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REGULAR ARTICLE

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Neurodevelopmental outcomes of a randomised trial of intact cord resuscitation

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Abstract

Aim: It has been suggested that intact cord resuscitation can reduce the risk of brain damage. We investigated the effects on neurodevelopment at two years of age.

Methods: This study was performed in Kathmandu, Nepal. In 2016, 231 late preterm and term infants born vaginally and not breathing were randomised to resuscitation with an intact cord or the standard practice of early cord clamping (CC). At two years of age, the World Health Organization's Infant and Young Child Development tool was used to assess the child's neurodevelopment, during telephone interviews with caregivers.

Results: We followed up 138 infants (59.7%) at a mean age of 24.8 ± 0.8 months. A significant difference was seen in the development for age *Z*-score, between the group resuscitated with an intact umbilical cord and the group resuscitated with early CC. The median (range) scores were 1.0 (0.1-2.1) vs 0.9 (−2.0 to 1.8), respectively (P = .04). There was no difference in the motor, language-cognitive and socio-emotional domains.

Conclusion: Neurodevelopment improvements were observed at two years of age in infants resuscitated with an intact rather than early clamped umbilical cord. No definitive conclusions could be drawn due to protocol violations and a low follow-up rate. More research is needed.

KEYWORDS

clamping, intact cord, neurodevelopment, resuscitation, umbilical cord

1 | INTRODUCTION

One of the goals in the 2030 Agenda for Sustainable Development, which was adopted by the United Nations in 2015, is to ensure access to quality early childhood development.[1] The Global Strategy for Women's, Children's and Adolescents' Health (2016-2030) aims to achieve the highest attainable standard of health for children.[2]

More than 95% of all deaths and impairments after intrapartum complications occur in low-income and middle-income countries.[3] Intrapartum-related events, formerly referred to as birth asphyxia, account for 26% of neonatal deaths worldwide.[4] Infants

Abbreviations: CC, cord clamping; HBB, Helping Babies Breath; ICR, intact cord resuscitation; IYCD, Indicators of Infant and Young Child Development; SpO_2, peripheral capillary oxygen saturation.

who survive the hypoxic event face a risk of developing neonatal encephalopathy,[3] a strong predictor of long-term impairment.[5]

Disturbances in the transition from the umbilical cord circulation to the extra-uterine circulation or disturbances in the initiation of breathing are the major reasons for hypoxia, which can progress to ischaemic insults and death.[6] Initiatives such as Helping Babies Breathe (HBB), based on the International Liaison Committee on Resuscitation guidelines,[7] have been shown to reduce neonatal mortality up to 47%. HBB does this by teaching the initial steps for neonatal resuscitation and giving a better start to infants who struggle to breathe at birth.[8] The algorithm is specifically designed for environments where human and technical resources are limited.[8]

Another way to improve outcomes for infants in need of resuscitation could be to facilitate haemodynamic transition at birth.[9] Experimental research has shown that improved cardiovascular function can be obtained if ventilation occurs before CC.[10]

In infants who need resuscitation, early improvements in peripheral capillary oxygen saturation (SpO_2) and increased cerebral tissue oxygenation at 12 hours of life have been seen when CC has been delayed.[11] In the original trial for this study, we saw improved SpO_2 and higher Apgar scores in infants when resuscitation was initiated with an intact cord.[12]

The increasing evidence of the long-term benefits with delayed CC in vigorous infants[13] has led to a change in recommendations, from early CC, namely umbilical CC before 30 seconds, to delayed CC.[7] The additional blood volume and red blood cells provided to the infant during delayed CC[14] has been shown to improve iron status up to eight months of age[15-17] and to be associated with long-term positive effects on neurodevelopment.[18,19]

Mercer et al[20] proposed that infants in need of resuscitation may benefit from receiving a placental transfusion and that resuscitation might be initiated with an intact umbilical cord. Their suggestion was based on the benefits of delayed CC as a non-interventional, simple and cost-effective approach and the results from experimental animal studies. However, the American Heart Association Guidelines and the International Liaison Committee on Resuscitation state that until more evidence is available, infants who are not breathing should have their cord clamped and resuscitation measures initiated promptly. They say exceptions can be made if they are part of a delayed CC research protocol.[7,21] This prevents infants in need of resuscitation from having delayed CC, even though these infants could be the most likely to benefit from placental transfusion and the continued placental gas exchange that is potentially received with delayed CC.[9] The aim of this study was to evaluate the long-term effects on neurodevelopment in children who had been resuscitated, either by standard practice, where the cord is cut early, or by intact cord resuscitation (ICR).

Key notes

- This study compared the neurodevelopment of 138 two-year-old children who had been resuscitated at birth when their cord was still intact or had undergone early cord clamping.
- The development for age *Z*-score was significantly higher in the intact umbilical cord group.
- No differences were seen in the motor, language-cognitive and socio-emotional domains, but further research is needed as the overall findings were not definitive.

2 | PATIENTS AND METHODS

2.1 | Randomisation of the original trial

This was a two-year follow-up of our original single-centre randomised clinical trial at the Paropakar Maternity and Women's Hospital in Kathmandu, Nepal. That study focused on infants born vaginally from April 20 to August 27, 2016, who needed to be resuscitated at birth. Women were considered eligible if they were assigned to the low-risk Maternal and Neonatal Service Centre at the tertiary government hospital. The hospital's criteria for admission to the hospital centre were the following: uncomplicated pregnancies, no complications on admission, healthy mothers, expected vaginal delivery, gestational age between 33 and 41 weeks, and singleton pregnancy. After admission to the hospital centre, mothers were informed about the study and asked for consent. A random digit generated list was used to prepare sequentially numbered opaque envelopes. One of the authors prepared the envelopes. The author had no further clinical involvement in the trial. After the parents gave consent, the research team member took the next opaque numbered envelope. The infants who needed resuscitation after vaginal birth were then resuscitated according to the allocation group. The infants were either resuscitated with an intact umbilical cord if randomised to delayed CC after 3 minutes or more, or after CC at less than 1 minute on a resuscitation table if randomised to early CC and standard care, as previously described (Figure 1).[12] According to the HBB algorithm, an infant who is not breathing despite thorough drying and additional stimulation is considered to be in need of resuscitation.[8] The HBB algorithm was routine at the hospital but, before the study, all staff underwent training on the HBB algorithm and training sessions with the modified algorithm with intact cord resuscitation were included. Neither the mother giving birth nor the midwife performing the intervention could be blinded to the randomisation, but all staff involved in collection or analysis of data were blinded to the allocation group. In the original study, 780 women were randomly assigned to delayed CC and 780 to early CC. Of the 1560 included infants, 231 required resuscitation: 134 received ICR and 97 received resuscitation after CC. Only 65 (48.6%) cases followed the allocated intervention in the ICR group.

2.2 | Study participants

All 231 children who were resuscitated during the original study were eligible for the follow-up study, subject to parental consent.

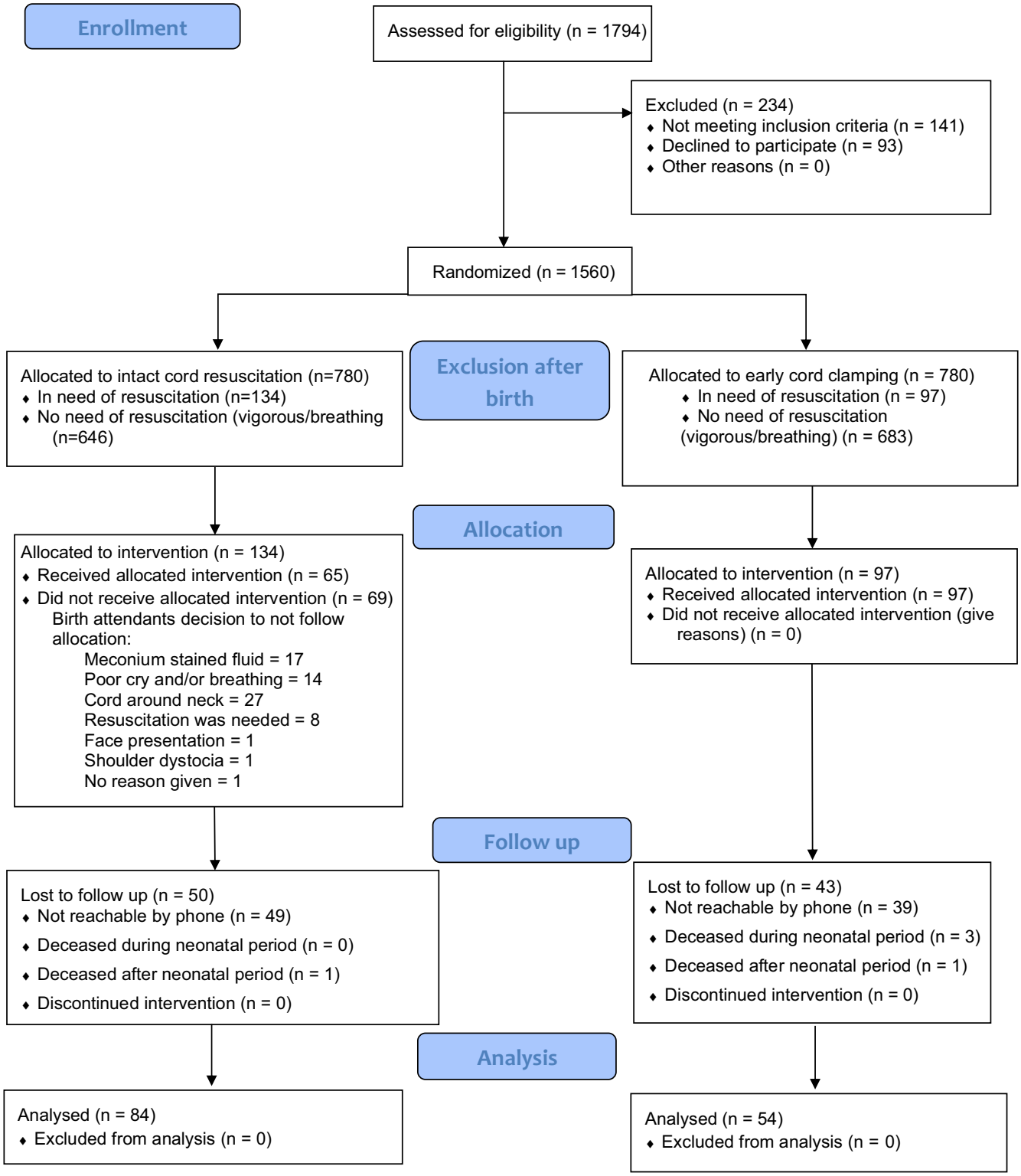

FIGURE 1 Trial profile. Flow diagram adapted from the CONSORT flow diagram (http://www.consort-statement.org/)

2.3 | Data collection

Data were collected by telephone interviews with the children's caregivers. Three trained native nurses made two telephone calls to caregivers during the study period. Initial contact was made to obtain verbal consent for the follow-up and to collect, and use, the background data gathered (Table 1). When the infant was approximately two years old, they underwent a neurodevelopmental follow-up. These took place between June and October 2018.

Neurodevelopment was assessed by using the World Health Organization (WHO) Indicators of Infant and Young Child Development (IYCD).[22] The IYCD provides a standardised method

to estimate development, at the population level, for children up to three years of age across cultures. Start and stop points of the tool are determined by age. The IYCD is intended to evaluate the impact of an intervention or prevention by comparing groups rather than to screen or diagnose individual children.

The IYCD contains four subdomains and 100 items.[23] In this study, the IYCD tools for 19-24 and 25-36 months were used, depending on the actual age of the child when the caregiver was interviewed. The tool for 19-24 months comprises 65 items: 20 fine and gross motor, 22 language and cognitive and 13 socio-emotional. The tool for 25-36 months comprises 58 items: 16 fine and gross motor, 18 language and cognitive and 14 socio-emotional. There was one additional subdomain, general behaviour, comprising 10 items, not age-depended and asked to all infants. This subdomain was under development and could therefore not be used in data analyses. The last socio-emotional question for the age interval 25-36 months is asked in a negative way and this was confirmed by one of the authors of the IYCD, Gareth McCray, after Skype contact on November 30, 2018. Therefore, the results of this item were withdrawn from all children, resulting in 13 socio-emotional items instead of 14. For the motor and language-cognitive domains, there are three choices: yes, which scores one point, and no or do not know, which both score no points. The socio-emotional domain has four choices: always, which scores two points, sometimes, which scores one point, and never or do not know, which both score no points each.

The IYCD items were administered to the caregiver during the second telephone call, having gained their consent during the initial call. The three research nurses who performed the interviews had digital tablets, and the child's age was automatically calculated in month intervals when their birthdate and the date for the interview were entered. Children younger than 24.5 months were considered to be 24 months, and the 19-24 months tool was used. The 25-36 months tool was used for children over that age. The answers to each question were entered into the tablet and saved digitally.

The manual suggested a scoring mechanism that took the sum score of the participant and their age and produced a development for age Z-score (DAZ). In order to calculate the DAZ score, a spreadsheet was created. The raw score was the total sum score with an added adjustment factor. The manual assumes that a normally developing young child would answer affirmatively to items asked for younger ages, and therefore, older children receive points to questions not asked. The decimal age was the age in days divided by 365.25. The raw score, obtained after the interview, and decimal age, calculated by the tablet, were copied into a spreadsheet, provided by the IYCD tool, to calculate the DAZ score.

The WHO IYCD questionnaire is open access and can be used as long as data-sharing agreements exist. The Nepalese research team members received training to use the IYCD before the study. The English IYCD questionnaire was translated to Nepali, and the assessments of the children by telephone interviews were conducted in Nepali.

2.4 | Outcome

The main outcome was the total DAZ score for the IYCD, an age-corrected score calculated according to the manual. The secondary outcomes were the total scores for the subdomains: motor, language-cognitive and socio-emotional. In addition, we constructed an at-risk cut-off score by defining the 15th percentile from the score in the total results and in the subdomains.

2.5 | Statistical analysis

This study was a follow-up of a randomised clinical trial, and the sample size was considered fixed. For background, the group randomised to ICR was compared with the group randomised to early CC regarding maternal and newborn infant data. Means and standard

TABLE 1 Baseline characteristics of mothers and newborn infants who were randomised to resuscitation with an intact cord (intervention) or after early CC (control)

Characteristic	Cord clamping group, mean (standard deviation)		
	Intact cord > 3 min (n = 84)	Early CC < 1 min (n = 54)	*P*-value[a]
Mothers' age (y)	22.9 (3.8)	22.4 (3.4)	.44
Monthly income (Nepalese rupee)[d]	25 000 (3000-200 000)	25 000 (9000-200 000)	.56[b]
Gestational age (wk)	39.5 (1.4)	39.8 (1.2)	.20
Birth weight (g)	3082 (426)	3110 (328)	.68
Age at IYCD (mo)	24.7 (0.8)	24.8 (0.8)	.86
Female sex, n (%)	33 (39.3%)	19 (35.2%)	.72[c]

[a]Group comparisons were performed by a two-tailed unpaired Student's *t* test.

[b]Group comparisons were performed by a two-tailed unpaired Student's *t* test, except for the Mann-Whitney *U* test.

[c]Group comparisons were performed by a two-tailed unpaired Student's *t* test, except for Fisher's exact test.

[d]Presented as median (min-max).

deviations (SD) were used for normally distributed variables, medians and ranges for skewed or ordinal variables, and numbers and percentages were used for categorical variables. For comparisons between the groups, we used Fisher's exact test for categorical variables and the Mann-Whitney U test for ordinal variables and for variables with skewed distribution. An unpaired two-tailed *t* test was used for variables with approximately normal distribution. We used IBM SPPS Statistics, version 25.0 (IBM Corp, New York, USA). Data were analysed both according to intention to treat and per protocol. Fisher's exact test was used to calculate differences at group level for infants at risk with scores below the 15th percentile (Figure 2), and we used an online calculator, the JavaStat calculator on https://statpages.info/ctab2x2.html, to determine relative risks and 95% confidence intervals.

Due to sufficient homogeneous background characteristics (Table 1), additional statistical analyses, such as multivariate regression analysis, were considered superfluous. Due to the high loss at follow-up, detailed in the Results section, we performed non-response analyses on the background statistics.

3 | RESULTS

Telephone interviews were conducted between June and October 2018. Follow-up was successful in 138 (59.7%) out of 231 cases. The mean age at follow-up was 24.8 ± 0.8 months, ranging from 23.0 to 26.9 months. We followed up 84/134 (62.7%) infants resuscitated with an intact cord and 54/94 (55.7%) infants resuscitated by standard care, including early CC (P = .49) (Figure 1). Reasons for loss at follow-up were that the phones were switched off (n = 27), the phone numbers were wrong (n = 15), and the caregivers were unreachable (n = 46). Three infants died during resuscitation, all in the early CC group. During follow-up, two caregivers reported that their infants had died, one in each intervention group. Data on mortality for the non-responders are not available.

The baseline and background characteristics are presented in Table 1. The mean and standard deviation age at follow-up was very similar to the original group, with a mean difference of 0.75 days. Of the 138 infants, 86 (62.3%) were male. There was no significant difference in the distribution of the sexes between the two groups at baseline and follow-up. No significant differences between ICR and early CC groups were seen with regard to maternal characteristics, the median and range family income or neonatal baseline data, such as gestational age or birth weight. When we compared the infants in the study to those lost at follow-up, no difference was seen regarding the mothers' age, gestational age, birth weight or sex distribution. Monthly income was not examined in the original trial, so that could not be compared.

The primary outcome was the total IYCD score, and intention to treat was analysed with Mann-Whitney U test. This showed that the group resuscitated with an intact cord had a significantly higher DAZ score, compared to the group resuscitated according to standard practice, with early CC, (P = .04) (Table 2). If protocol violations were excluded, there was no significant difference the between groups (P = .25) (Table 3).

When the total raw score was compared between the groups by unadjusted analysis, no significant difference was seen (Table 2). As the manual's DAZ score is meant to be corrected for age, we performed an ordinal regression analysis on the intention-to-treat groups by correlating the total raw score for age. This showed that the odds of there being a higher score in the group with ICR was 1.91 (95% CI, 1.05-3.50) times that of the early clamped group. This was a statistically significant effect, with a chi-square of 4.44, (P = .04). The IYCD total raw and subdomain scores are presented in Table 2, and the results per protocol are in Table 3.

Infants at risk were prespecified as the lowest 15th percentile. Relative risks consequently favoured the ICR group in the motor domain, but at a non-significant level (Figure 2) (P = .06).

The relative risk for the total score was 0.68 (95% CI 0.30-1.16). For the motor domain, it was 0.59 (95% CI 0.25-1.04), for the language-cognitive domain, it was 0.70 (95% CI 0.35-1.13), and for the socio-emotional domain, it was 0.94 (95% CI 0.33-1.48).

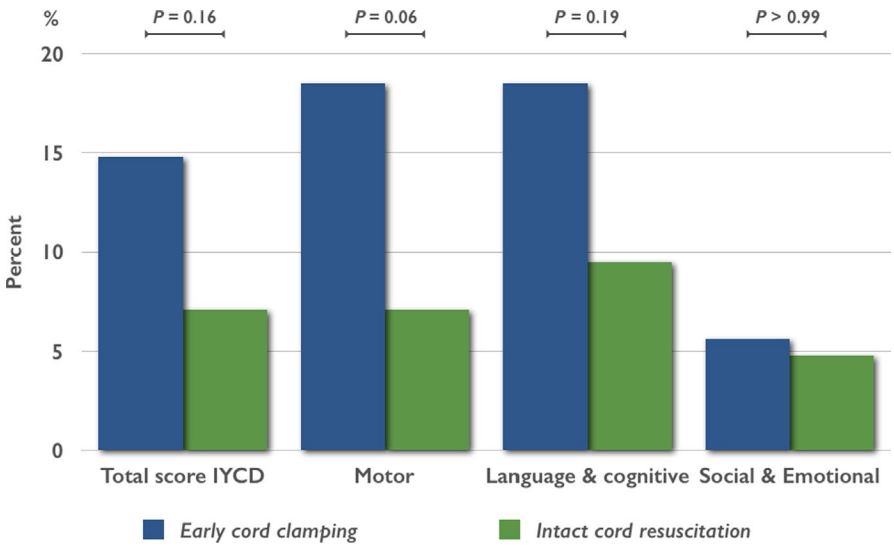

FIGURE 2 Infants at risk (lowest 15th percentile) of developmental delay at two years of age. Early CC (blue) vs intact cord resuscitation (green).Total score and each of the domains (motor, language-cognitive and social-emotional)

TABLE 2 IYCD scores at two years of age in infants who were randomised to resuscitation with intact cord or after early CC

	Cord clamping group, median (min-max)		
	Intact cord > 3 min (n = 84)	Early CC < 1 min (n = 54)	*P*-value[a]
Development for age Z-score (DAZ)	1.0 (0.1-2.1)	0.9 (−2.0 to 1.8)	.04
Total raw score	57 (49-64)	55.5 (34-62)	.07
Motor (gross and fine)	18 (13-20)	17 (11-20)	.05[b]
Language-cognitive	20 (14-22)	20 (10-22)	.82
Socio-emotional	19 (15-25)	18 (11-22)	.07

Note: Intention-to-treat analyses.

[a]Group comparisons performed by Mann-Whitney *U* test.

[b]*P* = .047.

TABLE 3 IYCD scores at two years of age in infants who were randomised to resuscitation with intact cord or after early CC

	Cord clamping group, median (range)		
	Intact cord > 3 min (n = 45)	Early CC < 1 min (n = 54)	*P*-value
Development for age Z-score	1.0 (0.2-2.1)	0.9 (−2.0 to 1.8)	.25
Total score	56 (49-64)	55.5 (34-62)	.28
Motor (gross and fine)	17 (13-20)	17 (11-20)	.08
Language-cognitive	20 (14-22)	20 (10-22)	.68
Socio-emotional	19 (15-25)	18 (11-22)	.29

Note: Per protocol with protocol violations excluded.

4 | DISCUSSION

In this follow-up study, infants resuscitated with an intact umbilical cord had significantly higher age-corrected developmental total scores compared to those infants who had their cord cut early. Motor domain scores were also significantly higher in the intact group, compared to early cord clamped group. To our knowledge, no other studies have been published on neurodevelopmental outcomes after ICR, but our results agree with follow-up trials where delayed CC was compared to early CC in vigorous newborn infants. Delayed CC has been associated with higher scores in fine motor and personal-social domains at four years of age, especially in boys.[18] A study of Nepalese children of 12 months of age found higher neurodevelopmental scores in the communication, gross motor and personal-social domains.[19] Improved motor outcomes have also been seen at 18-22 months of age in preterm infants who received a brief delay in CC.[24]

One explanation for the neurodevelopmental improvement may be related to the increased iron stores seen after delayed CC.[15,16] Mercer et al[25] showed that delayed CC was associated with increased ferritin levels and increased brain myelination at four months. They suggested that it might have been due to a neurophysiological link between delayed CC and early myelin development and that iron could be the potential underlying mechanism.[25] Rapid brain development and growth have been shown to occur during the first years of life, and iron is essential for the development of the central nervous system.[26,27] Shafir et al[28] showed a linear relationship between severity of iron deficiency, with or without anaemia, and lower gross motor function at nine months of age.

When infants need resuscitation, ICR may also have the potential to protect them from brain injuries. In our original study, peripheral capillary oxygen saturation and Apgar scores improved earlier in the ICR group, which might have facilitated recovery.[12] The ameliorated hypoxic, acidotic and hypoglycaemic state that might follow placental transfusion in the acute situation could theoretically lead to a reduction in brain damage.[20]

This study had some limitations. In the original trial, the proportion of infants that needed resuscitation in each group was 134 (17.2%) and 97 (12.4%), respectively.[12] The discrepancy in the proportion of resuscitations was significant. As infants were randomly assigned in the two groups, this was unexpected and we have not been able to find any reasons for this unbalance. In the original trial, the allocated intervention was followed in 65 (48.6%) cases in the ICR group in contrast with 97 (100%) in the early CC group.[12] The high degree of protocol deviation in the ICR group could mean these infants were in a more compromised state than the ones remaining in the ICR group, as previously described.[12] A separate analysis comparing outcomes between the subgroup of infants randomised to ICR but who received CC before 180 seconds, namely protocol violations, and the early CC group could not demonstrate any negative effects in the protocol violation group. Healthcare staff were accustomed to delayed CC, and an extensive training programme was performed before the study, but this was not enough to avoid protocol deviations. The significance in our results was lost when analysed per protocol, while the differences between groups were mainly unaltered, implying insufficient number of remaining participants in each group. Follow-up rates were low, hampering the generalisation of the applicability of the results. One reason why it was difficult to reach the caregivers by mobile phone could be that people have cheap and easy access to new telephone SIM cards in Nepal, which leads to frequent number changes. The lack of early and regular check-ups after birth in Nepal could be another reason, as there was no routine check-up where the interviews could have taken place. A third reason for the loss at follow-up might be that two years from the original trial were too long.

Finally, the IYCD is a new tool and this could have affected the interpretation of results. However, it is designed for settings all over the world, compared to many other tools developed in high-income and western cultures that use material that would be unfamiliar to children in the Nepalese culture. We therefore considered the IYCD a good option for our study. In a systematic review about

measurement tools for early child development in low-income and middle-income countries, the IYCD rated strongly for accuracy and feasibility criteria. However, it rated low in training and validity and moderate in reliability as the tool is still under evaluation and development.[29]

Several papers have suggested that neonatal resuscitation performed with an intact umbilical cord may facilitate the postnatal transition.[9,20] Presently, research on ICR is not regarded to have rendered enough evidence to be included in recommendations,[7] and therefore, this it is not standard practice. In our study, the combination of delaying CC and resuscitation measures did not seem to be associated with any harm. Despite several limitations, we believe the results of this paper are important, as we believe they are the first to show long-term outcomes after neonatal resuscitation with an intact umbilical cord.

5 | CONCLUSION

ICR was associated with neurodevelopment improvement at two years of age when compared to infants who received standard practice including early CC. To be able to reach the goals of the 2030 Agenda for Sustainable Development, we need attainable and equitable options that can reduce newborn infant mortality and morbidity, as well as improve early development. Intact cord resuscitation is a low-cost physiological management with the potential to improve neonatal recovery and long-term outcomes for infants after an intrapartum event. Future studies on ICR are needed, and long-term neurodevelopmental follow-up should be implemented. Our findings need to be verified or disproved in settings where fewer infants are lost to follow-up and larger numbers are included.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICAL APPROVAL

Ethical approval was obtained from the Nepal Health Research Council (NHRC) National Ethical Guidelines for Health Research in Nepal, reg. no. 218/2018. The original study was registered at clinicaltrials.gov NCT02727517, 2016/04/04. The caregivers were called in March and April 2018 to obtain their verbal consent for the assessments, which took place between June and October 2018.

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