Randomized Trial of Early Developmental Intervention on Outcomes in Children after Birth Asphyxia in Developing Countries

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Objective To determine if early developmental intervention (EDI) improves developmental abilities in resuscitated children.

Study design This was a parallel group, randomized controlled trial of infants unresponsive to stimulation who received bag and mask ventilation as part of their resuscitation at birth and infants who did not require any resuscitation born in rural communities in India, Pakistan, and Zambia. Intervention infants received a parent-implemented EDI delivered with home visits by parent trainers every other week for 3 years starting the first month after birth. Parents in both intervention and control groups received health and safety counseling during home visits on the same schedule. The main outcome measure was the Mental Development Index (MDI) of the Bayley Scales of Infant Development, 2nd edition, assessed at 36 months by evaluators unaware of treatment group and resuscitation history.

Results MDI was higher in the EDI (102.6 ± 9.8) compared with the control resuscitated children (98.0 ± 14.6, 1-sided P = .0202), but there was no difference between groups in the nonresuscitated children (100.1 ± 10.7 vs 97.7 ± 10.4, P = .1392). The Psychomotor Development Index was higher in the EDI group for both the resuscitated (P = .0430) and nonresuscitated children (P = .0164).

Conclusions This trial of home-based, parent provided EDI in children resuscitated at birth provides evidence of treatment benefits on cognitive and psychomotor outcomes. MDI and Psychomotor Development Index scores of both nonresuscitated and resuscitated infants were within normal range, independent of early intervention. *(J Pediatr 2013;162:705-12)*.

Failure to initiate or sustain spontaneous breathing at birth, also called birth asphyxia,[1] is a leading cause of perinatal mortality, neonatal encephalopathy, intellectual disability, cerebral palsy, and other childhood neurodevelopmental disorders,[2,3] particularly in low- and middle-income countries (LMIC).[4] Birth asphyxia accounts for about 23% of the 3.5 million neonatal deaths that occur each year worldwide, 98% of which occur in LMIC.[5] About 30% of infants who survived following birth asphyxia in LMIC had abnormal neurologic examinations at 2 months, accounting for 50% of the infants referred for an abnormal neurologic examination at this age.[4] An estimated 1 million children who survive birth asphyxia each year develop problems such as learning difficulties, cerebral palsy, and other disabilities.[6] Birth asphyxia is estimated to result in a loss of over 41 million disability adjusted life years, one of the leading causes for all ages worldwide.[7] Mortality and morbidity from birth asphyxia disproportionately affect more infants in LMIC.

About 6%-10% of all infants fail to initiate or sustain spontaneous breathing at birth and need some assistance to establish normal breathing.[8,9] Resuscitation at birth decreases fresh stillbirths[10] and early neonatal mortality.[9,11,12] Although

ASQ	Ages and Stages Questionnaire, 2nd edition
ASQ:SE	Ages and Stages Questionnaire: Social-Emotional
BSID-II	Bayley Scales of Infant Development, 2nd edition
BSID-III	Bayley Scales of Infant Development, 3rd edition
EDI	Early developmental intervention
LMIC	Low- and middle-income countries
MDI	Mental Development Index
PDI	Psychomotor Development Index
WHO	World Health Organization

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neonatal resuscitation training programs for perinatal health care providers are standard in high- income countries, these programs have had limited penetration in many LMIC, in part because of the concern of saving infants at risk for neurodevelopmental disorders.

It has been estimated that more than 200 of the approximately 700 million children under 5 years of age fail to reach their potential for cognitive development.[13] Programs of early developmental intervention (EDI) use structured experiences in an attempt to prevent or limit impaired cognitive function early in life. Positive effects of EDI have been demonstrated in numerous controlled trials,[14-16] but few studies have been conducted in infants with birth asphyxia and in LMIC. Although modifiable biologic and psychosocial risk factors and possible interventions have been determined,[17] a panel of international experts recommended trials to determine effective and scalable parental EDI strategies with larger and more diverse patient populations using strategies of outreach to disadvantaged children.[16] Furthermore, the most effective EDI programs appear to be those that provide direct learning experiences to children and families, are targeted toward younger and disadvantaged children, are of longer duration, high quality, and high intensity, and are integrated with family support and health and nutrition counseling,[16] but there is no consensus on whether or not EDI programs should be recommended for these patients in LMIC.

Methods

The current trial, the Brain Research to Ameliorate Impaired Neurodevelopment: Home-based Intervention Trial (registered at ClinicalTrials.gov: NCT00639184), was designed to test the primary hypothesis that a well designed[16] home-based, parent-implemented early intervention program improves cognitive abilities as indicated by a higher Mental Developmental Index (MDI) at 36 months on the Bayley Scales of Infant Development, 2nd edition (BSID-II) among a group of infants who received bag and mask ventilation as part of their resuscitation but did not have severe encephalopathy during the neonatal period compared with a control group. To enable comparison, a group of infants from the same communities who did not require resuscitation at birth were also randomized concurrently to the same intervention or control home visits.

This parallel design randomized controlled trial was implemented in 2 populations: (1) infants with birth asphyxia unresponsive to stimulation and the initial steps of resuscitation who received bag and mask ventilation; and (2) infants who did not require any resuscitation. Infants in each cohort were randomized individually to 1 of 2 trial conditions (EDI plus health and safety counseling or control that included health and safety counseling only) using 1:1 concealed parallel allocation, matched for country and chronological time using variable block sizes to assure allocation concealment (**Figure**; available at www.jpeds.com). There were no changes in trial design or outcome measures following commencement of enrollment other than home visits were continued every other week between 12 and 36 months of age instead of the planned every fourth week visits to increase the intensity of the intervention. The trial was approved by the institutional review boards at the University of Alabama at Birmingham, Research Triangle Institute International, and each participating clinical site. Details on the trial design have been published.[18]

Infants who received bag and mask ventilation for resuscitation at birth, in rural, poor communities in 3 sites in India, Pakistan, and Zambia during and immediately following the First Breath Trial[10] were screened for enrollment into this trial. Birth asphyxia was defined as the inability to initiate or sustain spontaneous breathing at birth using the World Health Organization (WHO) definition.[1] Infants were ineligible if they met any of the following exclusion criteria: (1) the birth weight was less than 1500 g at birth; (2) their neurologic examination at 7 days was severely abnormal (grade III by Ellis classification)[19]; (3) the mother was <15 years of age or unable/unwilling to participate; or (4) the mother was not planning to stay in the study communities for the following 3 years. Infants with birth asphyxia (resuscitated) and infants without birth asphyxia or other perinatal complications (nonresuscitated) matched for country and chronological time born from January 2007 through June 2008 were randomly selected during the 7-day follow-up visit after birth from infants enrolled in the First Breath Trial.[10] A list of potential enrollees was distributed to the investigators in each country to obtain consent for the trial. Written informed consent was obtained during the second week after birth following the 7-day neurologic assessment and before randomization.

Intervention Procedures

A home-based, parent-implemented EDI model was selected to strengthen parent-child interaction. The *Partners for Learning*[20] curriculum and supplemental materials were used by parent trainers to introduce playful interactive learning activities depicted on cards given and modeled to the parents during home visits using the Portage Model.[21] *Partners for Learning* covers a full spectrum of competences, organized into the 4 areas: (1) cognitive and fine motor; (2) social and self-help; (3) gross motor; and (4) language skills. Investigators at each research site selected EDI parent trainers (high school graduates in 2 sites and 4-year graduates after high school in 1 site) who were trained in an initial 5-day workshop at each research site. A second workshop was conducted before participating children began to reach 18 months of age to adapt the approach to children up to 36 months. Each parent-child pair was assigned to the same trainer throughout the trial whenever possible. Home visits were conducted every other week from enrollment (at 1-2 weeks) through 36 months. During each visit, the trainer presented 1 or 2 playful interactive learning activities using cards. Each activity targeted a developmentally appropriate competence. The parent practiced the activity in the presence of the trainer who provided feedback to the parents. The activity cards were left with the parents who were encouraged to apply the targeted