevent death or chronic lung disease in VLBW infants [8, 9], but it also increased the incidence of neurodevelopmental impairment, including cerebral palsy by a multicenter randomized trial demonstrated from Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network [10]. Additionally, some studies found that balance training, hand robotic and WalkAide functional electrical stimulation therapy was a useful tool for improving gait parameters, hand function and gait pattern and energy expenditure in children with cerebral palsy (CP) [11-13]. SHCT is a type of infant

massage therapy of traditional Chinese, and has potential therapeutic effects on depression and complete spinal cord injury [14, 15].

Thereby, this study aims to investigate the effect of early interventions with SHCT on neuropsychological development in VLBW premature infants, with the intention to support the development of post hospital discharge intervention programs.

Methods

Study design

The present study is registered in the Chinese Clinical Trial Registry with ID ChiCTR-INR-17-010454 (The title of the registration is "The early invention on improving survival quality of very low birth weight premature infants", access to http://www.medresman.org/pub/cn/proj/search.aspx). This randomized, double-blinded clinical trial was approved by the ethics committee of the Maternal and Child Health Center of Fujian province.

Patients

A sample size of 120 for this study was determined by a preliminary power test (power, 0.90; α, 0.05) and assuming a SD (SD values were defined according to outcome assessment tools including neuropsychological development scale for children aged 0-6 years, Chinese infant toddler social emotional assessment and infants-middle school students social skill measurement.). All premature infants with BW of 600-1,500 g and gestational age (GA) of 26-36 weeks admitted to the Maternal and Child Health Center of Fujian province from January 2012 to December 2013 were prospectively recruited into this study, and then included 125 patients were assigned to two groups (control group, 63 infants; SHCT group, 62 infants) (**Figure 1**). Inclusion criteria for the study were: 1) gestational age 26-36 weeks and birth weight from 600 to 1,500 g; 2) principle guardian of the preterm infant agreed to participate in the research and signed informed consent. Exclusion criteria were: 1) comorbidity of inherited metabolic diseases; 2) grade IV neonatal intraventricular hemorrhage; 3) severe hypoxic-ischemic encephalopathy; 4) history of invasive ventilation treatment; 5) Apgar score at birth < 4; 6) mother with diabetic ketoacidosis, severe preeclampsia, severe anemia or acute viral infection during pregnancy. Patients baseline information showed no differences between the two groups (P > 0.05, **Table 1**).

Randomization and blinding

A total of 148 premature infants were enrolled in this study. 8 infants were excluded from study because they failed to meet the inclusion criteria of birth weight, 15 infants lost follow-up. Randomization was performed by using random number table method. A statistical expert responsible for statistical analysis in this study prepared some papers which indicated whether each participant was divided into the control or SHCT group according to their random number. The papers were sealed in ordinary paper envelopes respectively, and each envelope was numbered consecutively. Patients and all physical therapists were blinded to patients' allocation. Assessment was performed by the same examiner who was blinded after assignment to treatment groups. Allocation occurred before the baseline assessment. The flow diagram of experimental design is shown in **Figure 1**.

Intervention

For each preterm infant of control group, we established electronic archives during the first clinic visit, conducting out-patient follow up at 4, 12 and 24 months (chronological age). The control group received conventional occupational therapy, including physical examination, neuropsychological development examination, hearing screening, retinopathy of prematurity screening and oral examination performed by pediatricians, as well as muscle stretching training (A therapy for stretching soft tissue, for example, the extension technique of stretching the wrist joints, the hyperextension technique of stretching the metacarpophalangeal and interphalangeal joints, the frog hip technique of stretching the thigh muscle group, and the ankle dorsiflexion technique of stretching the triceps surae, 15 seconds for each movement as well as 10 seconds for relaxing). This cycle repeats three times provided by manual therapists. The infants of SHCT group received conventional occupational therapy in conjunction with pediatric SHCT. As previously described [14-16], The pediatric SHCT protocol was performed by the physical therapists according to

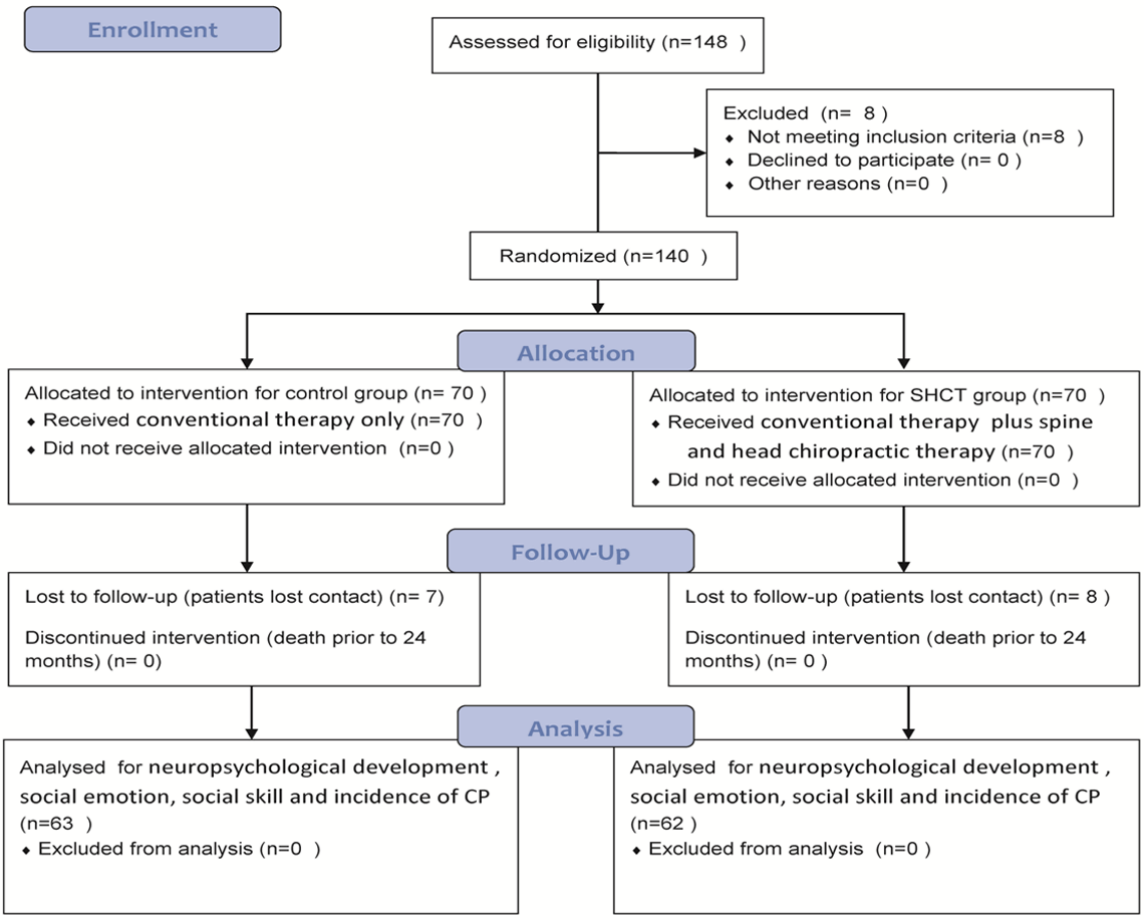

Figure 1. Flow chart showing the experimental design of the study. SHCT, spine and head chiropractic therapy; CP, cerebral palsy.

standard operation manual. The protocol was introduced briefly as follows: As showed in **Figure 2A** and **Table 2**, the thumb of both hands is straight, and the finger ends are placed on both sides of the spine. The thumb and forefinger knead the skin three times and then gently massages it one time, from Changqiang to Dazhui acupoint for a total of nine times. Finally, gently massage the back and head acupoints (including GV1 Changqiang, GV4 Mingmen, BL-23 Shenshu, BL21 Weishu, BL21 Weishu, BL20 Pishu, GV6 Jizhong, BL15 Xinshu, GV14 Dazhui, GV20 Baihui, GV24 Shengting, Ex-HN3 Yintang and Ex-HN5 Taiyang) for one time. The selection of back acupoints was shown in **Figure 2B** and **Table 2**. The concept of "inch" and election of head acupoints were described previously [16]. Pediatric SHCT lasted 20 minutes each session, 3 sessions a week for 20 consecutive months. All treatment had no adverse events (including spinal and soft tissue injuries, nausea, vomiting and serious adverse events) or unintended effects to infants.

Outcome assessment

Neuropsychological development scale for children aged 0-6 years: Beijing Gesell Development Schedule (Beijing GDS) used in this study was revised by the Capital Pediatric Institute and the Institute of Psychology, of the Chinese Academy of Science [17, 18]. Criterion-related validity was tested using Gesell developmental scales established in the district of Beijing. The scale covers five domains, including gross motor performance, fine motor movement, adaptive behavior/ability, language development and individual social skills. The development quotient (DQ) scores was calculated to assess the mental development and intellectual status of infants and young children. Age was not corrected for duration of gestation. All tests were

Table 1. Baseline information of the research subjects

Variables		Groups		P
		Control (N=63)	SHCT (N=62)	
Sex	Male	32 (50.8)	32 (51.6)	0.927
	Female	31 (49.2)	30 (48.4)	
Number of fetuses	Singleton	48 (76.2)	52 (83.9)	0.278
	Twins	13 (20.6)	9 (14.5)	
	Multiple	2 (3.2)	1 (1.6)	
Gestational age	≤ 28 W	9 (14.3)	8 (12.9)	0.315
	28^{+1}-32 W	47 (74.6)	42 (67.7)	
	32^{+1}-36^{+6} W	7 (11.1)	12 (19.4)	
Birth weight (g)		1276.5±179.7	1298.3±155.3	0.47
Birth length (cm)		38.7±3.2	38.8±2.7	0.762
Hospital stay (days)		38.1±13.5	34.9±13.4	0.181
Delivery mode	Vaginal	37 (58.7)	36 (58.1)	0.940
	Cesarean	26 (41.3)	26 (41.9)	
Apgar score		8.8±1.3	8.7±1.4	0.778
Newborn hypoxic-ischemic encephalopathy	Yes (mild to moderate)	4 (6.3)	5 (8.1)	0.744
	No	58 (93.7)	57 (91.9)	
Intracerebral hemorrhage	Grade I	12 (19.0)	12 (19.4)	0.981
	Grade II	4 (6.3)	7 (11.3)	
	Grade III	6 (9.5)	3 (4.8)	
	No	41 (65.1)	40 (64.5)	
Jaundice	Yes	7 (11.1)	7 (11.3)	0.975
	No	56 (88.9)	55 (88.7)	
Seizure	Yes	4 (6.3)	5 (8.1)	0.744
	No	59 (93.7)	57 (91.9)	
Patent ductus arteriosus	Yes	21 (33.3)	25 (40.3)	0.418
	No	42 (66.7)	37 (59.7)	
Hyperbaric oxygen therapy	Yes	3 (4.8)	4 (6.5)	0.717
	No	60 (95.2)	58 (93.5)	
Non-invasive positive pressure ventilation	Yes	25 (39.7)	21 (33.9)	0.501
	No	38 (60.3)	41 (66.1)	
Mother's age		28.9±5.2	28.5±4.5	0.652
Father's age		30.8±6.1	30.4±4.8	0.670

SHCT, spine and head chiropractic therapy; Values are expressed as number (percentage) of individuals or mean ± SD.

conducted by assigned pediatric mental health professionals who had been trained specifically, and standard instructions were used.

Chinese infant toddler social emotional assessment (CITSEA): Infant Toddler Social Emotional Assessment (ITSEA) was developed by Briggs-Gowan MJ group at Yale University and widely used for screening autism spectrum disorders and other psychopathology diseases in infants at 12 to 36 months age [19-22]. The diagnostic scale, CIESEA used in this study is a modification of ITSEA. CIESEA has 146 items with 4 domains, including externalizing, internalizing, dysregulation and competence domains. A three-tiered system is used for domain and items scoring. The original total score is calculated for each domain and then converted to T score. According to the national standardized model, the scale is suitable for children 1-3 years old and was completed by the professional pediatrician and parents of the enrolled preterm infants under the guidance of professional pediatrician.

Infants-middle school students social skill measurement (S-M scales) and diagnosis of CP: The Infants to Middle School Students Social

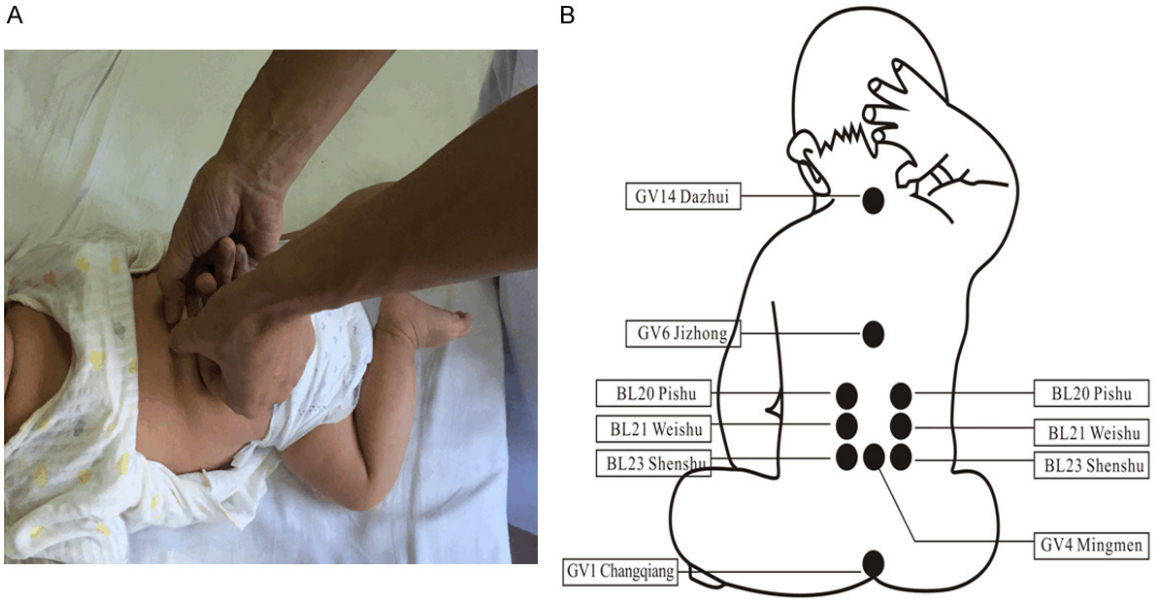

Figure 2. Chiropractic therapy and position of back acupoints. (A) Chiropractic therapy; (B) Position of back acupoints.

Table 2. The selection of back acupoints

Acupoints name	Acupoints position
GV1 Changqiang	Located between the tailbone and the anus
GV4 Mingmen	On the midline of the back, under the spinous process of the second lumbar spine
BL23 Shenshu	One and half inches to the left and right of GV4 Mingmen
BL21 Weishu	One inch above the above acupoint
BL20 Pishu	One inch above the above acupoint
GV6 Jizhong	On the midline of the back, under the spinous process of the eleventh thoracic spine
GV14 Dazhui	On the midline of the back, under the spinous process of the seventh cervical spine

Skill Measurement established by Qihua Zuo etc. was used. The scale is suitable for children aged 6 months to 14 years old, contains 132 questions, and includes 6 subscales including independence, athletic ability, targeted operation, communication ability, social competence and self-control [23]. The raw scores were conversed to T score, and defined as very low ($T \leq 6$), moderately low (T=7), slightly low (T=8), borderline (T=9), normal (T=10), above normal (T=11) and extraordinary (T=12). In this study, the normal, above normal and extraordinary were grouped together and considered normal ($T > 9$); the slightly low, moderately low and very low were grouped together and considered low ($T < 9$). The questionnaire was finished by the parents. Diagnosis of CP in VLBW premature infants was prescribed following AACPDM guideline [24, 25].

Statistical analysis

Epidata3.1 was used for database management, and double data entry was employed. SPSS 20.0 was used for statistical analysis and all tests were set to two-tailed. $P < 0.05$ was considered statistically significant. Independent sample t test and repeated measures analysis of variance were used for numeric data; x^2 or Fisher exact test were used for categorical data analysis; Mann-Whitney U rank-sum test was used for ordinal data.

Results

Mental development of the preterm infants

Because DQ is not suitable for infants in the early months, developmental age is reported at the 4, 12 and 24 months (chronological age).

Table 3. Neuropsychological developmental scale scores at different months age

Domains	Groups	4 months age	12 months age	24 months age
Gross motor	Control (N=63)	56.0±17.8	78.5±11.1	79.9±6.5
	SHCT (N=62)	56.3±16.5	86.6±10.3	86.1±8.4
	P	NS	**< 0.001**†	**< 0.001**†
Fine motor	Control (N=63)	64.1±14.1	83.0±9.4	73.2±13.3
	SHCT (N=62)	67.5±12.1	89.3±9.3	85.5±13.9
	P	NS	**< 0.001**†	**< 0.001**†
Adaptation	Control (N=63)	62.7±24.9	84.4±7.6	89.7±12.2
	SHCT (N=62)	69.8±18.7	90.6±7.8	96.9±11.3
	P	NS	**< 0.001**†	**< 0.01**†
Language	Control (N=63)	67.7±20.0	82.1±8.6	81.5±15.5
	SHCT (N=62)	66.4±20.1	83.3±9.4	85.6±12.5
	P	NS	NS	NS
Social skills	Control (N=63)	69.4±17.4	83.4±7.9	79.2±13.9
	SHCT (N=62)	72.3±17.3	88.9±10.0	84.5±13.6
	P	NS	**< 0.01**†	**< 0.05**†

SHCT, spine and head chiropractic therapy; Values are expressed as mean ± SD; †Bold *P* values are statistically significant difference.

Table 4. The scores on infant toddler social emotional assessment scale at 24 months age

Domains	Groups		P
	Control (N=63)	SHCT (N=62)	
Externalizing behavior	55.7±9.8	50.5±8.9	**< 0.01**†
Internalizing behavior	52.0±10.5	47.0±9.9	**< 0.01**†
Dysregulation	49.9±10.0	45.9±9.1	**< 0.05**†
Competence	48.0±5.6	51.9±7.9	**< 0.01**†

SHCT, spine and head chiropractic therapy; Values are expressed as mean ± SD; †Bold *P* values are statistically significant difference.

Table 5. The social skills and incidence of cerebral palsy at 24 months age

Groups	Social skills			CP
	Normal	Borderline	Low	
Control (N=63)	21 (33.3%)	18 (28.1%)	24 (38.1%)	8 (12.7%)
SHCT (N=62)	33 (53.2%)	14 (22.6%)	15 (24.2%)	1 (1.6%)
P	**< 0.05**†	NS	NS	
Total P	**< 0.05**†			**< 0.05**†

SHCT, spine and head chiropractic therapy; CP, cerebral palsy; Values are expressed as number of individuals (percentage); †Bold *P* values are statistically significant difference.

As shown in **Table 3**, all domains did not differ between groups at 4 months. Between two groups, language domain has no significant difference. However, at 24 months corrected age the DQ scores of each domain in the SHCT group (gross motor, 86.1±8.4; fine motor, 85.5±13.9; adaptation, 96.9±11.3; social skills, 84.5±13.6) were higher than the control group (79.9±6.5, P < 0.001; 73.2±13.3, P < 0.001; 89.7±12.2, P < 0.01; 79.2±13.9, P < 0.05, respectively).

Emotional and social assessment of the preterm infants

As shown in **Table 4**, the preterm infants in the SHCT group scored lower in externalizing behavior, internalizing behavior and dysregulation domains (50.5±8.9; 47.0±9.9; 45.9±9.1), and higher in the competence domain (52.0±7.9) than those in the control group (55.7±9.8, P < 0.01; 52.0±10.5, P < 0.01; 49.9±10.0, P < 0.05; 48.0±5.6, P < 0.01, respectively).

Social skill assessment of the preterm infants

Obviously, there were more infants with normal social skills in the SHCT group (33/62, 53.2%) than those in the control group (21/63, 33.3%, P < 0.05). Mann-Whitney U rank-sum test results also revealed that trend (Total P < 0.05, **Table 5**).

Incidence of CP

The follow-up was closed in March, 2013. Nine infants were diagnosed as spastic diplegia in this study. The incidence of CP in SHCT group (1/62, 1.6%) was lower than the control group (8/63, 12.7%, P < 0.05) at 24 months corrected age (**Table 5**).

The relationship between the SHCT efficacy and patient's demographics

The relationship between the SHCT efficacy and patient's demographics was performed by using t test, one-way ANOVA or Pearson correlation. The correlations between the SHCT efficacy and birth weight, birth length, hospital stay, Apgar score, mother's age and father's age were shown in the Supplementary Tables 1-3. Similarly, the effect of gestational age, infant

sex, number of fetuses, and/or delivery mode on SHCT efficacy had no statistical significance and was also shown in the Supplementary Tables 1-3. Because all infant's age were 24 months (corrected age), we did not analyze this demographic.

Discussion

In recent years, the survival rates of VLBW premature infants have been increasing gradually. Myelination of nerve cells is still incomplete in premature infants, and brain development is immature, putting brain development at risk of extrauterine insults, leading to abnormal mental development. Among VLBW premature infants, the incidence of cerebral palsy (CP) is 4.3%, moderate to severe mental retardation is 7.8%, visual and auditory disorders is 9% to 11% [26, 27]. In our study, VLBW premature infants have shown the similar incidence of CP. The period from birth to 3 years old is a critical period for brain development. As early as 1996, some scholars proposed that early developmental intervention could maximize the compensatory function of nerve cells and improve the development of premature infants [28]. Koldewijn K etc also demonstrated that early intervention improved the mental development of VLBW premature infants, reducing the incidence of mental retardation and cerebral palsy [28]. Based on Erikson's personality development theory and Piaget's cognitive structure development theory, early intervention with SHCT provides positive stimuli to infants during the critical period of brain development, repairs damaged brain, and helps the VLBW premature infants pass smoothly through the catch-up phase of postnatal development common to premature infants.

In our study, early intervention was provided to VLBW premature infants beginning as early as when they were discharged from the hospital, and their developmental status were monitored at 4, 12 and 24 months after birth. A self-designed "guidance for preterm infants care at home" program was used for out-of-hospital continuous health education to improve the parenting knowledge of the parents. Traditional Chinese acupuncture and herbal was performed that had good clinical efficacy on some diseases [30-32]. Similarly, manual therapies including Chinese massage, transcutaneous electrical nerve stimulation and standard integrated therapy is a safe and effective treatment for some nerve or muscle damage disease such as post-stroke spasticity of several muscle groups, developmental coordination disorder, upper cervical dysfunction and treatment of carpal tunnel syndrome [33-36]. Similarly, SHCT may improve gastrointestinal function, gastrointestinal motility and enhance immune function of infants through nerve stimulation. SHCT may also promote nutrient absorption, conversion and utilization. Additionally, SHCT can promote preterm infants' motor development and decrease the occurrence of preterm birth sequelae. This treatment can promote the adjustment of the physiological status and function of organs and meridians and stimulate the autonomic distributed visceral regions. By stimulating the surface distribution of these nerves, corresponding internal organ function can be adjusted by the affected neurohumoral interaction [37-39]. Indeed, the results of our study demonstrate that the early intervention protocol using SHCT in combination with conventional occupational therapy promoted the mental and motor development of VLBW premature infants as confirmed in the majority of domains. Consistent with previous reports, the stimulation of the skin and nerves on spine enhances the excitability of spinal circuits involved in generating locomotion or regulates gene expression in hippocampus [14, 15]. These may be the underlying mechanism of SHCT in promoting neuropsychological development. Interestingly, the protocol decreased the risk of CP for these infants and was a potential therapy of preventing poor neurodevelopmental outcome. Exploring genetic or biological markers of those infants is the guarantee of clarifying their functional mechanism.

Genetic factors are not the only factors that influence the social skills development of infants and young children. Mother's emotions also affect infant emotional and social development [40]. The brain is considered "the home of the soul" in traditional Chinese medicine, and head soft tissues therapy can increase the blood supply to the brain, stimulate the development of brain nerves and augment the sensitivity to external stimuli through effects on vision and hearing, as well as improving adaptation to one's environment. These salutary effects may result from changes in brain electrical signal transmission. This present study

demonstrated that our intervention promoted preterm infants' emotional reactions, social adaptability and cognitive capacity. SHCT may promote the cognitive processing of preterm infants, help them to establish normal sleep rhythm, and foster the development of an easy temperament. Our results demonstrate that the preterm infants of SHCT group scored lower in externalizing and internalizing behavior domains compared to control group, while scoring higher in competence domain. The rate of the individuals with poorer social skills was lower in SHCT group than control group. Notably, SHCT is a low-cost treatment and has fewer side effects.

In this study, treatment was only performed for 20 months. Observations of effects and side effects required longer treatment cycles and larger sample sizes. Additionally, increase of the analysis of biomarker is a guarantee for the further research.

Conclusions

Taken together, our results support the contention that early SHCT intervention can promote the neuropsychological development and effectively decrease the risk of CP in VLWB premature infants at 24 months corrected age. SHCT might be a safe and useful therapy for VLWB premature infants.

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Disclosure of conflict of interest

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