Neurodevelopmental outcomes at 2 and 3.5 years for very preterm babies enrolled in a randomized trial of milking the umbilical cord versus delayed cord clamping

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Abstract

Background: Guidelines published by the International Liaison Committee for Resuscitation and by the World Health Organisation recommend delaying to clamp the cord at birth as part of routine care for infants.

Objective: To study the use of four times milking of the cord as an alternative to enhance the redistribution of placental blood into the baby.

Methods: Prospective cohort study of neurodevelopmental assessment by Bayley III method of very preterm infants that had participated in a trial of delayed cord clamping versus cord milking at birth that was conducted in a neonatal tertiary care hospital. The primary outcomes were differences in cognitive, motor and language development at 2 and 3.5 years. Two-tailed analyses were performed with Chi-square test, Fisher's exact test, t-test, Mann-Whitney U-test and ANCOVA.

Results: Out of the 58 infants enrolled into the original study 39 infants (67%) were assessed at 2 years and 29 (50%) at 3.5 years of age. Neurodevelopmental outcomes at 2 and 3.5 years did not significantly differ between the two groups for the three Bayley III composite scores. At 3.5 years there was trend towards higher scores for girls in the language composite scores (girls: M = 121.6, SD = 15.22; boys: M=101.07, SD = 19.84), and on the motor scale (girls: M = 124.60, SD = 18.15; boys M = 97.86, SD =17.23).

Conclusions: In this small number of participants followed up to 2 and 3.5 years of age**,** four times milking of the cord did not have any long term adverse effect on neurodevelopmental outcome, suggesting cord milking could be used as an alternative to delayed cord clamping.

Trial registration: National Research trials Register UK, www.nihr.ac.uk/Pages/default.aspx. N0051177741

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List of abbreviations

BMI	Body mass index
M	Mean
SD	Standard deviation

Introduction

There is increasing evidence that a delay in clamping the umbilical cord following birth is beneficial in comparison to immediate clamping. Two reviews of fifteen randomized trials in preterm infants suggest that a delay of 30 seconds in clamping the cord enables redistribution of placental blood to the infant, which benefits them by reducing intra-ventricular haemorrhages and the need for blood transfusion, without adverse effects.[1,2] Milking the cord has been studied as an alternative method of enabling placental blood redistribution.[3] A recent RCT compared the two methods for enhancing placental blood redistribution in preterm neonates before 33 weeks gestation[4] provided basis of this study, specifically, clamping the cord for 30 seconds after delivery versus milking of the cord four times towards the infant. Milking the cord four times resulted in similar levels of placental blood redistribution compared to a slight delay in clamping the cord with similar short term outcomes.

Only one study has reported the neurodevelopmental outcomes of very low birth weight infants (VLBW) after a cord clamping intervention.[5] No significant differences in Bayley II scores (mental and motor subscales) were reported between infants in the immediate cord clamping and delayed cord clamping groups (30-45 seconds) at seven months corrected age. However, when confounding factors were controlled for, a brief delay in cord clamping was found to be associated with higher Bayley II motor scores for VLBW male infants at seven months corrected age. Specifically, compared to male infants with immediate cord clamping, males with delayed cord clamping had motor scores more than one standard deviation higher when controlling for NICU morbidities.

There are currently no studies which explore neurodevelopmental outcomes beyond seven months following a cord clamping trial in preterm infants. Moreover, no studies have explored neurodevelopmental outcomes in preterm infants following cord milking[4]. The aim of this prospective follow-up study was to compare developmental outcomes at 2 and 3.5 years for babies born very preterm who received either a short delay in cord clamping or milking of the cord at birth[4] in order to substantiate the hypothesis that both methods for redistribution of placental blood are safe.

Methods

The methods used in the trial are fully described elsewhere.[4]

Participants

Eligible participants were all children who had participated in the cord milking versus delayed cord clamping trial (National Research trials Register UK, www.nihr.ac.uk/Pages/default.aspx. N0051177741)[4]. The trial was conducted at a single tertiary healthcare centre (Royal Sussex County Hospital in Brighton, UK). Preterm neonates between 24 0/7 and 32 6/7completed weeks of gestation were included in the trial if antenatal informed consent could be obtained from the parents before delivery. Exclusion criteria were multiple pregnancies (twins and more), fetal hydrops, Rhesus sensitization, or known major congenital abnormalities. Before delivery, the fetuses were randomized into two groups. Those randomized to the clamping group were positioned 20 cm below the level of the placenta, between their mother's thighs (vaginal delivery) or to the mother's side (cesarean delivery). The umbilical cord was clamped at 30 seconds. In the milking group, the neonates were positioned 20 cm below the level of the placenta, between the mother's thighs (vaginal delivery) or to the mother's side (cesarean delivery), with the cord being milked toward the neonate four times at a speed of 20 cm/2 seconds. The study team recruited 58 neonates over an 18-month period from 212 women who were potentially eligible participants.

Design

Neurodevelopmental assessment was undertaken as a prospective cohort study of very preterm infants that had participated in a trial of delayed cord clamping versus cord milking at birth. The primary outcomes for this study were differences in cognitive, motor and language development at 2 and 3.5 years following the intervention.

Procedure

All families who partook in the original RCT were invited to take part in the follow-up study. Parents were sent a letter of invitation and information leaflet when the babies were approximately 20 months old and again at 36 months. This was followed by a phone call one week later to find out if they were happy to participate. An appointment for assessment was made at a convenient time and place. Consent forms were sent in a second letter confirming the appointment. Written informed consent was obtained before the start of each assessment and confidentiality, anonymity and the right to withdraw at any time were assured. Ethical approval was obtained from the regional ethics committee (09/H1111/37)

The infant developmental assessment was carried out by a researcher who was qualified and trained in the use of the Bayley Scales of Infant Development III.[6] The researcher was blinded to the random allocation of the original study. One or both parents were present throughout the assessment, which lasted for approximately 1.5 hours. Participants were debriefed and were also offered a brief summary of their baby's development after the assessment. Parents were offered the choice about whether the assessment were carried out at their home (n=16), the hospital outpatient clinics (n=23), or, in special circumstances, local health clinics (n=0). The original study was not powered for detecting differences in neurodevelopment.

Measures

Baseline data: Gestational age was determined by the obstetric team before enrolment, by date of last menstruation if available, and by early booking ultrasound scan (usually week 8). Demographic and other maternal data were collected from the mother's notes at the time of enrolment or after delivery. Neonatal data were obtained from clinical notes.

Infant Development: The infant's cognitive, language, and motor development were assessed using the Bayley Scales of Infant Development III.[6] These scales can be used to establish child development from one month to 42 months old. It is composed of rating scales and qualitative observations. It has been standardized and extensively reviewed for its psychometric quality and tested for reliability (*r* ranging from .86 to .93) and validity using large samples of children with and without developmental delay[6]. Raw scores from each scale were converted to three composite scores (*M*=100, *SD*= 15), one for cognition, one for language and one for motor development. We chose 3.5 years corrected age as the second time point, as this is the upper age limit for which the Bayley III test is validated and so the same examination method could be used for comparison.

Data analysis

Chi-square tests, Fisher's exact tests, *t*-tests, and Mann-Whitney *U*-tests were used to compare differences between cord clamping and cord milking groups for maternal age, BMI, smoking status (during pregnancy/at Bayley assessment time point), gestational age, birth weight, head circumference, and gender. Spearman's correlation coefficients were calculated to explore maternal and infant variables that were associated with neurodevelopmental outcomes at 2 years and 3.5 years. Variables that correlated significantly at $p < .05$ were controlled for in a series of ANCOVAs to explore the effect of the intervention on the Bayley composite scales. Partial Eta^2 was used as a measure of the effect size. The following values were used to interpret the size of the effect: small = 0.01; medium = 0.06; large = 0.14. All analyses were two-tailed.

Results

Participants

58 infants were enrolled into the trial and at the 2 year follow-up 39 children (67% retention) remained in the study (Figure 1). Six children died before the 2 year follow-up and the

remaining 13 were lost to follow-up. There were no differences between children lost to follow-up and children retained in the study regarding maternal and infant characteristics. At the 3.5 year follow-up 29 infants remained in the study (50% attrition from the original trial). Children who participated in the 3.5 year follow-up had a higher birth weight (Mdn = 1465g) compared to those lost to follow-up (Mdn = 980g); U = 192, $p < .001$. Children who participated in the 3.5 year follow-up also had higher gestational age (Mdn = 30.4weeks) compared to those lost to follow-up (27.9weeks); U = 212.5, $p < .001$. Mothers of children who participated in the 3.5 year follow-up were also less likely to have smoked during pregnancy compared to mothers lost to follow-up ($p < .05$).

Bayley sores at 2 years did not differ between those were tested at 3.5 years and those who were not (*p*s > .05). 27 children were seen at both the 2 year and 3.5 year follow-ups. For these children, there were no significant differences between the 2 year follow-up and the 3.5 year follow-up regarding cognitive, motor, and language composite scores (*ps* > .05)

Insert Figure 1 here

Parental and neonatal characteristics

Maternal and infant characteristics at the 2 and 3.5 year follow-up are shown in Table 1. No significant differences were observed between the two groups regarding infant (adjusted age, gender, gestation, birth weight, head circumference) and maternal characteristics (age, BMI, smoking status).

Insert Table 1 here

Associations between child development and background variables

Associations between child development and the background variables are presented in Table 1. At 2 years cognitive composite scores were positively associated with infant's head circumference (r_s = 0.3, p = 0.02). Motor scores were positively associated with birth weight (r_s = 0.5, p = 0.003) and negatively associated with mother's BMI (r_s = -0.4, p = 0.02). Language scores were not associated with any maternal or infant characteristics. At 3.5 years cognitive composite scores were negatively associated with mother's BMI (r_s = -0.5, p = 0.02). Girls also scored significantly higher than boys on the language and motor composite scales (Table 2). These significant background variables were therefore controlled for in subsequent analyses.

Insert Table 2 here

The effect of the intervention on child development at 2 and 3.5 years

2 years: A series of ANCOVAs were conducted to explore the effect of the intervention on the three Bayley composite scores, whilst controlling for the relevant significant maternal and infant variables. Neurodevelopmental outcomes at 2 years did not significantly differ between the two groups for the three Bayley composite scores (Table 3). However, it should be noted that the effect sizes associated with the cognitive and language scales are large.

3.5 years: A series of ANCOVAs were conducted to explore the effect of the intervention on the three Bayley composite scores, whilst controlling for the significant background variables. Neurodevelopmental outcomes at 3.5 years did not differ between the two groups for the three Bayley composite scores (Table 3). Again, it should be noted that the effect size associated with the language scale is large.

Insert Table 3 Here

Table 4 displays the number of infants with normal composite Bayley Scores (≥85), scores 1SD below normal (70-84), and scores 2SD below normal (<70). There were no statistically significant differences between the groups, which was tested by Fisher's exact test.

Insert Table 4 Here

Discussion

Strengths and weaknesses

This is the first study to compare developmental outcomes in babies born very preterm who either experience cord milking or delayed cord clamping at birth. It is also the longest follow-up of infants involved in a placental transfusion trial. A previous study comparing immediate and delayed cord clamping followed infants up to seven months of age but the authors recommended that follow-up should be at approximately four years as this is when motor outcomes stabilise.[5] However, the sample sizes at both time points in our trial were relatively small, and the pilot trial was conducted in a single tertiary centre. The sample size for the original study was based on known haemoglobin values after birth from previous studies on placental transfusion. In our perinatal centre 30 seconds of cord clamping in preterm infants is the routine procedure to enhance placental transfusion at delivery. It was therefore not deemed ethical to include a study group with immediate cord clamping time.

The attrition rate demonstrates the difficulties of conducting long term follow-up studies in ex-preterm infants. Often young families have a high mobility rate. As the children grow older and, especially if they are developing normally, parents might be less motivated to continue with formal follow-up research.

Correlations with baseline data

At two years cognitive composite scores were positively associated with larger infant head circumference and motor composite scores were positively associated with a higher infant birth weight. This finding is consistent with the research which suggests that low birth weight is associated with poorer cognitive development.[8] At two years motor scores were negatively associated with mother's BMI during pregnancy. A similar relationship was found between cognitive scores and BMI at the three and a half year follow-up. A previous study also reported that mothers' BMI during pregnancy may negatively affect infants' neurocognitive development.[9] Girls also scored higher than boys on the language and motor scales. Higher scores on the Bayley scales for girls compared to boys have also been reported in previous studies with very preterm infants.[10]

Comparisons with previous studies

No significant differences in Bayley scores were identified between the two groups. A previous study reported no differences between infants with delayed cord clamping and infants with immediate cord clamping[5]. However, they reported a gender-specific effect, which suggests that delayed cord clamping at birth appears to be protective of very low birth weight male infants against motor disability (assessed using the Bayley II scales) at seven months corrected age.[5]

Benefits and risks of redistribution of placental blood

In the past two decades there has been an increased interest in the topic of redistribution of placental blood by either delayed cord clamping or milking of the cord.[1, 2, 5] Studies have reported benefits in short term outcomes for preterm infants: improved circulatory adaptation after birth, less need for volume therapy, blood transfusions and inotropic support, increased superior vena cava blood flow, increased left ventricular output, shorter need for ventilatory support, higher oxygenation index, less incidence of overall intra-ventricular haemorrhage and necrotizing enterocolitis.[1, 3, 11]

The evidence from the existing studies has led to recommending a 30 to 60 second delay in cord clamping time as part of the initial resuscitation of preterm infants by the international stakeholders.[12, 13, 14, 15, 16] A recent study of delayed cord clamping and initiation of artificial ventilation before clamping the cord in a preterm lamb model demonstrated benefits with increased stabilization of circulatory parameters and increased blood flow into the lungs.[17]

More important lessons can be learned from such studies in order to find the best way for enhancing redistribution of placental blood into the baby at birth and guiding neonatal resuscitation in the future. Redistribution of placental blood is implemented into clinical practice[18] and used as part of transfusion guidelines[19] .

A recently published meta-analysis on the effect of milking the cord versus immediate cord clamping demonstrated positive safety and short term efficacy effects similar to those reported for delayed cord clamping.[20] Long term follow-up data such as ours provide vital information for assessing the efficacy and long term safety of different modes of placental blood redistribution. Thus publishing data from studies with small sample size will support future meta-analysis and can be viewed as a strength.

Conclusion

In our study we compared the long term outcome of infants who received placental transfusion through either a 30 second delay in cord clamping time or four times milking of the cord. Our results did not demonstrate a significant difference in neurodevelopmental outcome assessed by Bayley III scores at 2 and 3.5 years corrected age. Since the numbers were small, the study lacked power to detect clinically relevant differences in neurodevelopmental outcomes, if there were any. Yet, it is reassuring that no major issues were found in the group undergoing four times milking of the cord. Therefore, as of now, milking of the cord, which takes only about 10 seconds to perform, could be used as a substitute to a delay in cord clamping time when the attending clinician would not like to wait.

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Author contributions

Heike Rabe conceptualized and designed the study, drafted parts of the manuscripts, tables and figure, and approved the final manuscript as submitted.

Alexandra Sawyers carried out the initial analysis, drafted parts of the manuscripts, tables and figure, and approved the final manuscript as submitted.

Philip Amess conceptualized and designed the study, critically reviewed the manuscript, and approved the final manuscript as submitted.

Susan Ayers conceptualized and designed the study, carried out the initial analysis, critically reviewed the manuscript, and approved the final manuscript as submitted.

Figure 1. Flow chart of study follow-up

Table 1. Group differences on background variables

Table 2. Mean (*SD*) scores on Bayley composite scores for males and females

Table 3. Group differences based on composite Bayley III Scores

Table 4. Number of infants with normal composite Bayley Scores (≥85), scores 1SD below normal (70-84), and scores 2SD below normal (<70)

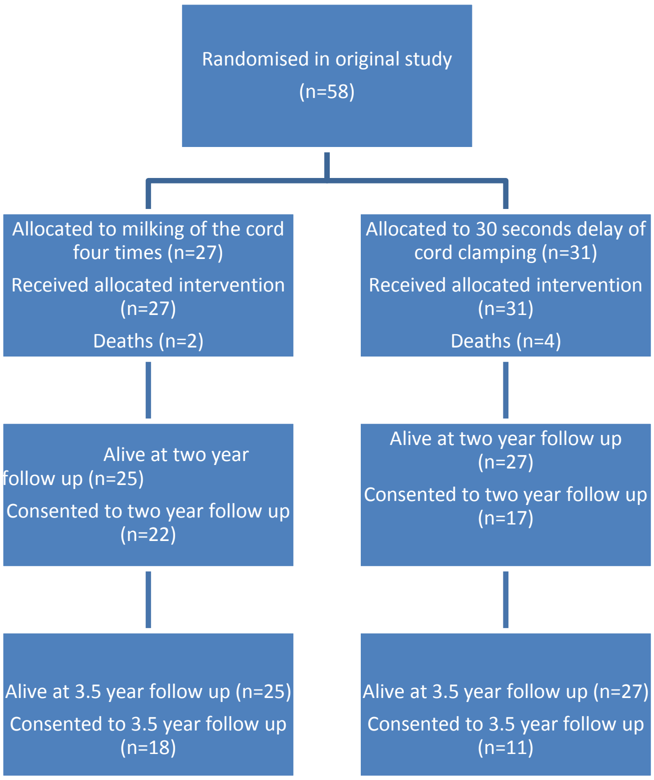

Figure 1. Flow chart of study follow-up

Table 1. Group differences on background variables

	Cord Clamping		
	Cord Milking	**Delayed Cord Clamping**	***p* value**
2 Year follow-up			
N	22	17	
Gender (F/M)	13/9	8/9	0.46
Adjusted age (months) Mean (*SD*) Range 22.7-29.8	26 (2.1)	26 (1.6)	0.85
Birth weight (grams) Mean (*SD*) Range 660-2245	1316 (461)	1391 (357)	0.58
Head circumference (cm)Mean (*SD*)	27.1 (2.6)	27.6 (2.0)	0.61
Gestational age (weeks) Mean (*SD*) Range 24.6-33.7	29.8 (2.5)	29.9 (2.0)	0.82
Mother's BMI Mean (*SD*)	25.0 (5.7)	25.3 (5.4)	0.79
Mother's age (years)Mean (*SD*)	30.5 (6.2)	29 (6.1)	0.45
Smoker during pregnancy (Yes/No)	3/19	4/12	0.43
Current smoker (Yes/No)	5/17	4/13	0.62
3·5 Year follow-up			
N	18	11	
Gender (F/M)	9/9	6/5	0.21
Adjusted age (months) Range 41.1-47.4	43.9 (1.5)	43.2 (1.7)	0.26
Birth weight (grams) Mean (*SD*) Range 770-2245	1408 (417)	1479 (398)	0.65
Head circumference (cm)Mean (*SD*)	27.7 (2.2)	27.9 (2.3)	0.88
Gestational age (weeks) Mean (*SD*) Range 26-33.7	30.5 (1.9)	30.1 (2.0)	0.54
Mother's BMI Mean (*SD*)	25.1 (6.3)	26.1 (5.2)	0.70
Mother's age (years)Mean (*SD*)	30.4 (6.2)	28.6 (6.3)	0.46
Smoker during pregnancy (Yes/No)	0/18	2/8	0.12
Current smoker (Yes/No)	2/16	3/8	0.34

Table 2. Mean (*SD*) scores on Bayley composite scores for males and females

	Bayley Scales		
	Cognitive	**Motor**	**Language**
2 year follow-up			
Male	110.8 (22.5)	98.2 (16.8)	97.9 (19.0)
Female	120.0 (20.0)	108.0 (15.2)	106.6 (21.3)
3.5 year follow-up			
Male	118.2 (25.2)	97.9 (17.2)*	101.1 (19.8)*
Female	139.7 (18.3)	124.6 (18.1)	121.6 (15.2)

Note. * $p < .01$

Table 3. Group differences based on composite Bayley III Scores

	Cord Milking	**Cord Clamping**	***p* value (partial η^2)**
2 Year follow-up	***N*=22**	***N*=17**	
Cognitive Comp. (*SD*)	119 (17.5)	111 (25.7)	0.08 (0.1)[a]
Language Comp. (*SD*)	108 (18.3)	95 (21.5)	0.05(0.1)[b]
Motor Comp. (*SD*)	105 (14.8)	102 (18.8)	0.39 (0.03)[c]
3·5 Year follow-up	***N*=18**	***N*=11**	
Cognitive Comp. (*SD*)	127 (19.8)	120 (26.6)	0.62 (0.01)[d]
Language Comp. (*SD*)	115 (18.1)	106 (22.8)	0.11(0.1)[e]
Motor Comp. (*SD*)	114 (23.0)	108 (20.9)	0.30 (0.04)[e]

Note. $\eta 2$ = eta squared (effect size) [a] Controlling for head circumference, [b] No background variables were controlled for, [c] Controlling for birth weight and mother's BMI, [d] Controlling for mother's BMI, [e] Controlling for infant gender·

Table 4· Number of infants with normal composite Bayley Scores (≥85), scores 1SD below normal (70-84), and scores 2SD below normal (<70). No infants had cerebral palsy, blindness or deafness.

	Bayley III composite scores normal (≥85)		**Bayley III composite scores 70-84**		**Bayley III composite scores < 70**	
	Cord Milking	**Cord Clamping**	**Cord Milking**	**Cord Clamping**	**Cord Milking**	**Cord Clamping**
2 Year follow-up	***N*= 22**	***N*= 17**	***N*= 22**	***N*= 17**	***N*= 22**	***N*= 17**
Cognitive Comp	21	14	1	2	0	1
Language Comp	20	13	2	2	0	2
Motor Comp	21	16	1	0	0	1
3·5 Year follow-up	***N* = 18**	***N* = 11**	***N* = 18**	***N* = 11**	***N* = 18**	***N* = 11**
Cognitive Comp	18	10	0	1	0	0
Language Comp	16	8	2	1	0	1
Motor Comp	16	10	2	0	0	1