

Effects of Timing of Umbilical Cord Clamping on Preventing Early Infancy Anemia in Japanese Term Infants With Planned Breastfeeding: A Randomized Controlled Trial

Eriko Shinohara (✉ eshino@yokohama-cu.ac.jp)

Department of Maternal Nursing, Graduate School of Medicine, Yokohama City University 3-9 Fukuura, Kanazawa-ku, Yokohama, Kanagawa, Japan <https://orcid.org/0000-0002-1309-9295>

Yaeko Kataoka

St Luke's International University: Sei Roka Kokusai Daigaku

Yukari Yaju

St Luke's International University: Sei Roka Kokusai Daigaku

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Abstract

Background

Japanese infants have relatively higher risk of anemia and neonatal jaundice. This study aimed to assess the effects of delayed cord clamping (DCC) on the prevention of anemia during early infancy in Japanese term infants with planned exclusive breastfeeding for 4 months. This study also aimed to explore the effects of DCC on neonatal jaundice.

Methods

We conducted an open-label, parallel-arm, multicenter randomized controlled trial of DCC (clamping the cord after more than a minute or pulsation stops) vs. early cord clamping (ECC; clamping the cord within 15 sec) at one birth center and two clinics in Japan. Pregnant women planning to have a vaginal birth and to exclusively breastfeed and term singleton infants delivered in cephalic presentation were included in this study. The primary outcome was spectrophotometric estimation of hemoglobin at 4 months. Secondary outcomes were anemia incidence at four months, four outcomes related to neonatal jaundice, hematocrit levels, and related outcomes.

Results

A total of 150 pregnant women were recruited. Participants (N = 138) were randomly allocated to two groups (DCC n= 68, ECC n = 70). There were no significant differences between the two groups in spectrophotometric estimation of hemoglobin at 4 months: mean difference = 0.1 g/dL, 95% confidence interval -0.14, 0.35, DCC 12.4 g/dL, ECC 12.3 g/dL. Only the hematocrit levels on days 3 to 5 were significantly higher in the DCC group than in the ECC group: DCC 57.0%, ECC 52.6%, mean difference = 4.4, 95% confidence interval 2.61, 6.20. There were no significant differences in other secondary outcomes, including outcomes related to neonatal jaundice.

Conclusion

Among Japanese term infants with planned exclusive breastfeeding, DCC showed no significant effects on spectrophotometric hemoglobin levels at 4 months compared with ECC. We observed significantly higher hematocrit levels in infants who underwent DCC, while these levels were within the normal range. Jaundice outcomes remained similar to those of infants who underwent ECC. Although a larger sample size is required to assess the effects of cord clamping on neonatal jaundice, DCC may prevent anemia in newborn infants.

Trial registration: UMIN-CTR; UMIN000022573, 06/01/2016 - retrospectively registered, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000023056

Background

Exclusive breastfeeding is one of the several risk factors for anemia in infancy [1]. In Japan, over half (54%) of mothers exclusively breastfeed for at least the first 3 months and over one-third continue exclusive breastfeeding at 6 months [2]. Although there has been no nationwide survey reported for infant anemia, a prefectural report from Okinawa concluded that 10–14% of breastfed infants have anemia; a higher rate of anemia than that among infants given formula [3]. Another study reported that exclusive breastfeeding was associated with a higher incidence of anemia in infancy compared with that with partial breastfeeding and formula [4].

Several randomized controlled trials have been conducted to clarify the effects of delayed cord clamping (DCC) on the prevention of anemia in infancy. In a Swedish study, ferritin levels at 4 months were significantly higher with DCC than that with early cord clamping (ECC) [5]. Likewise, in a Mexican study, ferritin and total body iron were significantly higher in the DCC group at 6 months [6]. In East Asia, a study from China reported that serum ferritin levels were significantly higher in the DCC group at 4 months [7]. A subgroup analysis in a previous study showed that DCC was particularly effective in neonates at high risk of anemia, in terms of increased body iron and stored iron, who were exclusively breastfed [6]. DCC may thus be considered a useful intervention among Japanese exclusively breastfed infants. However, DCC might increase the risk of neonatal jaundice. In the Swedish study, there was no significant difference between DCC and ECC groups for neonates treated with phototherapy [5]. Similarly, there were no significant differences for clinical jaundice between two groups in the Mexican study [6]. In East Asia, Chinese and Taiwanese studies reported no significant effects on jaundice-related outcomes of total serum bilirubin (TsB) [7, 8]; however, a Cochrane systematic review including unpublished data concluded that DCC might increase the risk of neonates requiring phototherapy [9]. Since East Asians are at relatively higher risk of neonatal jaundice [10], careful application of DCC is needed among this at-risk population, even though previous studies have reported potential benefits in preventing anemia in infancy [5–7]. Since the neonate is at high risk of hyperbilirubinemia resulting in clinical jaundice in Japan [11], and because of concerns that DCC increases the risk of developing hyperbilirubinemia in neonates, DCC has not yet been recommended [12]. In Japan, approximately 90% of clinics or hospitals have adopted a policy of ECC, conversely nearly 70% of midwifery birth centers have adopted the policy of DCC [13]. A retrospective cohort survey reported that only 1.8% of the neonates required phototherapy at a birth center where DCC was conducted [14]. In addition, a recent observational study reported no significant association between the timing of umbilical cord clamping, infant anemia at 3 to 5 months, and neonatal jaundice [15]. Although there is a need for high-quality research to be able to make the appropriate recommendation for the timing of umbilical cord clamping [12], there have been no randomized controlled trials of the timing of cord clamping in a Japanese population. Such a trial comparing DCC and ECC may also gather evidence suitable to other countries. Furthermore, updating evidence-based reviews is important for clinical decision-making. The most-recent Cochrane systematic review on the timing of cord clamping for term infants was updated in 2013 [9]. In contrast, the Cochrane review on the timing of cord clamping for preterm infants was updated in 2019, which suggested that DCC may reduce the risk of death among preterm infants before discharge [16]. Therefore, it is important to update the

review for term infants as well, and the results of this study may contribute to that by providing new clinical trial information.

Therefore, the main purpose of this study was to assess the effects of DCC on Japanese term infants, planned to be breastfed, at 4 months old in terms of preventing infant anemia. The secondary purpose was to assess whether DCC may increase the risk of neonatal jaundice.

Participants, Ethics, And Methods

Study design

This multicenter randomized controlled trial was conducted at two clinics and one birth center in Kanagawa, Japan from December 2015 to November 2016. The study protocol was approved by the Institutional Review Board of St. Luke's International University and registered with UMIN-CTR in Japan (UMIN000022573; dated June 01, 2016 - retrospectively registered, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000023056). This clinical trial adhered to the clinical research ethical guidelines for human subjects established on April 27, 2015 by the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labor and Welfare, Japan.

Participants

Participants were non-smoking pregnant Japanese women planning a vaginal birth and exclusive breastfeeding and neonates who were term, singleton, and cephalic presentations.

Participants were excluded if they had any maternal complications, fetal complications, or emergency cesarean section, were transferred to another hospital during pregnancy or delivery, were not literate in Japanese, or were unable to return in 4 months.

E.S chose study participants using medical records along with the study criteria. E.S or research assistants not in charge of the prenatal check-ups then recruited those participants who met the inclusion criteria. All potential participants who met the inclusion criteria were provided with both verbal and written research information, as well as a consent form to initial if they decided to partake in the study. After agreeing to participate in the study, they signed the consent form. For the inclusion of neonates in the study, their guardians (mother or father) were provided with the same explanation as that provided to pregnant women; they then signed the consent form on the infants' behalf.

Randomization and masking

Randomization was performed centrally using the Mujinwari system (Iruka System Corporation [17], Tokyo, Japan) with a block size of four via access to the internet. Because of different characteristics of participants in each facility, randomization was stratified by institution. E.S or research assistants performed allocations when normal progress leading to vaginal delivery was predicted (i.e. full dilation of the cervix in primiparas or 6–8 cm dilation of the cervix in multiparas). Allocations were provided to the

midwives who were to perform the intervention, and assistant midwives, who measured the time from neonatal delivery to cord clamping, were informed on the group assignment of the participants at the time of delivery. Masking was not applied in this trial. Because of the characteristics of the intervention, participants, and midwives in charge of the intervention were aware of treatment allocations. Research assistants and E.S, who evaluated the outcomes, were also aware of allocations.

Intervention

Midwives clamped the cord using a Kocher clamp after more than a minute following neonatal delivery or when the cord pulsation stopped in the intervention group and within 15 seconds after neonatal delivery in the control group. To assure similarity in settings, all neonates were placed on the chest or abdomen of their mothers just after delivery. Moreover, the position of the mothers was set to about 30-degree semi-Fowler position after neonatal delivery.

Midwives who were involved in the deliveries were instructed on the intervention procedure using the study protocol and had been trained before the study commenced.

Outcomes

The primary outcome was the spectrophotometric hemoglobin (SpHb) level at 4 months. Secondary outcomes were as follows: incidence of anemia (SpHb < 11.0 g/dL), TsB on days 3–5, incidence of “over the excess value of TsB,” incidence of phototherapy, transcutaneous bilirubin level on days 1–4, hematocrit on days 3–5, incidence of polycythemia, birth weight, infant vital signs (heart rate, respiratory rate, and temperature) after birth, infant growth (weight, height, head circumference, and chest circumference) at 1 and 4 months old, adverse effects (seizures, admission to neonatal intensive care units, neonatal death), and maternal hemorrhage (third stage, within 2 hours). Data were collected at the following time points: during hospital or clinic stay and at 1 and 4 months old.

Measurements

SpHb monitoring

Non-invasive and continuous Hb measurements using pulse oximeter (Radical-7®; Mashimo, Irvine, CA, USA) technology was conducted to determine the SpHb levels at 4 months. The non-invasive estimation of the Hb level by pulse-CO-oximetry in infants and neonates undergoing surgery showed a significant correlation with the invasive standard laboratory measurement of total Hb ($r = 0.73$, $p < .00$) and demonstrated clinically acceptable agreement with standard laboratory Hb measurements [18]. This continuous monitoring of SpHb in the stable state was required during measurement. E.S measured the value 2 minutes after a stable SpHb was detected.

Anemia

If the SpHb level was less than 11.0 g/dL at 4 months, infants were noted to be anemic.

TsB

Blood samples were collected for measuring the concentration of TsB on days 3–5. To minimize the invasiveness of the procedure for neonates, blood samples for measuring TsB were collected during routine blood sampling for congenital metabolic disorder mass screening. Blood was collected using hematocrit capillary tubes by a midwife or nurse and immediately centrifuged; then, the TsB level was measured using a BL-300 jaundice meter® (TOITU, Tokyo, Japan) or similar device.

Excess value of total serum bilirubin

The bilirubin nomogram by Imura [19] for prediction of hyperbilirubinemia was used because it is clinically most commonly used in Japan.

Phototherapy

The actual number of neonates who received phototherapy was counted.

Transcutaneous bilirubin

A non-invasive bilirubinometer (JM-103® or JM-105®; Konica Minolta, Tokyo, Japan) was used to measure the transcutaneous bilirubin concentration by putting the device to the chest and forehead of the neonate on days 1–4. The value used was determined as the average of one measurement each from the forehead and chest. Transcutaneous bilirubin shows a high correlation with TsB [20] and is routinely used for screening for hyperbilirubinemia in clinical settings.

Hematocrit

The same blood samples collected for measuring TsB were also used for determining the hematocrit. The hematocrit was measured after centrifuging capillary blood.

Polycythemia on days 3–5

If the hematocrit level was $\geq 65\%$, infants were noted to be polycythemic.

Data collection

Mothers and neonates were checked by midwives or nurses immediately after birth, at 1 hour, and then at 2 hours and cared for according to routine practice. The data on maternal hemorrhage and neonatal vital signs were collected at those times. In two facilities, mothers stayed 5 days, except for those who were willing to be discharged earlier or needed to be sent to another hospital for abnormalities. In one clinic, the routine stay was 3 days. In all facilities, they had rooming-in, and breastfeeding was encouraged from soon after birth. All neonates' transcutaneous bilirubin levels were checked using a bilirubinometer every morning. At day 4, they usually had blood collection for mass screening. At that time, additional blood was collected for measuring TsB and hematocrits. However, the neonates whose transcutaneous bilirubin levels were high during daily checks had blood tests performed on other days as well. For the neonates who had blood tested several times, the highest values of the TsB or hematocrit were used as outcome data. After discharge, they usually had a check-up at 2 weeks to evaluate weight and jaundice, and the mothers also had support for breastfeeding from midwives. At the 1-month check-up, the doctor or

midwives evaluated the neonates' health including growth, jaundice, and nutrition (exclusive breastfeeding, mixed, or formula milk). One month's data were collected at that point. At 4 months, the researcher collected the data of neonates' growth, nutrition, and SpHb. At a time convenient for the mothers, E.S or research assistants collected demographic characteristics of mothers and neonates and delivery outcomes.

Sample size

This study explored the effects of cord clamping timing on Hb status at 4 months old by comparing the DCC and ECC groups. From a previous cohort study [15], the estimated mean SpHb value in the ECC group was about 11.5 g/dL. Previous studies [21, 22] indicated that the Hb level was 11.5 g/dL in the ECC group and 12.0 g/dL in the DCC group, and an effect size of 0.5 g/dL was predicted. For the primary outcome measure of SpHb, based on 80% power to detect a significant difference of 0.5 g/dL with a 0.8 g/dL standard deviation ($\alpha = 0.05$, two-sided), 40 participants were required for each study group. Assuming a dropout rate of 20%, a minimum total of 100 patients was required.

Statistical analysis

Descriptive statistics were used to summarize the participant's backgrounds. To compare the DCC and ECC groups, a *t*-test was used for the primary outcome of mean difference (MD) in SpHb. For secondary outcomes, *t*-testing was used for MDs, the Mann-Whitney *U* test was used for non-parametric variables, and the chi-squared test was used for bivariate analysis. Risk ratios (RR) and their confidence intervals (CI) were calculated, as well as confidence intervals for difference in means.

The primary outcome was assessed according to the intention-to-treat principle. One participant in the DCC group was not included in the analysis because their data was missing due to technical difficulties. However, one subject in the DCC group who did not complete the protocol was included. Secondary outcomes were assessed using intention-to-treat principles for continuous variables and intention-to-treat for nominal variables. Per-protocol analysis and as-treated analysis were performed as adjunct methods. In per-protocol analysis, participants who deviated from the protocol were excluded from the analysis. In as-treated analysis, analysis was conducted as if participants were treated, regardless of allocation. All data were analyzed using IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY).

Results

Baseline characteristics

Between December 2015 and June 2016, a total of 263 women were screened for eligibility, and about half were excluded after either not meeting the inclusion criteria or declining to participate in the study. A total of 150 women agreed to participate, of whom 138 were randomly allocated to the DCC group ($n = 68$) or ECC group ($n = 70$). Figure 1 displays a flow diagram of trial recruitment and follow-up. As of 4 months, only one infant in the DCC group had been lost to follow-up. Thus, in the final analysis, there were 67 infants in the DCC group and 70 in the ECC group. Some data for secondary outcomes and

baseline characteristics were missing, but the number of missing values was small and considered to be missing at random, therefore imputation of missing values was not performed.

Baseline characteristics of mothers and neonates did not differ significantly between the two groups (Table 1). The median time of cord clamping was 8 s (SD = 30 s, range 3-185 s) in the ECC group and 123 s (SD = 124 s, range 5-622 s) in the DCC group. One neonate in the DCC group underwent clamping before 60 s, and six neonates in the ECC group underwent clamping after 15 s (Fig. 1). In each group, two infants were exclusively being fed formula at 4 months (Fig. 1).

Primary and secondary outcomes

SpHb levels at 4 months were 12.4 g/dL in the DCC group and 12.3 g/dL in the ECC group, showing no significant differences between the intervention and control groups (MD 0.1, 95% CI -0.14-0.35) (Table 2). Only one infant in the DCC group had a SpHb level lower than 11.0 g/dL and was screened as anemic (Table 2).

Four markers of neonatal jaundice were used to compare the effects of DCC and ECC on neonatal jaundice as secondary outcomes: highest TsB level (at days 3–5); excess value of TsB; receiving phototherapy; and transcutaneous bilirubin levels during days 1–4. The TsB level (at days 3–5) was 12.8 mg/dL in the DCC group and 12.2 mg/dL in the ECC group, showing no significant difference (RR = 0.6, 95% CI -0.61-1.80; Table 2). Six neonates (9.1%) were over the excess value of TsB in the DCC group, compared with five (7.6%) in the ECC group (RR = 1.2, 95% CI 0.39–3.74; Table 2). Seven neonates (10.3%) in the DCC group and five (7.1%) in the ECC group received phototherapy, showing no significant difference (RR = 1.4, 95% CI 0.48–4.25; Table 2). Although no significant differences were evident, the DCC group tended to show higher values for all the four markers of neonatal jaundice compared with that in the ECC group. These differences also seemed slightly wider in the per-protocol analysis and as-treated analysis (Tables 3, 4). Some TsB values were missing for days 3–5 in 6 neonates (4.3%; DCC, n = 2; ECC, n = 4); these values were impossible to collect, because five neonates had been transferred to other hospitals, and one value was not recorded on the data collection sheet. For the same reason, five values were missing for phototherapy (3.6%; DCC, n = 2; ECC, n = 3) (Table 2). For transcutaneous bilirubin levels during days 1–4, data could not be collected, because the neonates were transferred to other hospitals or the days of hospitalization were shortened by 4 days because of the policy of the facility or desires of the mother.

Only the hematocrit level at days 3–5 was significantly higher in the DCC group (57.0%) compared with that in the ECC group (52.6%; MD 4.4, 95% CI 2.61–6.20) (Table 2). Although no significant differences were identified, the MD in infant weight between groups was 88.5 g (95% CI -27.26-204.19 g) at birth, 30.1 g (95% CI -129.64-189.93) at 1 month, and -3.3 g (95% CI -258.62-252.09) at 4 months (Table 2). Other secondary outcomes showed no significant differences (Table 2).

Per-protocol and as-treated analyses

Per-protocol analysis and as-treated analysis were performed to compare the results between the two groups. The median time of cord clamping was 7 s (SD = 3 s; range, 3–15 s) in the ECC group and 126 s (SD = 125 s; range, 17–622 s) in the DCC group with per-protocol analysis and 7 s (SD = 3 s; range, 3–15 s) in ECC group and 123 s (SD = 122 s; range, 17–622 s) in the DCC group with as-treated analysis. Even with these two sub-analyses, no significant differences were seen for the primary outcome of SpHb at 4 months between the intervention and control groups (Tables 3, 4). Likewise, no significant differences between groups were evident for neonatal jaundice or other secondary outcomes. Only the hematocrit at 3–5 days showed a significant difference (Tables 3, 4).

Discussion

Main findings

This randomized controlled trial comparing ECC and DCC sought to explore their effects on the prevention of anemia in infancy at 4 months of age in a high-risk population of mothers and neonates who were planned to be breastfed. Our results indicated that a delay in clamping the cord after more than a minute or when pulsation stopped had no significant effect on infant SpHb level at 4 months compared with that in the ECC group, in which the median clamping time was 8 s according to intention-to-treat analysis. The secondary outcome of jaundice showed no significant difference between the DCC and ECC groups. DCC increased hematocrit levels at days 3–5 within the normal range

Strengths

This was the first randomized controlled trial to report timing of cord clamping for Japanese term breastfed infants. The targeted population had a high rate of exclusive breastfeeding and was considered at high risk for infant anemia as well as high risk of neonatal jaundice because of an East Asian ethnicity. The results of this study may contribute to recommended clinical guidelines especially considering the risks of DCC for jaundice. World Health Organization guidelines suggest that the risk of serious hyperbilirubinemia associated with DCC should be examined [23]; furthermore, Japanese guidelines mention the need for high-quality research related to timing of cord clamping to make recommendations [12]. The results of this study provide strong evidence for making such recommendations in the Japanese guidelines. Another strength of this study was the high follow-up rate for participants at 4 months.

Limitations

Several limitations of this study warrant acknowledgment. First, we used the SpHb to evaluate anemia, rather than hematological indices such as ferritin or mean corpuscular volume, which are more detailed measures for assessing iron deficiency and have reportedly shown significant effects from DCC in previous studies [5, 6]. Second, although an acceptable correlation ($r = 0.73$) has been identified between SpHb and serum Hb [18], SpHb cannot be simply compared with serum Hb. Third, the population in this study included only breastfed, healthy, term infants with mothers who had no maternal complications; thus, this result may not apply to mothers and neonates with complications.

Interpretation (in light of other evidence)

This study targeted mothers who were willing to exclusively breast feed and found that delay in clamping the cord after more than a minute or when pulsation stopped had no significant effect on infants' SpHb level at 4 months, compared with that in the ECC group (cord clamped within 15 seconds). The secondary analyses: per-protocol, and as-treated analysis, did not change the outcomes. Over 80% of mothers were exclusively breastfeeding in this targeted population. The results of this study are similar to those of previous studies in different racial groups [24, 25]. Conversely, an Indian study showed significantly higher Hb concentrations in the DCC group [26]. Maternal Hb levels were lower (Hb < 10.0 g/dL), and both birth weights and Hb levels in infants were much lower than in the current study [26]. In addition, a Mexican study comparing the timing of cord clamping found a greater effect in infants who were born to mothers with low ferritin levels and had DCC than for those born to mothers with normal ferritin levels with respect to infant body iron and stored iron [6]. Anemia in pregnancy is associated with increased rates of low birth weight [27], and low birth weight infants are at high risk of anemia in infancy [28]. This study hypothesized that participants were at high risk of anemia in infancy due to being exclusively breastfed at 4 months, but the population in this study may not have been at high risk. Only one neonate showed positive results from screening for anemia, the rates of maternal anemia were average, and birth weight and growth were normal. Therefore, in addition to exclusive breastfeeding, further randomized controlled trials using DCC and ECC, and targeting subtypes such as populations at higher predicted risk of anemia, appear warranted.

For neonatal jaundice, no significant difference was evident between the DCC and ECC groups. However, the DCC group tended to have higher values for all four outcomes related to hyperbilirubinemia, compared with the ECC group. These results were similar to those of other studies in East Asian populations. Previous randomized controlled trials in China and Taiwan reported no significant effects on jaundice-related outcomes [7, 8]. Although not significant, MDs in transcutaneous bilirubin values of 0.5–0.6 mg/dL have been reported in DCC groups [7, 8]. In the high-risk Nepali population, in terms of living at high altitude, comparisons of the timing of cord clamping resulted in no significant differences for transcutaneous bilirubin values [29]. A Cochrane systematic review [9] reported that fewer infants in the ECC group required phototherapy for jaundice than in the DCC group. The possibility that neonatal jaundice is increased in the DCC group is thus undeniable. However, we consider that the differences in total serum or transcutaneous bilirubin levels of about 0.6 mg/dL, with average values of 12.2–12.8 mg/dL, may have no large effects clinically, assuming the effects may be limited. Participants of this study were low-risk women and neonates delivered at birth centers or clinics, and obstetric outcomes related to jaundice, such as prolonged labor or vacuum extraction, were few. From our results, we assume that the danger of jaundice does not warrant recommending the practice of ECC for low-risk births at birth centers or clinics. In addition, the rate of exclusive breastfeeding is higher in those who deliver at birth centers than in those who give birth in hospital [30]. Even though there was no positive outcome detected for DCC in this study with regard to SpHb, considering the negative effect on preventing infant anemia and the potential risk of exclusive breastfeeding, ECC may not be an appropriate practice for this

population. Recommendation of timing of cord clamping may differ by characteristics of women and neonates.

The only values that were significantly higher with DCC than with ECC were for hematocrit at days 3–5, with analysis according to the intention-to-treat principle, per-protocol analysis, and as-treated analysis. In all analyses, values were within the normal range in both groups (DCC = 57% vs. ECC = 52–53%), with about a 4.5% higher mean in the DCC group. This may be an indication of the positive effects from DCC in terms of preventing anemia in the neonatal period. These results were similar to those of previous studies that found a significantly higher hematocrit with DCC [21, 31]. A previous study suggested that the effects lasted 2 months [31]. In these studies, no harmful outcomes from polycythemia-related effects were reported [21, 31]. Although no statistically significant differences were evident, the MD in infant weight was 88.5 g, and weight tended to be higher in the DCC group. This increased hematocrit in DCC may be the result of increased blood volume, since there was no difference in other baseline data related to hematocrit. High hematocrit contributed to preventing anemia in the neonatal period but can also lead to increased bilirubin [32]. Bilirubin is produced when the erythrocyte disintegrates [32]. A higher hematocrit may thus presumably be related to increased TsB values or other outcomes of neonatal jaundice among DCC in this study, but any effects appeared limited.

In addition, the effects of placental transfusion because of gravity need to be taken into consideration. In this study, neonates were placed on the chest or abdomen of the mother after birth. One reliable study explored the effects of gravity and found no significant difference in birth weight between introitus- and abdomen-level groups [33], but since a small, reliable study posited gravity effects for placental transfusion, the results in other populations must be interpreted with caution.

Conclusion

In this study, we found that DCC had no significant effect on SpHb levels at 4 months compared with that of ECC. However, DCC increased hematocrit levels at days 3–5 within the normal range, which may be an effect in terms of preventing anemia in the newborn period. Additionally, there was no statistically significant effect of DCC on the four studied outcomes of neonatal jaundice (TsB value at 3–5 days, over the excess value of TsB, phototherapy, and transcutaneous bilirubin value at days 1–4).

To assess the effects of DCC on infant anemia more clearly, further research should be conducted in a targeted population of mothers or infants at higher risk of anemia of infancy. In addition, although there remained the possibility of an increase in the values of jaundice-related outcome in the DCC group, the clinical effects appeared limited. Further study with a larger sample size is needed to assess the effects of cord clamping on neonatal jaundice.

List Of Abbreviations

95% CI, 95% confidence interval; DCC, delayed cord clamping; ECC, early cord clamping; MD, mean difference; RR, risk ratio; SD, standard deviation; SpHb, spectrophotometric hemoglobin; TsB, total serum bilirubin.

Declarations

Ethics approval and consent to participate

All study participants provided informed consent, and the study design was approved by the Institutional Review Board of St. Luke's International University, Tokyo, Japan (Approval no. 15-064). The date of approval was November 20, 2015.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Eriko Shinohara: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - Original Draft, Writing – Review & Editing, and Project administrating.

Yaeko Kataoka: Conceptualization, Methodology, Validation, Supervision, and Writing – Review & Editing.

Yukari Yaju: Methodology, Data curation, Supervision, and Validation.

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Tables

Table 1				
Baseline Characteristics of Participants (N=138)				
	DCC (n=68)		ECC (n=70)	
Maternal characteristics				
Maternal age	30.5	(5.0)	31.1	(5.0)
Parity				
primipara	24	(35.3)	21	(30.0)
multipara	44	(64.7)	49	(70.0)
Anemia (Hb < 11.0g/dl)	32	(47.1)	37	(52.9)
Blood type O (all Rh +)	17	(25.0)	16	(22.9)
History of photo therapy (only for multipara; n=93,DCC=44,ECC=49)	7	(10.3)	7	(10.0)
Neonatal characteristics				
Gender				
male	34	(50.0)	36	(51.4)
female	34	(50.0)	34	(48.6)
Gestational age				
37w	8	(11.8)	0	(0.0)
38w	5	(7.4)	13	(18.6)
39w	34	(50.0)	26	(37.1)
40w	17	(25.0)	23	(32.9)
41w	4	(5.9)	8	(11.4)
Low birth weight (\geq 2500g)	3	(4.4)	6	(8.6)
Maximum weight loss (%) (n=134,DCC=67,ECC=67)	7.5	(1.8)	7.1	(1.7)
Meconium was not excreted at day 4 (n=109, DCC=54 ECC=55)	25	(46.3)	28	(50.9)
Increased weight 0-4mths (g)	3603	(595.0)	3701	(685.1)
Delivery				

Type of delivery				
Duration of delivery	507	(372.1)	509	(381.7)
Duration of third stage of labor (mins)	9.2	(5.9)	8.2	(5.2)
Instrumental delivery (vacuum or forceps)	3	(4.4)	0	(0)
Position of delivery				
semi-Fowlers	66	(97.0)	66	(94.3)
knees	1	(1.5)	3	(4.3)
lateral	1	(1.5)	1	(1.4)
Use of oxytocine (induction of labor)	4	(5.9)	7	(10.0)
Use of oxytocine immediately after birth (in the third stage)	57	(83.8)	54	(77.1)
Placenta (g)	569	(80.4)	563	(85.7)
Apgar score (1min) less than 7	1	(1.5)	3	(4.3)
Apgar score (5min) less than 7	0	(0)	0	(0)
Cephalohematoma	0	(0)	2	(2.9)
Nutrition				
Type of nutrition (during confinement)				
exclusive breast feeding	40	(59.7)	48	(70.6)
mixed	27	(40.3)	20	(29.4)
formula milk	0	(0)	0	(0)
Type of nutrition (1 month)				
exclusive breast feeding	50	(74.6)	53	(75.7)
mixed	17	(25.4)	17	(24.3)
formula milk	0	(0)	0	(0)
Type of nutrition (4 month) (n=137; DCC=67, ECC=70)				
exclusive breast feeding	54	(80.6)	61	(87.1)
mixed	11	(16.4)	7	(10.0)
formula milk	2	(3.0)	2	(2.9)

Weaning food (4 month)	0	(0)	0	(0)
Data are presented as mean (<i>SD</i>) or <i>n</i> (%).				

Table 2								
Primary and Secondary Outcomes Analyzed by Intent to Treat								
	DCC		ECC		Relative risk (95%CI) /			
					Mean difference (95%CI)		<i>p</i> value	
Primary outcome								
Transcutaneous Hb (SpHb) at 4 months (<i>n</i> =137/DCC=67,ECC=70)	12.4	(0.8)	12.3	(0.6)	0.1	[-0.14, 0.35]	0.40	
Secondary outcome								
Neonates								
1) Anemia (SpHb < 11.0 g/dl) (<i>n</i> =137/DCC=67, ECC=70)	1	(0.7)	0	(0)	0.9	[0.64, 1.25]	0.49	
2) Total serum bilirubin (TsB) (day 3 to 5) (mg/dl) ^a (<i>n</i> =132/DCC=66, ECC=66)	12.8	(3.4)	12.2	(3.6)	0.6	[-0.61, 1.80]	0.33	
3) Over the excess level of TsB (%) ^b (<i>n</i> =132/DCC=66, ECC=66)	6	(9.1)	5	(7.6)	1.2	[0.39, 3.74]	1.00	
4) Photo therapy (%) ^c (<i>n</i> =133/DCC=66, ECC=67)	7	(10.3)	5	(7.1)	1.4	[0.48, 4.25]	0.37	
5) TcB level (during day 1 to 4) (mg/dl)								
day1 (<i>n</i> =137/DCC=68, ECC=69)	5.0	(1.8)	4.6	(1.9)	0.3	[-0.29, 0.95]	0.29	
day2 (<i>n</i> =135/DCC=67, ECC=68)	8.7	(2.2)	8.6	(2.2)	0.1	[-0.63, 0.87]	0.75	
day3 (<i>n</i> =126/DCC=62, ECC=64)	11.4	(2.6)	10.9	(2.9)	0.5	[-0.45, 1.50]	0.29	
day4 (<i>n</i> =119/DCC=58, ECC=61)	11.9	(2.7)	11.4	(3.1)	0.5	[-0.57, 1.53]	0.37	
6) Haematocrit level (at day	57.0	(5.2)	52.6	(5.2)	4.4	[2.61,	<0.01*	

3 to 5) (%)^a (n=132/DCC=66, ECC=66)						6.20]	
7) Polycythemia (Hct\geq65%)	3	(4.6)	2	(3.0)	1.5	[0.26, 8.82]	0.68
8) Birth weight (g)	3118	(332.5)	3030	(354.5)	88.5	[-27.26, 204.19]	0.13
9) Vital signs after birth							
After birth							
heart rate (times/mins) (n=131/DCC=64, ECC=67)	154	(15.3)	150	(13.2)	3.9	[-1.05, 8.83]	0.12
respiration (times/mins) (n=129/DCC=63, ECC=66)	59.3	(9.5)	61	(11.6)	-1.7	[-5.45, 1.96]	0.35
body temperature (°C) (n=129/DCC=63, ECC=66)	37.0	(0.5)	37.0	(0.5)	0.0	[-0.14, 0.20]	0.75
SpO2 (%) (n=132/DCC=65, ECC=67)	98	(1.8)	98	(2.0)	-0.3	[-0.93, 0.37]	0.40
1 hour							
heart rate (times/mins)	150	(10.4)	150	(11.8)	0.3	[-3.42, 4.09]	0.86
respiration (times/mins) (n=137/DCC=68, ECC=69)	56	(11.6)	57	(9.1)	0.5	[-4.61, 2.40]	0.54
body temperature (°C) (n=137/DCC=68, ECC=69)	37.3	(0.5)	37.2	(0.5)	0.0	[-0.14, 0.22]	0.67
SpO2 (%)	99	(1.2)	99	(1.2)	-0.1	[-0.48, 0.32]	0.70
2 hour							
heart rate (times/mins) (n=137/DCC=67, ECC=70)	142	(13.3)	140	(12.9)	1.6	[-2.85, 6.00]	0.48
respiration (times/mins) (n=137/DCC=67, ECC=70)	52	(7.3)	52	(8.9)	-0.3	[-3.09, 2.44]	0.82

body temperature (°C) (n=137/DCC=67, ECC=70)	37.2	(0.4)	37.2	(0.4)	0.0	[-0.14, 0.15]	0.93
SpO2 (%) (n=137/DCC=67, ECC=70)	99	(1.1)	99	(1.5)	0.1	[-0.35, 0.54]	0.68
10) Infant growth							
1 month weight (g) (n=136/DCC=67, ECC=69)	4206	(517.2)	4175	(421.4)	30.1	[-129.64, 189.93]	0.71
4 month weight (g) (n=137/DCC=67, ECC=70)	6727	(751.1)	6731	(759.7)	-3.3	[-258.62, 252.09]	0.98
11) Adverse effects							
seizure (%)	0	-	0	-	-	-	-
admitted to NICU within 24hrs (%)	0	-	0	-	-	-	-
neonatal death (%)	0	-	0	-	-	-	-
Mother							
12) Haemorrhage at third stage of labor (g)	288	(224.3)	275	(185.0)	13.3	[-55.84, 82.41]	0.71
total (until 2 hours)	419	(283)	380	(194)	39.0	[-42.43, 120.26]	0.24
Data are presented as mean (<i>SD</i>) or <i>n</i> (%).							
^a The highest value among blood sampling conducted during day 3 to 5 were used.							
^b Over the excess value are based on Standard of Imura (1985).							
^c Two (DCC=1, ECC=1) received phototherapy before meeting the standard of phototherapy for prevention. One (ECC=1) did not received phototherapy even over the level for the standard of phototherapy.							
* <i>p</i> < .05.							

Table 3							
Per-protocol Analysis for Transcutaneous Hb at 4 months , Neonatal Jaundice and Polycythemia							
	DCC		ECC		Relative risk (95%CI) / Mean difference (95%CI)		<i>p</i> value
Primary outcome							
Transcutaneous Hb (SpHb) at 4 months							
(<i>n</i> =127/DCC=65,ECC=62)	12.4	(0.8)	12.3	(0.7)	0.1	[-0.17, 0.35]	0.50
Secondary outcome							
Anemia (SpHb < 11.0 g/dl) (<i>n</i> =126/DCC=64,ECC=62)	1	(1.6)	0	(0.0)	1.0	[0.95, 1.02]	1.00
Neonatal jaundice							
Total serum bilirubin (TsB) (at day 3 to 5)^a (<i>n</i> =122/DCC=63, ECC=59)	12.8	(3.5)	12.1	(3.4)	0.7	[-0.55, 1.91]	0.27
Over the excess level of transcutaneous bilirubin (TsB)^b (<i>n</i> =122/DCC=63, ECC=59)	6	(9.5)	4	(6.8)	1.4	[0.42, 4.73]	0.75
Photo therapy^c (<i>n</i> =123/DCC=63, ECC=60)	7	(11.1)	4	(6.7)	1.7	[0.51, 5.40]	0.53
Polycythemia							
Hematocrit level (at day 3 to 5) (%)^a (<i>n</i> =121/DCC=62, ECC=59)	57.2	(5.3)	52.5	(5.2)	4.6	[2.74, 6.53]	<0.01*
Polycythemia (Hct≥65%) (<i>n</i> =121/DCC=62, ECC=59)	3	(4.6)	2	(3.0)	0.7	[0.10, 4.00]	0.68
Data are presented as means (<i>SD</i>) or <i>n</i> (%).							
^a The highest value among blood sampling conducted during day 3 to 5 were used.							
^b Over the excess value are based on Standard of Imura (1985).							
^c Two (DCC=1, ECC=1) received phototherapy before met to standard of phototherapy for preventively. One (ECC=1) did not received phototherapy even over level of the standard of phototherapy.							
* <i>p</i> < .05.							

Table 4								
As-treated Analysis for Transcutaneous Hb at 4 months, Neonatal Jaundice and Polycythemia								
	DCC		ECC		Relative risk (95%CI) / Mean difference (95%CI)		<i>p</i> value	
Primary outcome								
Transcutaneous Hb (SpHb) at 4 months								
(<i>n</i> =137/DCC=72, ECC=65)	12.4	(0.8)	12.3	(0.7)	0.1	[-0.18, 0.32]	0.59	
Secondary outcome								
Anemia (SpHb < 11.0 g/dl) (<i>n</i> =137/DCC=72, ECC=65)	1	(1.4)	0	(0)	1.0	[0.96, 1.01]	1.00	
Neonatal jaundice								
Total serum bilirubin (TsB) (at day 3 to 5) ^a (<i>n</i> =132/DCC=70, ECC=62)	12.9	(3.4)	12.0	(3.5)	0.9	[-0.33, 2.08]	0.15	
Over the excess level of transcutaneous bilirubin (TsB) ^b (<i>n</i> =132/DCC=70, ECC=62)	7	(10.0)	4	(6.5)	1.6	[0.48, 5.04]	0.54	
Photo therapy ^c (<i>n</i> =133/DCC=70, ECC=63)	8	(11.4)	4	(6.3)	1.8	[0.57, 5.69]	0.38	
Polycythemia								
Hematocrit level (at day 3 to 5) (%) ^a (<i>n</i> =131/DCC=69, ECC=62)	57.0	(5.1)	52.4	(5.2)	4.6	[2.84, 6.41]	<0.01*	
Polycythemia (Hct≥65%) (<i>n</i> =131/DCC=69, ECC=62)	3	(4.3)	2	(3.2)	0.7	[0.12, 4.54]	1.00	
Data are presented as mean (<i>SD</i>) or <i>n</i> (%).								
^a The highest value among blood sampling conducted during day 3 to 5 were used.								
^b Over the excess value are based on Standard of Imura (1985).								
^c Two (DCC=1, ECC=1) received phototherapy before met to standard of phototherapy for preventively. One (ECC=1) did not received phototherapy even over level of the standard of phototherapy.								

Figures

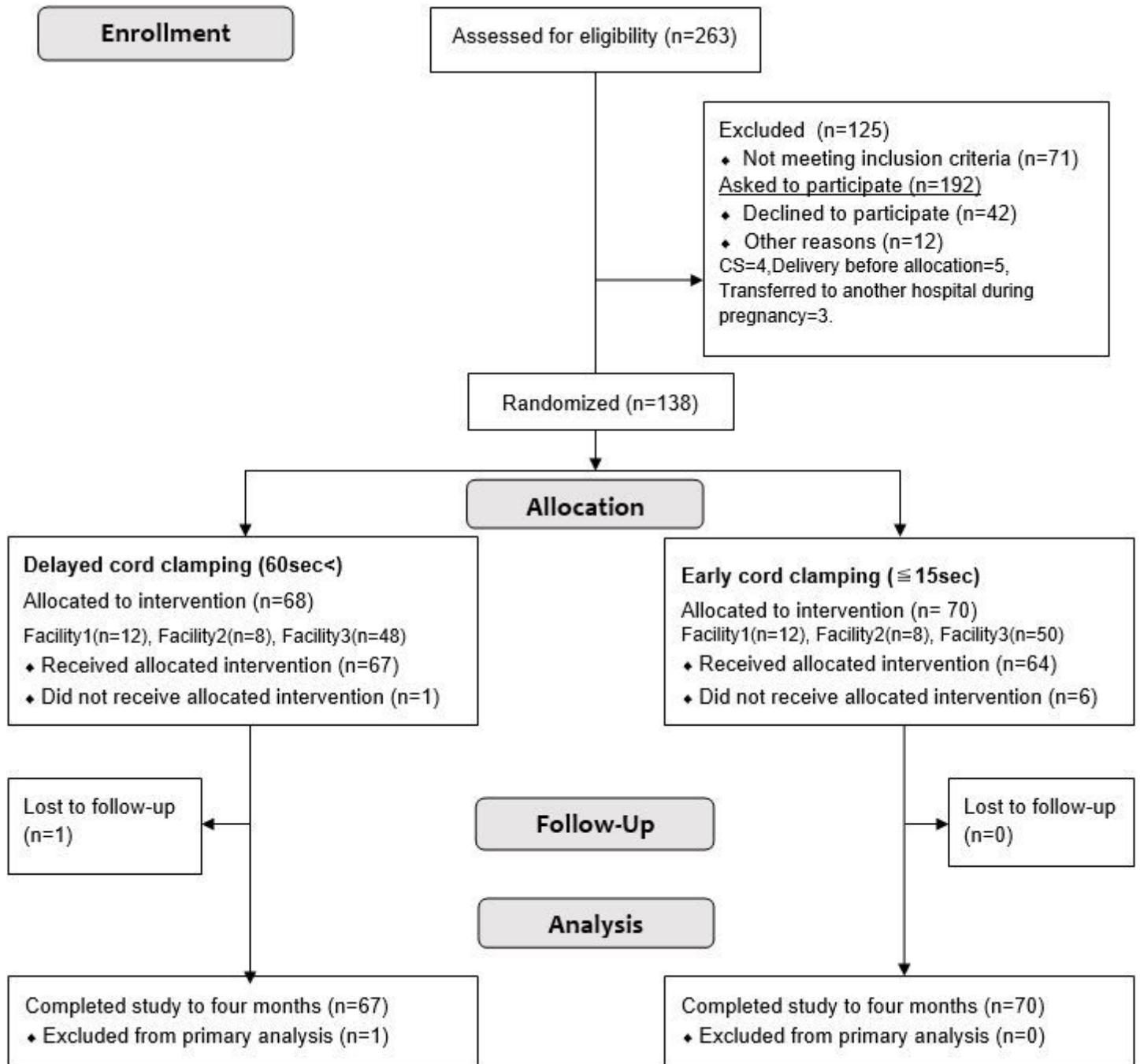


Figure 1

Flow diagram of the trial comparing timing of cord clamping, showing the number of patients followed up during the trial. a. Four (DCC n=2/ ECC n=2) were exclusively formula fed at four months