A Home-Based, Post-Discharge Early Intervention Program Promotes Motor Development and Physical Growth in the Early Preterm Infants: A Prospective, Randomized Controlled Trial

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Abstract

Background: Early intervention (EI) has been believed to improve the neurodevelopment of early preterm infants. However, its implementation in medical settings is time-consuming and resource-intensive, which limits its extensive use. In 2018, the Chinese Eugenics Association developed a home-based, post-discharge EI program. This study aims at evaluating the effect of this EI program on neurodevelopment and physical growth of early preterm infants through a prospective, partially blinded, randomized controlled trial, and a subsequent open phase.

Methods: A total of 73 infants born at 28⁺⁰–31⁺⁶ weeks' gestation with postmenstrual age of 36⁺⁰–39⁺⁶ weeks were randomly allocated to the first early intervention, then standard care (EI-SC) group (37 infants), and the first standard care, then early intervention (SC-EI) group (36 infants). Another 33 infants were retrospectively recruited as the reference group. The test of infant motor performance (TIMP) was the primary outcome, while development quotient (DQ) and anthropometric measures, including weight, length, and head circumference, were the secondary outcome. The assessment was carried out at the baseline (T0), termination of the randomized controlled trial (T1), and termination of the open phase (T2), respectively.

Results: During the randomized controlled trial, the EI-SC group had significantly higher delta change (T1-T0) than the SC-EI group in TIMP and anthropometric measures ($p < 0.05$), while no difference in DQ was noted between groups ($p > 0.05$). In terms of the delta change from T2 to T0, there was no significant difference in all outcomes between the EI-SC group and SC-EI group ($p > 0.05$). At the endpoint of T2, the EI-SC and SC-EI group had similar TIMP and anthropometric measures, but much higher than the reference group.

Conclusions: These findings demonstrated that a home-based, post-discharge EI program in this study was a practical approach to promote motor development and physical growth in early preterm infants.

Trial Registration: CHICTR, CTR1900028330, registered December 19, 2019, <https://http://www.chictr.org.cn/showproj.aspx?proj=45706>

Background

In the last two decades, the survival of early preterm infants (EPI) has dramatically improved due to the tremendous progress of neonatal intensive care. However, these survivors' high incidence of neurodevelopmental impairment is still of great concern to the neonatologist and pediatricians(1). Studies reported that 53%–72% of EPI experienced learning difficulties and had weaker performance in academics than their term peers, and 15% of them would develop cerebral palsy(2, 3). Currently, to improve the long-term outcome of EPI, particularly the neurodevelopment, is a significant challenge in the pediatric field.

Early intervention (EI) is believed to improve the neurological prognosis of infants born prematurely, who was at high risk for neurodevelopmental impairment(3–6). Preterm infants have considerable brain plasticity during the early stage of life, and their nervous system has excellent development potential(7). Applying EI to preterm infants can provide benign stimulus to the nervous system, modify the immature brain tissue, shape the brain structures, and ultimately improve the infant neurodevelopment(4–6, 8). A large body of literature has also demonstrated the effect of EI on promoting the physical growth of infants, including weight, length, and head circumference(9, 10).

Currently, most EI program was carried out in the hospital, follow-up clinics, or community-based medical settings. Implementation of an EI program is laborious, time-consuming, and resource-intensive, which limits its use on a large scale, particularly in some medical resource-limited regions. In 2018, the Chinese Eugenics Association developed a home-based, post-discharge EI program and tried to extend it to all appropriate medical facilities in China, aiming to promote the global development of preterm infants. This program makes parents the front-line executors of EI under the orientation of medical staff, and it seems to satisfy all requirements for an ideal EI model: flexibility, low-cost, and active involvement of infants and their families(11). This program provides an innovative approach to carry out EI. To our knowledge, so far, no literature regarding the effectiveness of this EI program has been published internationally. This study was aimed to evaluate the impact of this home-based, post-discharge EI program on neurodevelopment and physical growth in EPI.

Methods

Study design

This study was a single-center, prospective, partially blinded, randomized controlled trial (RCT), which was followed by an open phase. It was approved by the Institutional Review Board of Children's Hospital of Chongqing Medical University (No.2019-216) and was registered in ChiCTR (ChiCTR1900028330) with full protocol being available online. Written consent was obtained from the parents. Our study adhered to the CONSORT guidelines.

All enrolled infants were randomly allocated following simple randomization procedures (computerized random number) to the first early intervention, then standard care (EI-SC) group, or first standard care, then early intervention (SC-EI) group. The twins were allocated to the same group in favor of parental care. During the RCT period, infants in the EI-SC group had the opportunity to have a 30-day EI exposure superimposed with the standard care, while those in the SC-EI group were only given standard care at this stage. The assessment was performed for all infants at baseline (T0) and 60 days later (T1, primary endpoint). In the following open phase, the infants initially allocated to the EI-SC group continued standard care, while those initially allocated to the SC-EI group received a 30-day EI due to the ethical consideration. A repeated assessment was scheduled at 120 days of study (T2, second endpoint). All assessment was blinded to the assessors.

A sample of preterm infants meeting the same inclusion criteria was respectively recruited to provide a reference group in this study. The clinical data of these infants were extracted from our hospital follow-up dataset.

Participants

All EPI admitted to the Children's Hospital of Chongqing Medical University between Dec 1, 2019, and June 31, 2020, were eligible for this study. The inclusion criteria were as follows: (i) born at 28⁺⁰–31⁺⁶ weeks' gestation, with postmenstrual age of 36⁺⁰–39⁺⁶ weeks; (ii) stable vital signs, no oxygen requirement, reasonable daily weight gain; (iii) either of the parents being able to take round-the-clock care for the infants at home.

The exclusion criterion was as follows: (i) small for gestational age; (ii) presumed brain injury, including intraventricular hemorrhage $\geq$ grade II, various degree of periventricular leukomalacia, neonatal seizure; (iii) congenital or acquired sensory deficits; (iv) presence of a major dysmorphic feature, or laboratory-confirmed chromosomal abnormality; (v) single-family, or parents with language barriers, neurodevelopment impairment, or other disabilities expected to interfere with the implementation of EI; (vi) infants were given various interventions from specialist simultaneously, such as an occupational therapist, physiotherapist, and speech therapist; (vii) parents declined to participate.

Implementation of the EI program

Once the parents signed the consent to participate in this study, a training session would be arranged soon. A didactic lecture was delivered to the parents to provide a holistic view of this EI program, which was followed by a simulation workshop. This EI program mainly consists of three sections: intellectual, physical, and social section, which could be implemented separately. The intellectual section includes a hearing-induced training and a vision-induced training; the physical section involved a whole-body massage; the social section includes the kangaroo care and a hearing-vision integrated training (the video was available with hyperlinks in additional file 1). A researcher with rehabilitation backgrounds conducted all workshops. The parents were only eligible for performing EI independently after obtaining permission from the researcher.

Once the enrolled infant was discharged home, the parents should start the daily performance of EI promptly. Researchers would further assess the correctness of performance and suitability of the surrounding environment based on the video obtained from the parents. Parents should also fill out an information card daily, recording the time and duration of EI, the operator, and infant response. A researcher was designated to collect such information.

Standard care and follow-up clinic

Standard post-discharge care was provided to all eligible infants, including a bimonthly follow-up clinic and scheduled immunization. Pertinent advice and booklets dedicated to home-care were delivered to all

parents. The researchers recorded sporadic clinic visits due to infant unwellness.

Each follow-up clinic visit should perform the basic anthropometric measures, including weight, length, and head circumference (HC). All EPI received a comprehensive neurological assessment due to their high risk for neurodevelopmental impairment. The follow-up information was stored in a hospital follow-up dataset.

Outcome measures

Primary outcome measures

Test of Infant Motor Performance (TIMP) during the RCT was the primary outcome in this study, which was widely used to evaluate the effect of an intervention on infant motor performance(12). TIMP consists of 42 items organized into two subsets (observed and elicit items). A total raw score is summed from individual item score, which was analyzed in this study.

Secondary outcome measures

Development quotient (DQ) is a ratio statistic reflecting the global development of infants related to criteria logged in authentic social contexts. Gross motor, fine motor, social development, adaptiveness, and language skills were the five subdomains assessed in this study. An overall general DQ score was calculated by summing these subdomains, and more than 85 is considered normal(13).

The anthropometric measures, including weight, length, and HC were also recorded and analyzed as the secondary outcomes in this study.

Statistics

The sample size for RCT was calculated to detect a difference of 0.5SD in the raw score of TIMP between groups (on a 2-side test with $\alpha=0.05$; $\beta=0.80$). A total of 28 infants were needed in each group. Assuming a follow-up rate of 85%, the sample size was 33 in each group.

Clinical data were collected using Epidata 3.1 software, and all data analyses were carried out using SPSS 19.0. Normal distributed continuous data were expressed as the mean $\pm$ SD, which was compared using one-way ANOVA between groups. The categorical data were expressed as a percentage, which was compared using the chi-square or Fisher's exact test between groups. A p value<0.05 was considered significant.

We calculated the delta change of TIMP, DQ, and anthropometric measures from T0 to T1, and compare the delta changes between the EI-SC group and SC-EI group to verify the effect of EI program versus standard care on infant development and physical growth. Furthermore, the delta changes from T0 to T2 were also calculated and compared to test whether the 60-day delayed EI program had similar effects compared with the EI implemented at the beginning.

A third group retrospectively recruited was taken into the analyses as a reference group. At the endpoint of T2, all outcome measures were compared among the EI-SC, SC-EI, and reference groups using the one-way ANOVA and the Bonferroni test as a post hoc multiple comparisons.

Results

A total of 138 infants were eligible for the RCT trial; 65 infants were excluded, resulting in 73 objects being randomly allocated, 37 in the EI-SC group, and 36 in the SC-EI group. Besides, 33 infants were retrospectively recruited as the reference group (Fig. 1). No difference was noted among the three groups regarding demographic characteristics. The baseline TIMP, DQ, and anthropometric measures between the EI-SC group and SC-EI group were also comparable (Table 1).

Table 1
Baseline characteristics and assessment (T0)

	EI-SC group (n = 37)	SC-EI group (n = 36)	Reference group (n = 33)	For χ^2	p
Gestational age (weeks)	30.03 ± 1.79	30.72 ± 1.45	30.06 ± 1.39	2.264	0.109
Birth weight (gram)	1432.14 ± 200.00	1509.28 ± 201.56	1511.18 ± 187.06	1.899	0.155
Corrected gestational age (weeks)	36.92 ± 0.83	36.64 ± 0.90	36.97 ± 1.19	1.178	0.312
Weight at discharge (gram)	2529.19 ± 360.30	2453.06 ± 271.02	2504.94 ± 340.54	0.776	0.463
Female/male	25/12	20/16	19/14	1.258	0.053
Duration of maternal education (years)	14.24 ± 2.19	14.58 ± 2.82	14.82 ± 3.20	0.390	0.678
TIMP score	52.76 ± 9.19	50.81 ± 8.24	N/A	0.911	0.343
DQ total score	83.43 ± 6.61	80.28 ± 9.99	N/A	2.543	0.115
Gross motor	82.78 ± 14.46	79.47 ± 16.33	N/A	0.843	0.362
Fine motor	86.81 ± 27.71	78.28 ± 26.08	N/A	1.834	0.180
Adaptiveness	84.16 ± 19.94	80.56 ± 30.02	N/A	0.367	0.546
Social	79.35 ± 20.91	81.94 ± 18.59	N/A	0.313	0.578
Language	84.19 ± 14.16	81.17 ± 21.25	N/A	0.514	0.476
Physical growth					
Length (cm)	47.45 ± 2.17	46.74 ± 1.82	47.04 ± 1.95	1.182	0.311
Weight (kg)	2.89 ± 0.81	2.78 ± 0.72	2.80 ± 0.65	0.225	0.799
Head circumference (cm)	32.07 ± 1.27	31.98 ± 1.57	32.21 ± 1.70	0.204	0.816
N/A, no neurological assessment for the reference group at baseline (T0)					

Delta Change (t1-t0)

After a 30-day EI, the EI-SC group had more significant delta change than SC-EI group in TIMP, and physical growth (weight, length, and HC) ($p < 0.05$). However, no difference in general and individual subdomain DQ was noted between groups ($p > 0.05$) (Table 2).

Table 2
Increment of neurodevelopment score and physical growth between T1 and T0

	EI-SC group (n = 34)	SC-EI group (n = 31)	<i>F</i>	<i>p</i>
TIMP score	30.12 ± 8.85	25.35 ± 8.4	5.059	0.028
DQ total score	4.08 ± 1.34	3.77 ± 1.03	1.023	0.316
Gross motor	5.29 ± 2.20	4.42 ± 2.87	1.923	0.170
Fine motor	1.88 ± 0.81	2.13 ± 1.73	0.560	0.457
Adaptiveness	3.62 ± 2.40	2.71 ± 1.85	2.880	0.095
Social	4.29 ± 3.25	5.45 ± 3.73	1.785	0.186
Language	5.29 ± 3.85	4.16 ± 1.92	2.180	0.145
Physical growth				
Length (cm)	7.07 ± 1.93	6.01 ± 1.84	5.069	0.028
Weight (kg)	1.49 ± 0.63	1.21 ± 0.46	4.095	0.047
Head circumference (cm)	3.92 ± 1.10	3.31 ± 1.16	4.705	0.034

Delta Change (t2-t0)

In terms of delta change from T2 to T0, there was no significant difference in all outcomes between the EI-SC group and SC-EI group ($p > 0.05$). However, the marginal difference was noted regarding the language development and weight increment, with a p-value of 0.085, and 0.065, respectively (Table 3).

Table 3
Increment of neurodevelopment score and physical growth between T2 and T0

	EI-SC group (n = 28)	SC-EI group (n = 29)	F	p
TIMP score	60.96 ± 9.92	58.10 ± 8.98	1.304	0.258
DQ total score	8.26 ± 1.05	7.92 ± 1.84 s	0.725	0.398
Gross motor	11.39 ± 4.48	9.52 ± 4.99	2.227	0.141
Fine motor	5.14 ± 2.17	5.83 ± 2.89	1.016	0.318
Adaptiveness	7.07 ± 3.69	7.10 ± 3.60	0.001	0.974
Social	8.82 ± 5.14	10.28 ± 6.41	0.890	0.350
Language	8.86 ± 4.93	6.86 ± 3.55	3.085	0.085
Physical growth				
Length (cm)	12.68 ± 1.93	12.00 ± 1.87	1.807	0.184
Weight (kg)	2.80 ± 0.51	2.54 ± 0.52	3.533	0.065
Head circumference (cm)	7.99 ± 1.21	7.55 ± 1.30	1.689	0.199

Assessment At The Endpoint Of T2

At the endpoint of T2, the EI-SC and SC-EI group had similar TIMP, and anthropometric measures, which were significantly higher than that of the reference group by the Bonferroni test. In terms of general and subdomain DQ, no difference was noted among the three groups ($p > 0.05$) (Table 4).

Table 4
Comparison of the outcomes at T2 assessment

	El-SC group (n = 28)	SC-El group (n = 29)	Reference group (n = 33)	<i>F</i> or χ^2	<i>p</i>
TIMP score	113.54 ± 12.05 ^a	109.33 ± 11.005 ^a	101.18 ± 12.98 ^b	8.332	0.001
DQ total score	90.56 ± 6.14	87.08 ± 10.34	85.06 ± 7.14	1.538	0.130
Gross motor	94.50 ± 16.50	89.00 ± 17.71	84.94 ± 14.16	2.675	0.075
Fine motor	90.36 ± 21.88	83.10 ± 21.54	81.55 ± 15.63	1.673	0.194
Adaptiveness	89.04 ± 19.13	90.55 ± 30.54	88.45 ± 21.00	0.062	0.940
Social	88.57 ± 22.56	88.31 ± 18.73	85.70 ± 25.86	0.153	0.858
Language	90.57 ± 16.62	84.66 ± 13.74	84.67 ± 10.50	1.772	0.176
Physical growth					
Length (cm)	59.83 ± 2.77 ^a	58.61 ± 2.61 ^a	56.53 ± 2.45 ^b	12.614	0.001
Weight (kg)	5.56 ± 0.92 ^a	5.24 ± 0.95 ^a	4.74 ± 0.99 ^b	5.547	0.005
Head circumference (cm)	38.91 ± 2.15 ^a	39.38 ± 1.93 ^a	38.20 ± 2.15 ^b	5.492	0.006
^{a, b} denotes the significant difference by the Bonferroni test					

Discussions

EI means the intervention should be carried out as soon as possible, commonly started within the first 12 months of life. Post-discharge EI has been widely performed in the follow-up clinics or at a community-based setting, which imposes high costs for the health care system. Taking Massachusetts, United States, as an example, the mean cost per infant for EI was 6 614 dollars among the infants born at 24–31 weeks' gestation, with a total EI cost of 65 910 379 dollars for all infants between 2009 and 2012(14). Such a huge number implied that the EI program might not be affordable in all countries, even in some developed countries. Meanwhile, some factors, such as traffic barriers, household overwork, and expensive accommodation cost, also limit the parents to access the EI programs. Therefore, exploring a low-cost, family-based, flexible EI program was urgent for the medical providers and some families in need.

Amid this background, Sgandurra et al. developed a new technological smart modular system as a tele-rehabilitation tool for EI, which could be implemented by parents at home under the orientation of rehabilitation staff. They demonstrated that this home-based EI significantly improved infant motor and

visual development(15). However, drawbacks also was evident; the occurrence of technique errors seemed unavoidable for an internet-based system, and getting acquainted with a new system was also a challenge for some parents (16). In this study, we conducted an innovative approach to carry out the home-based EI program, which was independent of any technological equipment, and was free of knowledge gap for parents to perform it. Our study demonstrated that this EI program could promote motor development of EPI, as well as physical growth.

TIMP is the primary outcome measure in this study. Our results of RCT period (T1-T0) showed the delta change of TIMP in EI-SC group was significantly higher than in SC-EI group, which was consistent with Sgandurra's study(15); however, it conflicted to many previous studies, which did not show any significant effect of EI on motor development(4, 6, 17). Some factors might contribute to the discrepancy. The frequency of EI performed in this study is once daily over four weeks, much higher than other studies which mostly ranged from once weekly to twice weekly(4). Sgandurra et al. demonstrated that amount of EI performance could affect the improvement of motor development (15). Meanwhile, our program added some good evidence-based interventions to the basic intervention, including body massage and kangaroo care. Body massage has been shown to effectively enhance motor development in various children population, including infants(18, 19). The effect of kangaroo care on infant development was also well confirmed(20). Massage and kangaroo care superimposed on basic intervention might generate a synergistic effect. Besides, distinct assessment tools might also lead to the different results. Most previous studies used the Bayley physical development index (BPDI) to assess motor development, whereas our study used the TIMP instead. TIMP was approved to be a reliable and valid measurement of motor development, showing a highly significant correlation with BPDI(21); TIMP is suitable for assessing infants < 6 months, while six months is the lower age limit for BPDI. Some studies indicated that the effect of EI on motor development was significant in infancy, but was not noted in the long term. Therefore, a positive result in this study might be partially due to a relatively earlier assessment.

RCT did not show any significant difference in the DQ score between EI-SC group and SC-EI group. Improvement of motor development demonstrated by TIMP was not present during DQ assessment, which may be attributed to the structural limitation of the DQ tool. Each subdomain of DQ only has one or two items under each month, scored as "observed" or "unobserved"; some minor changes cannot be specified. Meanwhile, DQ might delay identifying some subtle improvement, even some of which have already been noted by the parents(22). In terms of physical growth, this EI program generally promoted the growth of weight, length, and HC, which was considered the results of a combination of many factors. Body massage has been shown to have the potential to improve gastrointestinal function, and ultimately increase physical growth(23). Literature also indicated that Kangaroo care could shape preterm infant sleep behavior and prolong the duration of deep sleep(24); a longer duration of deep sleep is a good predictor of optimal physical growth(25). The integrated EI program also could improve infant feeding behavior, increase feeding volume, and positively affect physical growth(26, 27).

We conducted the open phase after the RCT, creditable from the consideration of ethics. No difference was noted between the EI-SC and SC-EI group regarding delta change (T2-T0) in all outcomes, which gave

rise to the inference that the 60-day delayed EI had a similar effect with the EI at the beginning. Assessment at T2 endpoint also confirmed that no difference in TIMP and physical growth measures existed between the EI-SC and SC-EI group, but both were much higher than the reference group. It was an encouraging result for some parents who are concerned about the effect of the delayed intervention for their infants due to a variety of causes. However, currently, to carry out an EI program as soon as possible is still recommended.

Our study had certain limitations. We did not perform a long-term follow-up, hampering the evaluation of the long-term effect of this EI program. Meanwhile, the parent's performance should alert the effectiveness of the EI program. It was impossible to keep all parent's performance identical in this study. Fortunately, during the teaching session, our researchers should ensure that every parent had the basic skills to perform EI. In this study, we also cannot completely rule out the situation that some parents performed additional EI than the study protocol; even the parents have initially signed the consent to comply with the study protocol.

Conclusions

This study introduced a home-based, post-discharge EI program, which was less-cost, particularly suitable in medical source-limited regions. This EI program could significantly promote motor development and physical growth of EPI, at least in a short-term period. However, there is still a need to perform long-term follow-up to identify the long-term effect of this program on infant development.

Abbreviations

EPI: early preterm infants; EI: early intervention; RCT: randomized controlled trial; EI-SC group: first early intervention, then standard care group; SC-EI: first standard care, then early intervention group. HC: head circumference; TIMP: test of infant motor performance; DQ: development quotient; BPD: Bayley physical development index

Declarations

Ethics approval and consent to participate

Subjects were enrolled in the study after written informed consent obtained from their parents. This study was approved by the Institutional Review Board of Children's Hospital of Chongqing Medical University (No.2019-216).

Consent for publication

A written consent for publication has obtained from the parents of the infant shown in our supplementary video.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JF and JHW contributed to study conceptualization, data acquisition and data analysis, drafting the initial manuscript, and revising the manuscript before submission. JHW and XG contributed to the data acquisition, and writing the initial manuscript. XHZ, RYH and SSH contributed to data analysis, and revising the manuscript. MY, YJS and XJT contributed to data analysis, compiling tables and figures. LJH contributed to study conceptualization and design, data analysis, reviewing and revising the manuscript. All authors made substantial contributions to the conduct of the study and approved the final manuscript as submitted.

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Figures