Effect of Delayed Cord Clamping on Neurodevelopment at 4 Years of AgeA Randomized Clinical Trial

jamanetwork.com/journals/jamapediatrics/fullarticle/2296145

July 1, 2015

Abstract

Importance Prevention of iron deficiency in infancy may promote neurodevelopment. Delayed umbilical cord clamping (CC) prevents iron deficiency at 4 to 6 months of age, but long-term effects after 12 months of age have not been reported.

Objective To investigate the effects of delayed CC compared with early CC on neurodevelopment at 4 years of age.

Design, Setting, and Participants Follow-up of a randomized clinical trial conducted from April 16, 2008, through May 21, 2010, at a Swedish county hospital. Children who were included in the original study (n = 382) as full-term infants born after a low-risk pregnancy were invited to return for follow-up at 4 years of age. Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) and Movement Assessment Battery for Children (Movement ABC) scores (collected between April 18, 2012, and July 5, 2013) were assessed by a blinded psychologist. Between April 11, 2012, and August 13, 2013, parents recorded their child's development using the Ages and Stages Questionnaire, Third Edition (ASQ) and behavior using the Strengths and Difficulties Questionnaire. All data were analyzed by intention to treat.

Interventions Randomization to delayed CC (≥180 seconds after delivery) or early CC (≤10 seconds after delivery).

Main Outcomes and Measures The main outcome was full-scale IQ as assessed by the WPPSI-III. Secondary objectives were development as assessed by the scales from the WPPSI-III and Movement ABC, development as recorded using the ASQ, and behavior using the Strengths and Difficulties Questionnaire.

Results We assessed 263 children (68.8%). No differences were found in WPPSI-III scores between groups. Delayed CC improved the adjusted mean differences (AMDs) in the ASQ personal-social (AMD, 2.8; 95% CI, 0.8-4.7) and fine-motor (AMD, 2.1; 95% CI, 0.2-4.0) domains and the Strengths and Difficulties Questionnaire prosocial subscale (AMD, 0.5; 95% CI, >0.0-0.9). Fewer children in the delayed-CC group had results below the cutoff in the ASQ fine-motor domain (11.0% vs 3.7%; *P* = .02) and the Movement ABC bicycle-trail task (12.9% vs 3.8%; *P* = .02). Boys who received delayed CC had significantly higher AMDs in the WPPSI-III processing-speed quotient (AMD, 4.2; 95% CI, 0.8-7.6; *P*

= .02), Movement ABC bicycle-trail task (AMD, 0.8; 95% CI, 0.1-1.5; *P* = .03), and fine-motor (AMD, 4.7; 95% CI, 1.0-8.4; *P* = .01) and personal-social (AMD, 4.9; 95% CI, 1.6-8.3; *P* = .004) domains of the ASQ.

Conclusions and Relevance Delayed CC compared with early CC improved scores in the fine-motor and social domains at 4 years of age, especially in boys, indicating that optimizing the time to CC may affect neurodevelopment in a low-risk population of children born in a high-income country.

Trial Registration clinicaltrials.gov Identifier: NCT01581489

Introduction

Iron deficiency is a global health issue among preschool children that is associated with impaired neurodevelopment affecting cognitive, motor, and behavioral abilities.[1,2] High growth velocity combined with limited ability to absorb iron results in markedly reduced iron stores during the first year of life.[3] Iron deficiency affects 5% to 25% of preschool children in high-income countries and up to 100% of young children in low-income countries.[4,5] Iron administration to high-risk groups is associated with improved psychomotor and cognitive development and fewer behavioral symptoms.[6,7]

Delaying umbilical cord clamping (CC) by 2 to 3 minutes after delivery allows fetal blood remaining in the placental circulation to be transfused to the newborn.[8,9] This transfusion can expand the blood volume by 30% to 40% (25-30 mL/kg).[10] After physiologic hemolysis, hemoglobin-bound iron is transferred into iron stores. Consequently, delayed CC is associated with improved iron status at 4 to 6 months of age.[11,12] Delayed CC has the potential to contribute approximately 75 mg of iron, corresponding to more than 3 months' requirement in a 6- to 11-month-old infant.[13] We have previously demonstrated a 90% reduction in iron deficiency at 4 months in healthy full-term infants who received delayed CC with no adverse neonatal effects.[14] However, there is a lack of knowledge regarding the long-term effects and evidence of no harm, causing policy makers to be hesitant to make clear recommendations concerning delayed CC in full-term infants, especially in settings with rich resources.[15]

We hypothesized that delayed CC and the associated reduction of iron deficiency during the first 4 months of life would result in improved neurodevelopment. Therefore, we conducted a follow-up of a randomized clinical trial[14] to assess the long-term effects of delayed CC compared with early CC on neurodevelopment at 4 years of age.

At a Glance

- Iron deficiency is associated with impaired neurodevelopment affecting cognitive, motor, as well as behavioral abilities; delaying umbilical cord clamping for 3 minutes reduces iron deficiency at 4 to 6 months of age.
- In a follow-up of a randomized trial, 263 children (69% of the original study population) were assessed for neurodevelopment at 4 years of age.
- Delayed cord clamping compared with early cord clamping improved scores and reduced the number of children having low scores in fine-motor skills and social domains.
- Boys, who were more prone to iron deficiency, were shown to have the most improved results, especially in fine-motor skills.
- Optimizing the time to cord clamping may affect neurodevelopment in a low-risk population of children born in a high-income country.

Method

Study Design

This study is a follow-up of a randomized clinical trial conducted at the Hospital of Halland from April 16, 2008, through May 21, 2010.[14] Follow-up was conducted at the same location from April 11, 2012, through August 13, 2013. The original trial and the follow-up study were approved by the Regional Ethics Review Board at Lund University (protocols 41/2008 and 23/2012), and written patient consent was obtained from parents separately for the study and follow-up. Both studies were registered with Clinicaltrials.gov (NCT01245296 and NCT01581489). The full study protocol can be found in the trial protocol in Supplement 1.

Randomization and Masking of the Original Trial

Full-term newborns with a gestational age of 37 to 41 weeks were eligible if the mother was healthy, was a nonsmoker, and had an uncomplicated pregnancy with expected vaginal delivery. Randomization assignments (1:1), consisting of delayed (≥180 seconds after delivery) or early (≤10 seconds after delivery) CC, were contained in sealed, numbered, opaque envelopes that were opened by the midwife when delivery was imminent.[14] The mother and the midwife could not be masked, but all staff and researchers involved in the collection or analysis of data were blinded to the allocation group.

Study Participants

All children included in the original study (n = 382) were eligible for the follow-up. An invitation letter for the follow-up study was sent 1 month before the child's fourth birthday.

Procedures

The children were assessed by a psychologist (B.L.) at 48 to 51 months of age. This age was chosen to enable assessment of cognitive function using the older-age band (4-7 years) of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III).[16] This test provides composite scores that represent intellectual functioning in the following verbal and cognitive performance domains: full-scale IQ, verbal IQ, performance IQ, processing-speed quotient, and general language composite. Scores are standardized to a mean (SD) of 100 (15). A subnormal score was defined as a result lower than 85.

Fine-motor skills were assessed by the manual dexterity area from the Movement Assessment Battery for Children, Second Edition (Movement ABC), which includes 3 subtests: time for posting coins into a slot (both hands), time for bead threading, and drawing within a bicycle trail.[17] The reference mean (SD) for each test is 10 (3). A score of less than 7 reflects performance below the 15th percentile and is regarded as an at-risk score. The psychologist also assessed the child's pencil grip and classified findings as mature (static or dynamic tripod) or immature (palmar supinate or digital pronate).[18,19]

Parents reported their child's development using the Ages and Stages Questionnaire, Third Edition (ASQ) 48-month questionnaire, which was translated into Swedish (by permission from Paul H. Brookes Publishing Co).[20] The ASQ contains 5 subdomains: communication, gross motor, fine motor, problem solving, and personal-social, each consisting of 6 items with a maximum score of 60, resulting in a maximum total score of 300 (higher scores indicate more developmental milestones reached). Cutoff scores were created according to the ASQ manual, and scores that were 2 SDs less than the mean score of the respective subdomain were considered subnormal. If questionnaires were not completely answered, scores were adjusted according to the ASQ manual.[20]

Behavior was assessed using the Strengths and Difficulties Questionnaire (SDQ),[21] which is directed at children aged 3 to 4 years. In the SDQ, 25 items in 5 subscales are scored. Four of these subscales—emotional difficulties score, conduct difficulties score, hyperactivity difficulties score, and peer problems score—are added together to form a total difficulties score (based on 20 items; maximum score, 40; higher scores indicate more difficulties). The fifth subscale, the prosocial score, is evaluated separately (5 items; maximum score, 10; higher scores indicate better prosocial behavior). A cutoff score was defined according to the criteria given for borderline and abnormal in the manual, Scoring the Informant-Rated Strengths and Difficulties Questionnaire.[22]

Outcomes

The WPPSI-III full-scale IQ was prespecified as the primary outcome. Prespecified secondary outcomes included the WPPSI-III composite scores (verbal IQ, performance IQ, processing-speed quotient, and general language composite), fine-motor skills (Movement ABC, manual dexterity area and subtests), psychomotor development (ASQ, total and 5 subdomains), and behavior (SDQ, total and subscales). Children's sex and gestational age at birth were prespecified confounders. The child's pencil grip was also recorded.

Statistical Analysis

This study is a follow-up of a randomized clinical trial, and the sample size is considered fixed.

For summary statistics (Table 1), delayed CC was compared with early CC with respect to maternal and newborn data with means and SDs or numbers and percentages, as appropriate. An unpaired 2-tailed *t* test was used for variables with normal distribution, and categorical variables were compared between groups using the Fisher exact test.

For comparison of continuous test scores (WPPSI-III, Movement ABC, and ASQ), the mean difference between delayed CC and early CC was calculated and the *t* test was used for *P* value estimation (Table 2). For ordinal scale variables from the SDQ test scores, the Mann-Whitney test was used.

For adjusted analyses, analysis of covariance was used for test scores from the WPPSI-III, Movement ABC, and ASQ, and ordinal regression analysis was used for scores from the SDQ. Children's sex and parents' level of education were chosen a priori as adjustment variables for known predictors of children's development, and children's age when performing the test was chosen a posteriori because it was significantly correlated with several of the outcome variables.

Test scores were dichotomized for logistic regression analysis (Table 3); unadjusted and adjusted analyses were conducted. Odds ratios (ORs) and 95% CIs were calculated.

To estimate an overall effect of fine-motor function, multivariate analysis of variance (MANOVA) was used. The MANOVA analysis was appropriate, with correlation coefficients for fine-motor outcome variables ranging from 0.2456 to 0.4221. The MANOVA analysis was conducted using the tests that are considered most specific for fine-motor function, including the WPPSI-III processing-speed quotient, Movement ABC manual dexterity, and ASQ fine-motor sections, with randomization as a grouping variable and sex, parents' level of education, and age when performing the test as independent factors.

A subgroup analysis was conducted for sex as prespecified in the protocol. Analysis of covariance and logistic regression were conducted using the designated adjustment variables (eTable 1 and eTable 2 in Supplement 2). $P < .05$ was considered significant for all the above-mentioned tests.

The Statistical Package for Social Sciences (SPSS) for Windows, version 18.0 was used (SPSS Inc), and STATA, version 10.1 (StataCorp LP) was used for MANOVA and logistic regression analysis. All data were analyzed by intention to treat.

Results

Study Patients

The study was conducted between April 18, 2012, and July 5, 2013 (WPPSI-III and Movement ABC). The ASQ and SDQ were completed by parents between April 11, 2012, and August 13, 2013. Data from all 4 tests were acquired from 243 of 382 children (63.6%) and from at least 1 test from 263 children (68.8%) (Figure 1). There was no significant difference in response rates between the delayed- and early-CC groups. Two responses were excluded from the ASQ analysis because they were answered after the defined time frame (51 months after birth). Baseline characteristics of participants in the follow-up did not differ between the 2 groups (Table 1). As previously reported, birth weights were higher in the delayed-CC group as a result of the intervention.[14] At 4 years, there were no group differences in the mean (SD) weight or height measurements, which were 17.3 (2.1) kg and 104 (4) cm in the delayed-CC group (n = 136) vs 17.1 (2.1) kg and 104 (4) cm in the early-CC group (n = 120) ($P = .45$ and $P = .90$, respectively).

Because the attrition rate was higher than expected, background data were compared between participants in the follow-up study and nonparticipants (eTable 3 in Supplement 2). In the participant group, mothers were 1.3 years (95% CI, 0.32.2 years) older, and the infants' mean head circumference at birth was 0.3 cm (95% CI, 0.1-0.6 cm) less than in the nonparticipant group. Other background data did not differ.

Primary Outcome

Full-scale IQ did not differ between the randomization groups for the mean scores (Table 2) or the proportion of children with a subnormal score of less than 85 (Table 3).

Secondary Outcomes

The WPPSI-III composite scores for verbal IQ, performance IQ, processing-speed quotient, and general language composite did not differ between the randomization groups (Tables 2 and 3). The groups did not differ in mean scores for fine-motor skills as assessed by the Movement ABC manual dexterity test (Table 2). However, for the bicycle-trail task, the

proportion of children with a score of less than 7 (ie, at risk) was significantly lower in the delayed-CC group than in the early-CC group (3.8% vs 12.9%; *P* = .02) (Table 3). The proportion of children with an immature pencil grip was significantly lower in the delayed-CC group than in the early-CC group (13.2% vs 25.6%; *P* = .01) (Table 3).

The delayed-CC group had significantly higher scores leading to significant adjusted mean differences (AMDs) in the ASQ personal-social (AMD, 2.8; 95% CI, 0.8-4.7) and fine-motor (AMD, 2.1; 95% CI, 0.2-4.0) domains. In the ASQ fine-motor domain, the proportion of children with a score 2 SDs below the mean was lower in the delayed-CC group (3.7%) than in the early-CC group (11.0%; *P* = .02). After adjusted logistic regression analysis, there were also fewer children with a score 2 SDs below the mean in the ASQ problem-solving domain (adjusted OR, 0.3; 95% CI, 0.1 to <1.0). There were no differences between groups for the total score or the other subdomains (Tables 2 and 3).

The SDQ did not show any differences in the total difficulties scale or in the 4 difficulties subscales between the 2 groups. The delayed-CC group scored higher in the prosocial subscale (median, 9; interquartile range, 8-10) than the early-CC group (median, 8; interquartile range, 7-9; AMD, 0.5; 95% CI, >0.0-0.9; *P* = .05).

To estimate the overall group difference in each outcome measure, MANOVA analysis was conducted using the subtests and subdomains as dependent variables. This analysis demonstrated that the ASQ showed a significant difference between randomization groups (*P* = .02; fit of model, <0.0001) while the WPPSI-III, Movement ABC, and SDQ did not.

A MANOVA analysis that included the tests considered most specific for fine-motor function (WPPSI-III processing-speed quotient, Movement ABC manual dexterity, and ASQ fine motor), with randomization as a grouping variable and sex, parents' level of education, and age when performing the test as independent factors, showed a significant difference between groups (*P* = .02; fit of model, <0.0001).

Effect of Children's Sex and Gestational Age on Outcome

In girls, there were no differences between the groups for any of the assessments. However, boys who received delayed CC had higher mean (SD) scores in several tasks that involved fine-motor function, including the WPPSI-III processing-speed quotient (AMD, 4.2; 95% CI, 0.8-7.6), Movement ABC bicycle-trail task (AMD, 0.8; 95% CI, 0.1-1.5; *P* = .03), and ASQ fine-motor score (AMD, 4.7; 95% CI, 1.0-8.4). Furthermore, the ASQ personal-social score was higher (AMD, 4.9; 95% CI, 1.6-8.3) in the delayed-CC group (eTable 1 in Supplement 2).

An at-risk result in the bicycle-trail task was less prevalent in boys who received delayed CC compared with those who received early CC (3.6% vs 23.1%; *P* = .008); findings were similar in the ASQ fine-motor domain (8.9% vs 23.6%; *P* = .03). A similar trend was

present for the number of boys who had a score of less than 85 on the WPPSI-III processing-speed quotient (2.0% vs 12.5%; *P* = .06) (Figure 2 and eTable 3 in Supplement 2). The MANOVA of the tests that were considered most specific for fine-motor function showed a significant interaction term for randomization by sex, indicating that the effect of randomization depends on sex (*P* = .005) and showing a highly significant difference between groups among boys (*P* = .008; fit of model, 0.0033) but not among girls (*P* = .80; fit of model, 0.3706). There was no significant interaction between gestational age at birth and the intervention on any of the outcomes.

Discussion

Our results indicate that delaying CC for 3 or more minutes after delivery is associated with better fine-motor function in 4-year-old children. However, in this pronounced low-risk population, delayed CC did not have any effect on full-scale IQ or behavior difficulties. For the whole study population, delayed CC was associated with a significantly higher proportion of children with a mature pencil grip and with higher scores for the ASQ personal-social and fine-motor domains as well as for the SDQ prosocial scale. When the proportions of children with subnormal performance on the various tasks were compared, delayed CC was associated with fewer children having a score below the normal range in the Movement ABC bicycle-trail task and the ASQ fine-motor domain. In the ASQ personal-social domain, 3 of the 6 items involve fine-motor skills, such as if the child serves himself or herself, brushes his or her teeth, and can dress himself or herself. Also, the higher proportion of children in the early-CC group having an immature pencil grip indicates the effect of the timing of CC on fine-motor capabilities at 4 years of age. Our findings are supported by data from other studies that demonstrate associations between low umbilical cord ferritin levels and poorer fine-motor skills at 5 years of age and between a low level of ferritin at 1 year and poorer fine-motor scores at 6 years.[23,24] Previous data on the study population demonstrated significantly higher levels of ferritin at 4 months of age but no persisting effect of the intervention on ferritin levels at 12 months.[14,25] This finding, which indicates a period of motor development vulnerability to low iron stores during early infancy, was also demonstrated in a systematic review of early iron supplementation.[6]

When the results were analyzed according to children's sex, differences in neurodevelopment between the randomization groups became more evident; in boys, delayed CC was associated with higher scores on several tests: the processing-speed quotient, the bicycle-trail task, and the ASQ fine-motor and personal-social domains. However, no differences were shown in girls. The effect by sex is consistent with previous results from the same study population at 12 months, which showed a significant interaction between the intervention and sex on ASQ outcomes; boys who had delayed CC performed better, but the intervention had the opposite effect on ASQ in girls.[25] Other studies have shown that boys have lower iron stores than girls at birth and during infancy.[26,27] In an analysis involving 6 studies from Ghana, Honduras, Mexico, and

Sweden, Yang et al[28] found a higher risk (adjusted OR, 4.6; 95% CI, 2.5-8.5) for iron deficiency among male infants. The increased risk for male infants to develop iron deficiency is a probable explanation for why delayed CC seems to have a more beneficial effect in boys. Other studies have also shown that delayed CC in very preterm infants is associated with improved motor outcomes among boys at follow-up after 7 months.[29]

This study has limitations. The initial study was powered to demonstrate increased infant ferritin levels (which it did) but not differences in neurodevelopment. The attrition rate was relatively high (31.2%). We cannot exclude a possible bias in the overall development of the children whose parents chose to return for the follow-up, although no major differences in baseline data were demonstrated, and there were no differences in baseline data between the randomization groups in children who participated in the follow-up. The limitations in study design and attrition rate must be weighed against the novelty and originality of the study; this study is the first, to our knowledge, to assess the effects of delayed vs early CC on neurodevelopment after 1 year of age.

Conclusions

Delaying CC for 3 minutes after delivery resulted in similar overall neurodevelopment and behavior among 4-year-old children compared with early CC. However, we did find higher scores for parent-reported prosocial behavior as well as personal-social and fine-motor development at 4 years, particularly in boys. The included children constitute a group of low-risk children born in a high-income country with a low prevalence of iron deficiency. Still, differences between the groups were found, indicating that there are positive, and in no instance harmful, effects from delayed CC. Future research should involve large groups to secure enough power to draw clear conclusions regarding development. Definite recommendations for delayed CC have not been issued in full-term infants,[15,30] with one reason being the alleged increased risk of hyperbilirubinemia stated in the latest Cochrane report[11]; however, that report includes unpublished data. When future guidelines are developed regarding child birth and timing of CC, the effect on fine-motor function shown in our study might be taken into account pending larger studies.

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Article Information

Accepted for Publication: February 10, 2015.

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Published Online: May 26, 2015. doi:10.1001/jamapediatrics.2015.0358.

Author Contributions: Dr Andersson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

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Critical revision of the manuscript for important intellectual content: Andersson, Lindgren, Stjernqvist, Domellöf, Hellström-Westas.

Statistical analysis: Andersson.

Obtained funding: Andersson, Hellström-Westas.

Administrative, technical, or material support: Andersson, Lindquist, Stjernqvist, Hellström-Westas.

Study supervision: Stjernqvist, Domellöf, Hellström-Westas.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by grants from the Regional Scientific Council of Halland, the Linnéa and Josef Carlsson Foundation, the Southern Healthcare Region's common funds for development and research, H. R. H. Crown Princess Lovisa's Society for Child Care, Uppsala University, the Little Childs foundation, Sweden, and the Swedish Research Council for Health, Working Life and Welfare (Dr Andersson).

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Eivor Kjellberg, RN, and Monika Nygren, RN, Department of Pediatrics, Hospital of Halland, Halmstad, provided assistance in collecting the data; both received wages for their work. Per-Erik Isberg, PhD, Department of Statistics, Lund University, and Maria Lönn, MSc, Maple Medical Science, provided statistical advice. Maple Medical Science is a statistical consulting company that was paid on a time-charge basis.

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