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Developmental trajectories of children with birth asphyxia through 36 months of age in low/low–middle income countries

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ABSTRACT

Background: Resuscitation following birth asphyxia reduces mortality, but may be argued to increase risk for neurodevelopmental disability in survivors.

Aims: To test the hypothesis that development of infants who received resuscitation following birth asphyxia is not significantly different through 36 months of age from infants who had healthy births.

Study design: Prospective observational cohort design comparing infants exposed to birth asphyxia with resuscitation or healthy birth.

Subjects: A random sample of infants with birth asphyxia who received bag-and-mask resuscitation was selected from birth records in selected communities in 3 countries. Exclusion criteria: birth weight < 1500 g, severely abnormal neurological examination at 7 days, mother < 15 years, unable to participate, or not expected to remain in the target area. A random sample of healthy-birth infants (no resuscitation, normal neurological exam) was also selected. Eligible = 438, consented = 407, and ≥ 1 valid developmental assessment during the first 36 months = 376.

Outcome measure(s): Bayley Scales of Infant Development-II Mental (MDI) and Psychomotor (PDI) Development Index.

Results: Trajectories of MDI ($p = .069$) and PDI ($p = .143$) over 3 yearly assessments did not differ between children with birth asphyxia and healthy-birth children. Rather there was a trend for birth asphyxia children to improve more than healthy-birth children.

Conclusions: The large majority of infants who are treated with resuscitation and survived birth asphyxia can be expected to evidence normal development at least until age 3. The risk for neurodevelopmental disability should not justify the restriction of effective therapies for birth asphyxia.

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1. Introduction

Of the approximately one million neonatal deaths due to birth asphyxia, or failure to initiate or sustain spontaneous breathing at birth, about 98% occur in low/low–middle income countries (LMIC) [1]. Another one million children who survive birth asphyxia develop neurodevelopmental disorders, which can include learning disability, intellectual disability, and cerebral palsy [2–4]. As a result, 41 million disability adjusted life years (DALYs) are attributed to birth asphyxia

[5]. Birth asphyxia is therefore among the leading causes of mortality and morbidity in LMIC.

Resuscitation is required to establish normal breathing when asphyxia occurs at birth. About 6–10% of all neonates need some assistance to establish normal breathing [6–8]. Neonatal resuscitation could decrease neonatal mortality or morbidity an estimated 42% in LMIC [9]. If indicated, resuscitation can be applied to almost all newborn infants, including in poor areas of the world, with stimulation and bag and mask ventilation [10,11]. However, neonatal resuscitation training has had limited penetration in many LMIC despite findings that when implemented mortality decreases by 20%–50% [7,12,13].

The concern that infants with birth asphyxia who were resuscitated may be at increased risk for neurodevelopmental impairments may

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contribute to the reduced implementation of resuscitation interventions [4]. Survivors with disability would add to the burden of care in resource poor countries and decrease quality of life of these children in subsequent years. Therefore it is important empirically to examine the development of children with birth asphyxia who were treated with resuscitation in LMIC. Results could inform health policy decisions regarding neonatal interventions for birth asphyxia.

We had the opportunity to conduct such an examination using data collected from a multi-national controlled study (FIRST BREATH Trial) in which community birth attendants were trained in bag and mask ventilation with room air as part of essential newborn care training [14]. This intervention reduced 7-day neonatal mortality as well as mortality due to birth asphyxia [15]. Two subgroups of infants from the FIRST BREATH Trial were then followed as part of the randomized controlled trial (RCT) Brain Research to Ameliorate Impaired Neurodevelopment-Home-based Intervention Trial (BRAIN-HIT), including one group with birth asphyxia who required resuscitation and another group without birth asphyxia and resuscitation. As detailed elsewhere [16,17], BRAIN-HIT was designed to determine if a home-based early developmental intervention (EDI) can improve neurodevelopmental outcome compared to a control condition. Indeed, EDI was shown to improve

development at 36 months of age compared to the control condition in both resuscitated and not resuscitated children [16].

In the present study we do not evaluate the RCT. Rather we observe the development of infants exposed to birth asphyxia and resuscitation compared to infants without birth asphyxia and resuscitation, regardless of assigned intervention condition. Moreover, because developmental status was evaluated yearly through 36 months of age, developmental trajectories could be examined in relation to exposure to birth asphyxia and resuscitation, and not just status at the 36 month end point. The current study tests the hypothesis that infants who received resuscitation due to birth asphyxia (without severe encephalopathy during the neonatal period) and those who had healthy births and were not resuscitated would evidence developmental trajectories over the first 36 months that are *not* significantly different from one another.

2. Methods

2.1. Study population

This study was implemented in two populations born from January 2007 through June 2008 in rural communities marked by poverty in

Fig. 1. Participant flow chart of screening, randomization, and completion of developmental assessments, resulting in analysis sample.

defined regions in India, Pakistan, and Zambia that were enrolled in the BRAIN-HIT [17]:

2.1.1. Resuscitated

Infants with birth asphyxia unresponsive to stimulation who received bag and mask ventilation for resuscitation at birth from the FIRST BREATH Trial [14] were randomly selected during the 7-day follow-up visit after birth. Birth asphyxia was defined as the inability to initiate or sustain spontaneous breathing at birth using the WHO definition [18] (biochemical evidence of birth asphyxia could not be obtained in these settings). Infants were excluded if: (a) birth weight <1500 g, (b) neurological examination at seven days was severely abnormal (grade III by Ellis classification [19]), (c) mother <15 years of age or unable to participate, or (d) mother was not planning to stay in the community for the following three years. A total of three infants were excluded due to (a) and/or (b). No follow-up data could be collected on those who were excluded because they were not consented into this research.

2.1.2. Not resuscitated

Infants who did not require any resuscitation and had normal neurological exams at seven days of age were matched for country and chronological time and randomly selected for enrollment from the same settings as the resuscitated children.

A list of potential enrollees was distributed to the investigators in each country to invite for participation. Written consent was obtained during the second week after birth following the seven day neurological assessment and before randomization to intervention conditions of the BRAIN-HIT.

2.2. Design

The effects of exposure to birth asphyxia and resuscitation were prospectively observed during the first 36 months in infants enrolled in BRAIN-HIT. Details of BRAIN-HIT have been registered (clinicaltrials.gov ID# NCT00639184) and described elsewhere [16,17]. Resuscitated and not resuscitated infants were randomized individually to receive either EDI or a control intervention using variable block sizes to assure allocation concealment (see Fig. 1). Both intervention conditions were delivered in home visits scheduled every two weeks. The EDI was designed to enhance parent–child interactions using activities that encourage or improve early childhood development. Parent trainers followed a curriculum [20] covering a spectrum of developmental competences to introduce playful interactive learning activities to the parent. Whereas parents in both the EDI and control conditions received health education during every home visit, according to a WHO curriculum [21], this was the sole content of the control intervention. Both conditions are elaborated in Appendix 1 and elsewhere [16,17].

There was one change from the original trial design, when implementation of the interventions via home visits was continued bi-weekly between 12 and 36 months of age instead of every four weeks to increase the intensity of the intervention. The trial was approved by the institutional review boards at each research site. The RCT conditions were:

2.3. Developmental outcome measures

The primary outcome measure was the *Bayley Scales of Infant Development-II* (BSID) [22], which has been used in a number of LMIC. The BSID Mental (MDI) and Psychomotor (PDI) Development Index items were administered directly to each child in the appropriate language using standard and culturally appropriate material. Assessments occurred at ages 12, 24, and 36 months, or as close as possible. The evaluators, who were familiar with local language and culture, were trained in 4-day workshops before each yearly round of evaluations. They

were blinded to the children's resuscitation history and intervention condition.

Ages and Stages Questionnaire, 2nd edition (ASQ) [23] was used to assess parent-reported child development observed in the home environment at each yearly evaluation. The ASQ has been widely used to assess early development, including in numerous LMIC [24,25]. It consists of 30-items addressing communication, gross motor, fine motor, problem solving, and personal-social development using age-specific forms. To reduce the impact of variation in literacy, ASQ was administered in an interview with the parent, who was instructed to report on the child's behavior observed in the home or community. The Total score was used as secondary measure of development.

2.4. Child and maternal characteristics

Pre- and perinatal health variables were obtained from FIRST BREATH Trial [14] records regarding resuscitation (yes vs. no), gestational age (pre-term vs. term), and gender. Information on maternal and family demographics and resources were collected at enrollment in the trial. Of relevance here were: maternal age (25+ vs. ≤24) and education (illiterate vs. literate vs. university). A full range of child, maternal, and family characteristics have been presented elsewhere [16].

2.5. Statistical analysis

Basic characteristics were compared between the resuscitated and not resuscitated samples using Chi-square tests. The main hypothesis was addressed by comparing trajectories of the developmental measures (MDI, PDI, and ASQ) across the three yearly assessments between resuscitated and not resuscitated groups using linear mixed effect models with SAS PROC MIXED to account for repeated measurements over time. This analysis uses restricted maximum likelihood estimates that can include all cases with the developmental measurement on at least one occasion and are not missing data on the covariates. Mixed effect models will produce unbiased estimates if the data are missing at random. Because children's exact ages varied at the time of the assessments (i.e., some children may not have been exactly 12 months old at the planned 12-month assessment), actual age was included as a continuous variable in the models.

Table 1
Characteristics of study sample by resuscitation status.

Characteristic	All N (%)	Resuscitated N (%)	Not resuscitated N (%)	p
N	376	155	221	
Intervention condition				
EDI	185 (49)	74 (48)	111 (50)	0.635
Control	191 (51)	81 (52)	110 (50)	
Site				
A	94 (25)	35 (23)	59 (27)	0.007
B	123 (33)	40 (26)	83 (38)	
C	159 (42)	80 (52)	79 (36)	
Child gender				
Male	218 (59)	93 (61)	125 (58)	0.524
Female	150 (41)	59 (39)	91 (42)	
Gestational age				
Term	260 (70)	105 (68)	155 (71)	0.501
Pre-term	111 (30)	49 (32)	62 (29)	
Marital status				
Married	359 (95)	149 (96)	210 (95)	0.611
Not married	17 (5)	6 (4)	11 (5)	
Maternal age				
25+	196 (52)	63 (41)	117 (53)	0.019
≤24	180 (48)	92 (59)	104 (47)	
Maternal education				
Illiterate	172 (48)	64 (43)	108 (52)	0.116
Literate/university	185 (52)	84 (57)	101 (48)	

EDI = early developmental intervention.

Table 2
Developmental outcome scores by assessment age.

Assessment	12-Month	24-Month	36-Month	12- vs. 24-month	12- vs. 36-month	24- vs. 36-month
	Mean (SD)	Mean (SD)	Mean (SD)	t-test p	t-test p	t-test p
BSID-MDI	96.36 (15.35)	96.22 (15.23)	99.49 (11.55)	0.344	<0.001	<0.001
BSID-PDI	95.54 (20.25)	95.31 (15.74)	103.87 (16.01)	0.618	<0.001	<0.001
ASQ total score	241.91 (56.90)	230.87 (49.55)	244.83 (52.68)	<0.001	0.406	<0.001

Note: SD = standard deviation, BSID = Bayley Scales of Infant Development, MDI = Mental Development Index, PDI=Psychomotor Development Index, ASQ = Ages & Stages Questionnaire.

Each model included resuscitation status, age, trial condition, gestational age group, maternal resources (age, education), child gender, and country (designated A, B, and C here), as well as two interactions. Of particular interest was the interaction between age and resuscitation status, which tests the stated hypothesis that trajectories of developmental outcomes over time will not differ significantly between the resuscitated and not resuscitated groups. In addition, an age by site interaction term was included to account for site-level differences. By including the additional variables beyond resuscitation status, age and their interaction in the models, the study hypothesis is tested while controlling for the covariation of these other variables with developmental outcome, including the trial condition.

3. Results

3.1. Sample constitution

As shown in the flow diagram (Fig. 1), of 540 infants screened 438 were eligible (81%); 102 infants were excluded because 82 mothers reported they were not staying in the communities, 17 mothers were unable to be contacted within 7 days of birth, and 3 infants were less than 1500 g. Consent was obtained for 407 infants (93% of eligible) who were randomized into trial conditions. A valid developmental

assessment on at least one of the yearly assessments was obtained from 376 (92.4% of enrolled), which constitute the analysis sample.

As shown in Table 1, infants with younger mothers (≤ 24 years) were significantly more likely to have been resuscitated than those with older mothers (25+ years) (35% vs. 47%). In addition, one site (C) had higher enrollment of resuscitated infants than the other two.

3.2. Developmental trajectories

Table 2 presents the crude means for the developmental outcome scores at each assessment age. Table 3 presents effects on trajectories of development over time. The age by resuscitation status interaction effect on MDI was not significant at $p < 0.05$, as shown in Fig. 2 (top panel). Rather there is a general trend where resuscitated children had a greater increase in MDI over time than those who were not resuscitated ($p = 0.069$). Whereas resuscitated children had lower scores at 12 months, they experienced greater improvements in scores between 12 and 36 months (Fig. 2). Trajectories varied significantly by site (age $\times$ site interaction: $F(2532) = 18.17$, $p < 0.001$). Children at Site A had significantly greater increases in scores over time than those in Site C ($p < 0.001$).

As shown in Fig. 2 (middle panel), standardized PDI improved over time ($p = 0.003$). Whereas there was general trend for resuscitated children to experience a greater increase in PDI than those who were

Table 3
Mixed effects models of developmental outcomes by resuscitation status and demographics.

Variable	BSID-MDI		BSID-PDI		ASQ total score	
	Adjusted mean difference (SE)	p	Adjusted mean difference (SE)	p	Adjusted mean difference (SE)	p
Age-corrected (months)	−0.06 (0.07)	0.401	0.30 (0.10)	0.003	−1.46 (0.26)	<0.001
Resuscitation status						
Resuscitated	−3.68 (2.37)	0.122	−2.33 (3.16)	0.460	0.73 (8.49)	0.932
Not resuscitated	REF		REF		REF	
Age $\times$ resuscitation	0.13 (0.07)	0.069	0.14 (0.10)	0.143	0.08 (0.27)	0.759
Intervention condition						
EDI	1.65 (1.19)	0.167	2.48 (1.45)	0.087	4.57 (4.72)	0.334
Control	REF		REF		REF	
Site						
A	−23.03 (2.96)	<0.001	−4.16 (3.92)	0.289	−60.90 (10.74)	<0.001
B	−8.31 (3.03)	0.006	−12.27 (3.97)	0.002	−82.32 (11.15)	<0.001
C	REF		REF		REF	
Age $\times$ site						
Age: A	0.51 (0.09)	<0.001	−0.03 (0.12)	0.824	1.59 (0.33)	<0.001
Age: B	0.11 (0.09)	0.181	0.07 (0.12)	0.549	2.69 (0.32)	<0.001
Age: C	REF		REF		REF	
Gender						
Male	0.82 (1.22)	0.499	2.15 (1.48)	0.147	−0.46 (4.80)	0.923
Female	REF		REF		REF	
Gestational age						
Term	0.23 (1.33)	0.863	−0.45 (1.62)	0.779	1.93 (5.32)	0.717
Pre-Term	REF		REF		REF	
Maternal age						
25+	0.41 (1.32)	0.756	1.33 (1.60)	0.406	4.66 (5.19)	0.370
≤ 24	REF		REF		REF	
Maternal education						
Illiterate	−1.87 (1.75)	0.284	0.25 (2.13)	0.906	−2.66 (6.97)	0.703
Literate/university	REF		REF		REF	

Note: BSID = Bayley Scales of Infant Development, MDI = Mental Development Index, PDI = Psychomotor Development Index, ASQ = Ages & Stages Questionnaire, SE = standard error, EDI = early developmental intervention, REF = reference category. Bold indicates significant effect at $p < .05$. Overall age by site interaction effects by model are: MDI ($F(2532) = 18.17$, $p < 0.001$), PDI ($F(2532) = 0.37$, $p = 0.692$), and ASQ ($F(2502) = 35.97$, $p < 0.001$).

Fig. 2. Model adjusted developmental scores by resuscitation status.

not resuscitated, these trajectories did not differ significantly by resuscitation status ($p = 0.143$) or site ($p = 0.692$). As shown in Fig. 2 (bottom panel), the standardized ASQ also improved significantly over time ($p < 0.001$). There was no significant interaction between age and resuscitation status ($p = 0.759$). Trajectories of ASQ scores varied by site ($p < 0.001$), where Sites A and B indicated greater increases in ASQ scores over time than Site C ($p < 0.001$).

4. Discussion

Consistent with our hypothesis, resuscitated children's development during the first 36 months did not differ significantly from that of children who experienced no major birth complications and were not resuscitated. Rather there was no evidence that resuscitated children were disadvantaged in their development and both groups demonstrated positive development. Furthermore, the positive developmental trend for resuscitated children is evident even when adjusting for the effects on development from gender and gestational age, maternal age and education, site, and intervention condition. It is noteworthy that resuscitated children's development did not differ from that of not resuscitated children regardless whether or not they received EDI, which has been demonstrated to be effective for both groups in BRAIN-HIT [16]. That is, healthy development appears likely for resuscitated children even without EDI.

These findings of no differences between resuscitated and not resuscitated children add to previous findings from this research that resuscitated infants' development at 12 months is not different from that of not resuscitated infants [26] by extending outcome through 36 months of age and examining developmental trajectories over

time. Participants were part of a large international study in which training of birth attendants in neonatal resuscitation and other essential newborn care skills reduced stillbirths and perinatal mortality [14]. In a separate large multicenter study in one LMIC training midwives with the same program reduced neonatal and perinatal mortality [15]. Collectively these findings point to the fact that training birth attendants in resuscitation cannot only reduce mortality, but also lead the majority of survivors to demonstrate an outcome through three years after birth that is undifferentiated from that of infants who did not need resuscitation at birth.

One limitation with this study was that, despite the appearance of differences in developmental trajectories favoring resuscitated children over those not resuscitated (see Fig. 2), it was under-powered to detect any such differences. This study was not designed to test whether development would be similar between resuscitated and not resuscitated children. Results may not be generalizable to other LMIC or to other types of EDI programs. Also, this study excluded infants with severe encephalopathy because of the expectation that they would not survive or would not benefit from EDI. In actuality, only three neonates were excluded due to a severely abnormal neurological examination. Finally, as this study ended at age 36 months, it is unknown whether resuscitated children will have problems that will manifest later in life [27,28].

Thus developmental trajectories in infants who survived following birth asphyxia do not differ from those of infants who were healthy at birth. The surviving infants likely would have died if they did not get resuscitation at birth. Interventions aimed at achieving the childhood Millennium Development Goals are intended to reduce perinatal mortality, which results in survival of children at risk for neurodevelopmental impairment. However, our findings show that the overwhelming majority of birth asphyxia survivors will have normal developmental trajectories at least until 36 months. Consequently, the increased risk for disability should not be used to justify restriction of effective therapies for birth asphyxia. Rather, survivors should be provided with opportunities to reach their potential [29]. Low cost early developmental intervention programs can serve an important role in enhancing their development [30]. The outcomes reported in the current study should encourage the use of interventions to treat infants with birth asphyxia. Treatment of birth asphyxia is likely to result mostly in children with normal development.

Conflict of interest statement

None declared.

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Appendix 1

Participants were randomly assigned to one of two trial conditions [16,17]:

Early Development Intervention (EDI). A home-based, parent-implemented EDI model was applied to enhance parent-child

interactions using activities that encourage or improve early childhood development. EDI parent trainers were trained in two five-day workshops at each research site, one prior to the start of the intervention and again when participants began to reach 18 months. Parent trainers followed a curriculum [20] covering a spectrum of developmental competences to introduce playful interactive learning activities to the parent during home visits, which were scheduled every two weeks. During each visit, the trainer presented one or two learning activities that targeted developmentally appropriate skills. The parent practiced the activities in the presence of the trainer who provided feedback. Cards depicting the activities were left with the parent, who was encouraged to integrate them into daily life with the child until the next home visit. Supervision of parent trainers was provided during weekly group meetings and home visit observations.

Control intervention. Whereas parents in both conditions received health education during every home visit, this was the sole content of the control intervention. Content was based on a WHO curriculum [21], which included breast feeding, nutrition, hygiene, safety in the home and community, awareness of danger signs, management of diarrhea, and well-child checkups and vaccinations. The health education was provided by both the EDI and control trainers who had participated in a 5-day training conducted separately from the EDI training.

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