Impact of delayed cord clamping on respiratory distress in late preterm and early term infants in elective cesarean section: a single centre, phase III, randomised controlled trial

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Summary

Background Delayed cord clamping (DCC) has the potential to alleviate respiratory distress by augmenting blood volume and oxygenation, although there is currently a lack of direct evidence to support this. Late preterm and early term infants born via elective cesarean section (CS) are known to be more vulnerable to the neonatal respiratory distress (NRD). This study was designed to examine the effect of DCC on NRD of these infants.

Methods Conducted from January 1, 2019 to January 31, 2024 at Shanghai First Maternity and Infant Hospital, this single-centre, phase III, open-label randomised controlled trial included newborns delivered via elective CS between 34^{+0} and 38^{+6} weeks of gestation. Participants were excluded if fetus had suspected or confirmed congenital malformations, metabolic diseases, intrauterine growth restriction, late fetal heart rate deceleration or fetal distress. Pregnant women and their infants were randomised into immediate cord clamping (ICC) within 10 s of birth or DCC for 60 s and stratified by late preterm or early term. The primary outcome was the incidence of NRD which was defined as requiring oxygen or airway pressure support within the first 24 h of life. This study was approved from the Ethics Committee of Shanghai First Maternity and Infant Hospital, School of Medicine, Tongji University (KS 18126, KS1947). Chinese Clinical Trial Registry (ChiCTR1800017865), registered on August 18th, 2018.

Findings Of 2610 randomised women, 1418 neonates were included in the DCC group and 1419 in the ICC group. The mean maternal age for both groups was 33 (4) years, and all mothers were of Han ethnicity. The mean gestational age of the neonates was 37.9 (0.9) weeks in both groups. NRD occurred in 119 (8.4%) in DCC versus 135 (9.5%) in ICC (Adjusted Relative Risk [aRR] 0.93, 95% CI 0.75–1.14). There were no significant differences in infant and maternal adverse events such as low Apgar score (aRR 0.74, 95% CI 0.25–2.19), hypothermia (aRR 1.00, 95% CI 0.89–1.12), hypoglycemia (aRR 1.04, 95% CI 0.77–1.38), maternal intrapartum massive bleeding (aRR 0.96, 95% CI 0.76–1.19), or the requirement for transfusion (aRR 0.34, 95% CI 0.10–1.15).

Interpretation Delayed cord clamping was safe for both mothers and infants in late preterm and early term delivered by elective cesarean section, while it did not reduce the risk of early respiratory diseases.

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Research in context

Evidence before this study

Late preterm and early term infants are at an increased risk of respiratory morbidities, especially when born via elective cesarean sections (CS) without labour. Delayed cord clamping (DCC) might reduce these respiratory morbidities by enhancing the pulmonary blood flow and oxygenation of such infants. We searched the MEDLINE (via PubMed), Embase, and the Cochrane Central databases for clinical trials published in English between January 1, 2010, and September 1, 2019. The search terms included "delayed cord clamping", "late preterm", "early term", "elective cesarean section", and "respiratory distress". The search results indicated that DCC in CS is safe and effective, with outcomes comparable to those in spontaneous vaginal deliveries (SVDs). However, DCC is still underutilized in many regions. Some cohort studies and quality improvement initiatives have shown the benefits of DCC on the respiratory systems of these infants. Nevertheless, randomised controlled trials (RCTs) that specifically address neonatal respiratory distress (NRD) as a primary outcome in late preterm and early term infants are scarce.

Added value of this study

This large - scale, single - centre, phase III, open - label RCT focused on late preterm and early term infants delivered by elective CS. It is one of the largest studies of its kind, offering robust data from a substantial sample size of 2837 neonates. We stratified the infants by gestational age (34–36 weeks and 37–38 weeks) to conduct a more in - depth analysis. This allowed for a more detailed understanding of DCC's effects on different maturity levels. The results clearly demonstrated that DCC is safe for both mothers and infants during elective CS, without increasing the risk of maternal or neonatal adverse events. Although DCC did not significantly reduce the incidence of NRD within 24 h after birth compared to immediate cord clamping, it significantly increased neonatal haemoglobin and hematocrit levels in the first 1–2 h after birth. This finding is crucial for understanding the short - term physiological effects of DCC in this population.

Implications of all the available evidence

The available evidence, including this study, strongly advocates for the increased implementation of DCC in guidelines, emphasizing that DCC is safe for both mothers and infants in late preterm and early term deliveries via elective CS. Healthcare providers should be more confident in applying DCC during CS, as it does not pose additional risks. However, the lack of a significant reduction in NRD indicates that DCC alone may not be sufficient to prevent respiratory morbidities in these infants. Additionally, integrating advanced monitoring techniques and more detailed risk factor stratification may help identify subgroups of newborns who could benefit most from DCC. Overall, these implications can guide clinical decision - making and further research in the field of neonatal care during CS.

Introduction

Delayed cord clamping (DCC) has emerged as a widely embraced practice in spontaneous vaginal deliveries (SVDs), as it enhances placental transfusion, increases neonatal blood volume, and elevates haemoglobin levels.[1,2] Both the American College of Obstetricians and Gynecologists (ACOG) and the Neonatal Resuscitation Program (NRP®) endorse DCC for longer than 30–60 s postpartum to optimize these advantages.[3,4] However, while DCC in SVDs is a well-established practice, its application in cesarean sections (CS) has historically been met with uncertainty due to concerns about the absence of uterine contractions, maternal anesthesia effects, and altered haemodynamic status during surgery.[5,6]

Recent randomised controlled trials (RCTs) have provided robust evidence supporting the safety and efficacy of DCC in CS, demonstrating outcomes comparable to those observed in SVDs without increasing maternal or neonatal risks.[7,8] These findings have been incorporated into guidelines advocating for broader adoption of DCC.[3,4] Nevertheless, DCC remains underutilized in many regions. For instance, a Dutch trial reported that DCC is common practice in vaginal deliveries in the Netherlands and is implemented in 90% of SVDs but only 19% of CS.[9] Similarly, In China, a national survey has revealed that the overall implementation of DCC was 52.5% in SVDs and 32.5% in CS, respectively.[10] These variations in clinical practice highlight both the opportunity and need for further research on DCC, as well as targeted initiatives to promote its adoption, particularly in settings where its implementation remains low.

Late preterm (34–36 weeks) and early term (37–38 weeks) infants, who constitute a significant portion of births, are at increased risk of respiratory complications, particularly when born via elective CS without labour. This risk is attributed to lung immaturity, impaired lung fluid clearance, and reduced surfactant release.[11,12] While DCC has been proven effective in reducing mortality and morbidities in very preterm infants, its impact on late preterm and early term infants, who have lower mortality but are prone to acute respiratory conditions, such as respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), and persistent pulmonary hypertension of the newborn (PPHN),[13,14] warrants further investigation.

DCC has been shown to enhance pulmonary blood flow and ventilation in asphyxiated preterm lambs[15] and improve physiological stability, including heart rate and oxygen saturation in term infants shortly after birth.[16] Historical cohort comparison studies[17] and quality improvement initiatives[18] have reported significantly lower rates of delivery room intubation and respiratory distress syndrome in infants following increased DCC implementation. However, RCTs specifically addressing respiratory distress as a primary outcome in late preterm and early term infants remain scarce. This RCT aims to evaluate the impact of DCC on neonatal respiratory distress and its safety for late preterm and early term infants undergoing elective CS and their mothers.

Methods

Study design and participants

This study is a single-centre, phase III, open-label randomised controlled trial registered in the Chinese Clinical Trial Registry (registration number: ChiCTR1800017865) on August 18th, 2018, to address the differences of DCC versus immediate cord clamping (ICC) in the incidence of respiratory distress between late preterm and early term infants delivered via elective CS from January 1, 2019, to January 31, 2024.

Participant eligibility criteria included pregnant women between 34^{+0} and 38^{+6} weeks of gestation who delivered by elective CS for various indications without labour (Supplementary Table S2). Participants were excluded if the fetus had suspected or confirmed congenital malformations, metabolic diseases, intrauterine growth restriction, late fetal heart rate deceleration, or fetal distress. In the original study protocol, we tried to exclude the pregnant women with gestational diabetes mellitus (GDM) requiring medication or unstable blood serum glucose level during the pregnancy, due to the belief that this condition may elevate the risk of NRD of their infants. However, GDM affected approximately 20% of this population and using medication was common in our pilot study. Therefore, GDM was removed from the exclusion criteria before ethical approval.

Ethics

The study was approved by the Ethics Committee of Shanghai First Maternity and Infant Hospital, School of Medicine, Tongji University (KS 18126, KS1947). And the study adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Written informed consent was obtained from all participants before the randomisation.

Randomisation

Eligible pregnant women were randomly assigned to either DCC or ICC. Random number sequences were generated by computer for each gestational age stratum (34–36 weeks and 37–38 weeks). Based on the pilot study, the ratio of late preterm infants to early term infants delivered via elective CS was 1:5. Consequently, the random sequence codes assigned to these infants adhered to the same 1:5 ratio. The randomisation process was managed by a statistician who was not involved in patient care to ensure unbiased allocation. Multiple births were assigned the same treatment. There was no crossover permitted between the immediate and delayed umbilical cord clamping groups. If safety was concerning, the infant underwent immediate umbilical cord clamping.

Due to the obvious DCC maneuver, DCC procedure was not concealed from the mothers, obstetricians and the birth attendant neonatal physicians. However, the neonatal physicians working in the neonatal and maternal wards were blinded to the assignment of the infants. Two statistical experts completed the statistical analysis and interpretation of the results from this study. One from the clinical research centre of the maternal hospital, and the other from a children's hospital. Neither of them participated in the randomisation and clinical management of the recruited newborns in this study.

Procedures

After acquisition of a scheduled elective CS (WC), the research coordinator (TTW) obtained the allocation of either DCC or ICC from the random number sequences after the informed consent was obtained from the eligible pregnant woman and her spouse, and told the neonatal physician who attended each delivery. For DCC during cesarean delivery, the scrub nurse held the infant at the level of the incision for a minimum of 60 s, wrapped in a preheating (34 °C) cotton, sterile towel. Infants were dried and gently stimulated to produce a respiratory effort. The neonatal physician observed the newborn and reported the time every 15 s and notified the obstetrician to cut the umbilical cord at 60 s. If the pregnant woman was assigned to the ICC group, the infant was transferred to the radial warmer after the umbilical cord was cut, within 10 s of birth.

Outcomes

All infants were managed according to the institutional protocols. Infants included in the study were vigilantly monitored through symptomatic assessment and pulse oximetry for oxygen saturation and pulse. Capillary blood samples were obtained within 2 h after birth under aseptic conditions and measured by the predetermined analyser (Radiometer ABL90). Respiratory support was initiated for infants exhibiting respiratory distress, assessed by the Silverman-Anderson Score, and included interventions. The primary outcome was neonatal respiratory distress (NRD) defined as the need for respiratory support within 24 h after birth and consisting of one or more of the following: supplemental

oxygen with a fraction of inspired oxygen of more than 0.30 for at least 4 continuous hours, the use of noninvasive ventilation (NIV) including continuous positive airway pressure (CPAP), noninvasive intermittent positive pressure ventilation (nIPPV) or high-flow nasal cannula for at least 2 consecutive hours, the use of mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

Secondary outcomes included a range of clinical indicators to comprehensively evaluate the health impact of DCC. These included the rate of admission to the neonatal intensive care unit, hospital stay, persistent pulmonary hypertension of newborn (PPHN), hyperbilirubinemia (defined as the requirement for phototherapy), measurement of neonatal haemoglobin and hematocrit. Polycythemia was addressed through partial exchange transfusion in neonates with symptoms with a hematocrit exceeding 75% and clinical manifestations. Additional exploratory outcomes involved neonatal anaemia (defined as haemoglobin level in the first 2 h less than 14.5 g/dL), neonatal hypoglycemia (defined as blood glucose levels less than 2.6 mmol/L at 1–2 h of life), hypothermia (defined as axillary body temperature less than 36.5 °C upon exiting the operation room). Clinical hyperbilirubinemia was evaluated within 14 days of life using a transcutaneous bilirubinometer (TcB, Konica Minolta JM-103) and confirmed by total serum bilirubin (TSB) estimation. Neonates with significant hyperbilirubinemia were managed and monitored according to institutional guidelines aligned with American Academy of Paediatrics and National Institute for Health and Care Excellence guidelines.

During the implementation of the study, the safety of mothers and infants was highly guarded, and the process was clearly documented for the safety review. Maternal intrapartum hemorrhage was closely monitored, with hemorrhage exceeding 500 mL, and the requirement of transfusion classified as massive maternal hemorrhage within 24 h after the CS. The maternal and infant outcomes were defined and listed in Supplementary Table S1. All outcome assessments were performed by blinded team members who were not involved in the care of the recruited neonates.

Statistics

The statistical analysis was designed to compare the outcomes between the ICC and DCC groups. Baseline characteristics were summarized using descriptive statistics. Continuous variables were tested for normality using the Shapiro–Wilk test and presented as means (SD) or median (IQR) as appropriate whereas categorical variables were reported as percentages. Two group analyses were conducted using a Student *t* or a Mann–Whitney U tests as appropriate for continuous variables and Chi-square or Fisher exact tests for categorical variables.

For the primary outcome of NRD, the incidence was compared between the two groups according to the intention-to-treat principle. Analyses were prespecified in the trial protocol or the statistical analysis plan before investigators were made aware of the results according to allocated group. The trial was planned to recruit 1356 participants in each group to detect a significance level (α) of 0.05 and a power level (1-β) of 0.8. This calculation was based on an expected primary outcome occurrence of 10% in the ICC group and 7% in the DCC group. Following ethical approval from the Institutional Review Board (IRB), the final aim was to reduce the occurrence of respiratory distress by 30% through the implementation of DCC. To account for potential attrition, a 5% allowance was incorporated, resulting in a decision to expand the sample size to 1420 infants per group.

For the primary and secondary dichotomous outcomes, log-binomial regression to obtain RRs and corresponding 95% CIs, and modified Poisson regression in case of nonconvergence. This approach facilitated the estimation of crude and adjusted risk ratios (RR and aRR) for the outcomes of interest. For secondary outcomes of continuous variables analysed using linear regression models, the crude and adjusted mean difference (MD and aMD) with 95% CI were calculated. The adjusted confounding factors in the model included gestational age (*continuous*), small for gestational age (SGA, *yes versus no*), twins (*yes versus no*), antenatal corticosteroid (ANS, *yes versus no*), and maternal gestational diabetes mellitus (GDM, *yes versus no*), pregnancy-induced hypertension (PIH, *yes versus no*).

Subgroup analyses were performed to investigate the effects within specific populations, including preterm and term infants, SGA and non-SGA infants, twins and singletons, and maternal conditions such as GDM and PIH, as well as sex differences (male or female). Crude RR and aRR were calculated focusing on the primary outcome.

To assess the robustness of our results, we performed several sensitivity analyses. First, per-protocol analyses were conducted, only including infants received assigned intervention, for both primary and secondary outcomes. Second, non-vigorous infants were seen as the contraindication for DCC. Using Apgar score less than 7 at 1 min as a surrogate for non-vigorous, we conducted an analysis after exclusion of those infants in either group. Third, infants born in the same birth (cluster) were randomised together to the intervention. However, it is recommended to assume that the outcomes of these infants from the same cluster are not independent.[19] Therefore, Generalized Estimating Equations (GEE) were conducted to account for the correlation within twin pairs by treating each pair as a cluster.

All statistical tests were two-sided, and a p-value of less than 0.05 was considered statistically significant.

Data were analysed using the statistical software Stata (StataCorp, Revision 21, 2017).

Role of the funding source

The funding source played no role in the study design, the data collection, analysis, and interpretation, the preparation of the manuscript, or the decision to submit it for publication.

Results

Recruited infants

A total of 2765 pregnant women planning for elective CS were screened for randomisation, resulting in 2610 women being randomised. The mean maternal age for both groups was 33 (4) years, and all mothers were of Han ethnicity. Of these, 1292 pregnant women and 1421 neonates were assigned to DCC, while 1318 women and 1419 neonates were assigned to ICC. After consent was withdrawn for 3 infants in the DCC group, 1418 infants in the DCC group and 1419 infants in the ICC group, with the same mean gestational age of 37.9 (0.9) weeks, were included in the intention-to-treat analysis (Fig. 1). Among all infants, 460 (16.2%) were multiple births, 1456 (51.3%) were male, and 275 (9.7%) were late preterm infants.

Treatment adherence

The adherence rates to randomisation were 1296 out of 1418 (91.4%) in DCC and 100% in ICC. The primary reasons for 122 infants non-adherence in the DCC group included 61 (50%) infants needing immediate resuscitation, 51 (41.8%) due to the refusal of the attending obstetrician, 10 (8.2%) DCC less than 60s. Of the infants who required immediate resuscitation, 55 received initial steps and crying, including warming and drying, and opening the airway. Six infants received positive pressure ventilation, none of them needed chest compression or further resuscitation.

Basic characteristics of DCC and ICC

The infant and maternal clinical characteristics were comparable between the DCC and ICC groups, including maternal age [mean (SD), 33 (4) years in DCC and 33 (4) years in ICC], GDM [n (%), 183 (12.9) in DCC and 191 (13.5) in ICC], pregnancy-induced hypertension [n (%), 129 (9.1) in DCC and 113 (8.0) in ICC], infant gestational age [mean (SD), 37.9 (0.9) weeks in both DCC and ICC], sex [male, 732 (51.6) in DCC and 724 (51.0) in ICC], birth weight [mean (SD), 3175 (459) grams in DCC and 3140 (459) grams in ICC], and SGA status [n (%), 66 (4.7) in DCC and 85 (6.0) in ICC]. However, the incidence of twin status differed significantly between the groups, with 14.5% (206/1418) in the DCC group compared to 17.9% (254/1419) in the ICC group (p = 0.017) (Table 1).

The major reasons for elective CS in these mothers included 1150 (40.5%) repeat CS, 460 (17.7%) twin pregnancies, 399 (14.1%) breech positions, and other reasons, as shown in Table 2.

Primary and secondary outcomes

In the intention-to-treat analysis, NRD occurred in 119 out of 1418 infants (8.4%) in the DCC group, compared to 135 out of 1419 infants (9.5%) in the ICC group (RR 0.88, 95% CI 0.70–1.12; aRR 0.93, 95% CI 0.75–1.14). NIV or MV was required in 44 infants (3.1%) in the DCC group and 42 infants (3.0%) in the ICC group (RR 1.05, 95% CI 0.69–1.59; aRR 1.11, 95% CI 0.78–1.57). MV was needed in 26 infants (1.8%) in the DCC group and 21 infants (1.5%) in the ICC group (RR 1.24, 95% CI 0.70–2.19; aRR 1.32, 95% CI 0.76–2.28). One newborn in the DCC group was diagnosed with PPHN, while none in the ICC group were diagnosed with the condition. No significant differences in the rate of admission [n (%), 256 (18.1) in DCC and 237 (16.7) in ICC], hospital stay [mean (SD): 5.9 (4.2) versus 6.2 (4.5) days] and hyperbilirubinemia [n (%), 204 (14.4) in DCC and 188 (13.3) in ICC] were observed between the groups. Infants in the DCC group had significantly higher levels of haemoglobin measured within the first 2 h of life [mean (SD): 22.7 (2.7) g/dL versus 21.6 (2.8) g/dL; MD 1.1, 95% CI, 0.9, 1.3 g/dL aMD 1.2; 95% CI 1.0–1.4 g/dL] and hematocrit [mean (SD): 69.5 (8.0) versus 66.0 (8.4)%; MD 3.4%, 95% CI 2.8, 4.0; aMD 3.5%, 95% CI 2.9–4.1%].

For the safety of infants and mothers during the study, there were no significant differences in infant and maternal adverse events such as low Apgar score [n (%), 6 (0.4) in DCC versus 9 (0.6) in ICC; RR 0.67, 95% CI 0.24, 1.87; aRR 0.74, 95% CI 0.25, 2.19], hypothermia in the delivery room [n (%), 437 (30.8) versus 437 (30.8); RR 1.00, 95% CI 0.90, 1.12; aRR 1.00, 95% CI 0.89, 1.12], hypoglycemia measured 1–2 h after birth [n (%), 86 (6.4) versus 83 (6.1); RR 1.05, 95% CI 0.78, 1.41; aRR 1.04, 95% CI 0.77, 1.38], maternal intrapartum massive bleeding [n (%), 134 (9.5) versus 144 (10.2); RR 0.93, 95% CI 0.74, 1.16; aRR 0.96, 95% CI 0.76, 1.19], or the maternal need for transfusion within 24 postpartum hours [n (%), 4 (0.3) versus 11 (0.8); RR 0.36, 95% CI 0.12, 1.14; aRR 0.34, 95% CI 0.10, 1.15] (Table 3).

Subgroup analyses

Due to the higher incidence of respiratory distress in late preterm compared to early term infants, the pregnant women were stratified into late preterm or early term strata and randomised, respectively. Subgroup analyses based on preterm and term infants revealed no significant differences in the risk of NRD, maternal and infant adverse events (Supplementary Table S2 and Table 4.). Furthermore, the effects of DCC versus ICC on the primary outcome of NRD did not differ by sex,

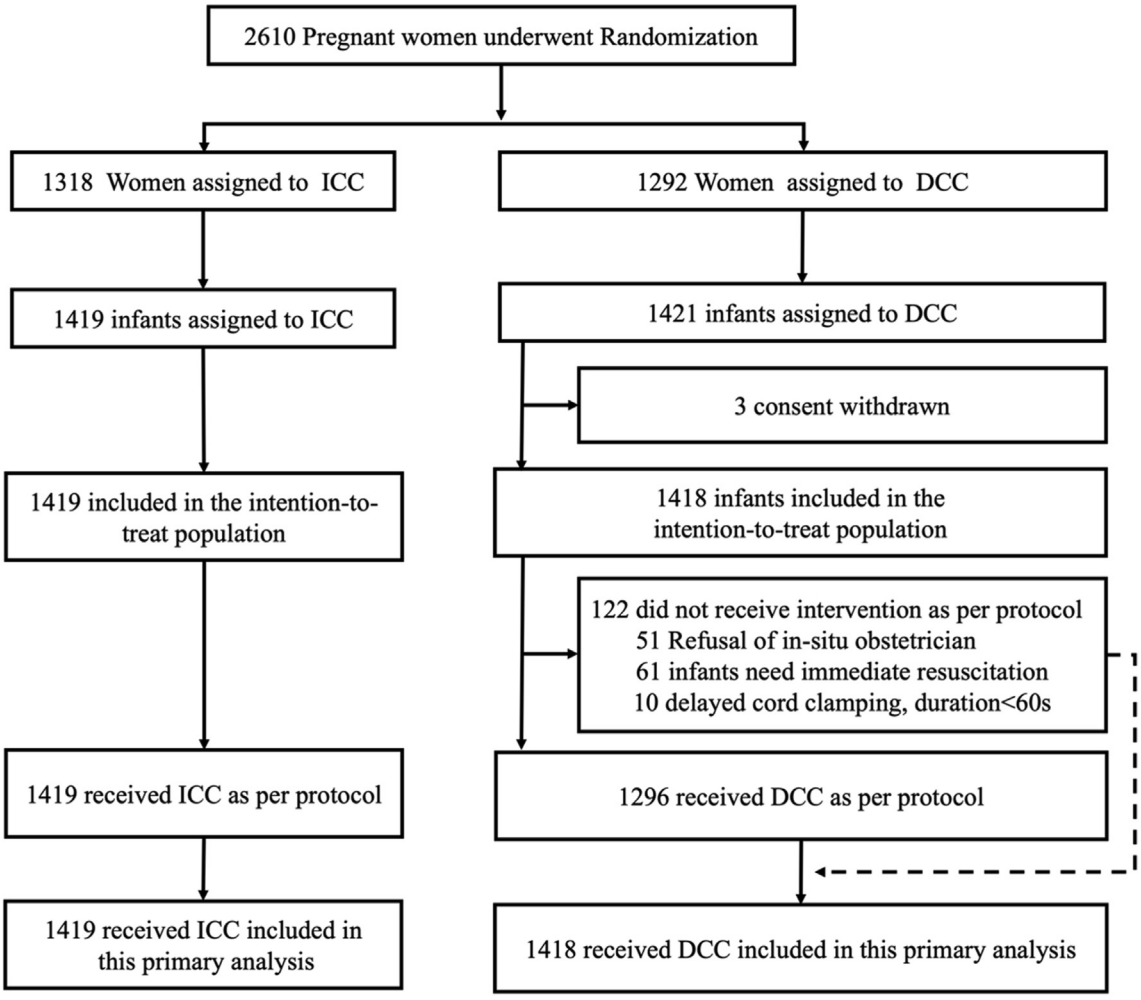


Fig. 1: Consort flow diagram. ICC, immediate cord clamping defined as clamping within 10 s after delivery; DCC, delayed cord clamping defined as clamping 60 s or more after delivery. The primary outcome was neonatal respiratory distress (NRD) defined as the need for respiratory support within 24 h after birth and consisting of one or more of the following: supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least 4 continuous hours, the use of noninvasive ventilation including continuous positive airway pressure (CPAP), noninvasive intermittent positive pressure ventilation (nIPPV) or high-flow nasal cannula for at least 2 consecutive hours, the use of mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

twin status, SGA, GDM, or PIH (Table 4 and Supplementary Tables S3 and S4).

Sensitivity analysis

Per-protocol analyses indicated that the incidence of the primary outcome did not differ significantly between the two groups or in subgroup analyses (Table 5 and Supplementary Table S5). Similarly, the secondary outcomes showed no significant differences, except for a notable increase in the level of infant haemoglobin in the DCC group [mean (SD): 22.8 (2.6) versus 21.6 (2.7) g/dL; aMD 1.3 g/dL, 95% CI 1.1–1.5 g/dL] and hematocrit, without causing significant adverse effects in either infants or mothers (Table 5 and Supplementary Table S5). After excluding infants with a 1-min low Apgar score, the results remained consistent, showing no significant difference in the primary outcome and safety outcomes (Supplementary Tables S6 and S7). GEE analysis, treating twins as clusters, also confirmed the robustness of these findings (Supplementary Table S8).

Discussion

The primary objective of this randomised controlled clinical trial was to assess the impact of DCC on the prevention of respiratory diseases in newborns delivered by elective CS at 34–38 weeks gestational age. Our study found that DCC was safe for the mothers and newborns during the elective CS delivery and resulted in

significantly higher median haemoglobin and hematocrit levels within the first 1–2 h after birth. However, it did not significantly reduce the incidence of NRD within 24 h post-birth compared to ICC.

Our findings align with previous research indicating that DCC can significantly elevate neonatal haemoglobin and hematocrit levels.[20] The physiological reasons for elevated haemoglobin include transfusion from the placenta to the infant and improved iron stores.[21,22] Higher postnatal haemoglobin levels are particularly important for preterm infants. DCC was associated with reduction in preterm mortality[15] and the need for packed red cell transfusion.[2,23] This also brings potential long-term benefits for preterm infants. For late preterm and early term infants, higher haemoglobin levels could potentially benefit their development, as iron stores are crucial for organ development, especially brain development.[24]

CS is a maternal life-saving practice and its rate is about 32.1–37.5% in United States and China.[25,26] It was well documented that the infants delivered by CS before the onset of spontaneous labour are associated with the high risk of respiratory morbidities and neonatal admissions.[27] This RCT focused on late preterm and early term infants delivered by elective CS, with a particular emphasis on respiratory diseases, as these are major causes for admission to neonatal nurseries or, in severe cases, intensive care units.[28–30]

Theoretically, DCC improves haemoglobin levels, leading to better oxygen delivery and potentially reducing the incidence of respiratory diseases in this population.[20] Retrospective data supported this premise; for example, a study of 705 twin pregnancies ≥24 weeks of gestation showed a significantly lower incidence of respiratory distress syndrome (RDS) in the DCC group compared to the ICC group (6.7% versus 15.2%, $p < 0.001$).[31] However, RCTs with respiratory distress or respiratory support as secondary outcomes have not demonstrated significant effects in reducing these risks. The latest Cochrane review[1] included only two RCTs involving gestational ages under 32–34 weeks and one with gestational ages above 32–34 weeks. These RCTs found no significant differences between DCC and ICC groups in the incidence of RDS (for infants <32–34 weeks: DCC 22/82 versus ICC 20/83, risk ratio 1.21 [0.64, 2.27]; for infants >32–34 weeks: DCC 3/42 versus ICC 4/44, risk ratio 0.79 [0.19, 3.30]).

Consistent with these findings, our study, with its large sample size, further demonstrated a non-significant impact of DCC on respiratory morbidities or their severity. Several factors might explain this lack of the significant reduction. First, it is speculated that increases in the haemoglobin and circulation oxygen delivery are not sufficient to prevent neonatal respiratory morbidities caused by delayed clearance of lung fluid due to elective CS. Second, the primary reason for respiratory distress in late preterm and early-term infants remains inadequate surfactant production, which can be attributed to relatively lower gestational age and immature pulmonary structures, as supported by the positive correlation between RDS incidence and gestational age.[32] Although DCC can potentiate the physiological transition from the fetal to the neonatal circulation,[1] it does not necessarily promote alveolar aeration or enhance surfactant production. Furthermore, subgroup analyses based on sex, gestational age, singleton versus twin status, and maternal conditions such as GDM, PIH also failed to demonstrate significant improvements in NRD outcomes.

Aligning with previous findings,[7] our study adds robust evidence supporting the safety of DCC in elective

Factor	DCC (n = 1418)	ICC (n = 1419)	p-value
Gestational age in weeks	37.9 (0.9)	37.9 (0.9)	0.11
Gestational age (weeks)			
34–36	138 (9.7)	137 (9.7)	0.95
37–38	1280 (90.3)	1282 (90.3)	
Birth weight, grams	3175 (459)	3140 (459)	0.045
Sex			
Female	686 (48.4)	695 (49.0)	0.76
Male	732 (51.6)	724 (51.0)	
Multiple-birth status			
Singletons	1212 (85.5)	1165 (82.1)	0.017
Twins	206 (14.5)	254 (17.9)	
Small for gestational age	66 (4.7)	85 (6.0)	0.13
Maternal age	33 (4)	33 (4)	0.18
Maternal age > 35 years	479 (33.8)	442 (31.1)	0.14
Chorioamnionitis	18 (1.3)	24 (1.7)	0.44
Gestational diabetes mellitus	183 (12.9)	191 (13.5)	0.70
Pregnancy-induced hypertension	129 (9.1)	113 (8.0)	0.28
Maternal Haemoglobin prior to delivery, g/dL	11.8 (1.1)	11.8 (1.1)	0.26
Pre-pregnancy maternal BMI	22.4 (3.3)	22.2 (3.4)	0.23
Antenatal Corticosteroid	34 (2.4)	33 (2.3)	0.90

DCC: Delayed Cord Clamping; ICC: Immediate Cord Clamping; BMI: body mass index. Data are n (%) or mean (SD).

Table 1: **Characteristics of mothers and infants, according to randomised treatment group.**

Reasons for ECS	DCC (N = 1418)	ICC (N = 1419)	Total
Twin pregnancy	206 (14.5)	254 (17.9)	460/2837 (16.2)
Placenta disease	48 (3.4)	133 (9.4)	181/2837 (6.4)
Repeat cesarean -section	627 (44.2)	523 (36.9)	1150/2837 (40.5)
Uterine disease	7 (0.5)	6 (0.4)	13/2837 (0.5)
Eclampsia	103 (7.3)	107 (7.5)	210/2837 (7.4)
Maternal health issues	17 (1.2)	20 (1.4)	37/2837 (1.3)
As requested	135 (9.5)	124 (8.7)	259/2837 (9.1)
Breech position	209 (14.7)	190 (13.4)	399/2837 (14.1)
Others	66 (4.7)	62 (4.8)	128/2837 (4.5)

DCC: Delayed Cord Clamping; ICC: Immediate Cord Clamping. Data presents as n (%).

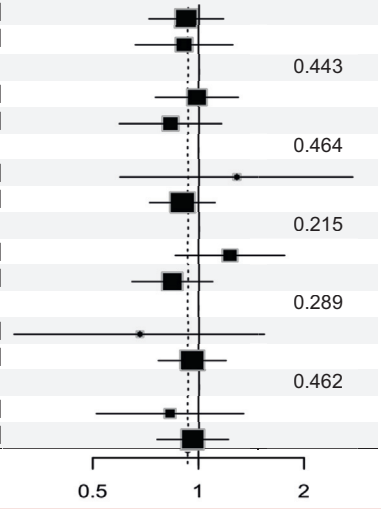
Table 2: **Reasons for elective cesarean section (ECS).**

Outcomes	DCC[a] (N = 1418)	ICC[a] (N = 1419)	Effect Variables	Effect (95% CI)	Adjusted Effect (95% CI)[b]
Primary outcome					
Neonatal respiratory distress	119/1418 (8.4)	135/1419 (9.5)	RR	0.88 [0.70, 1.12]	0.93 [0.75, 1.14]
Noninvasive ventilation or Mechanical ventilation	44/1418 (3.1)	42/1419 (3.0)	RR	1.05 [0.69, 1.59]	1.11 [0.78, 1.57]
Mechanical ventilation	26/1418 (1.8)	21/1419 (1.5)	RR	1.24 [0.70, 2.19]	1.32 [0.76, 2.28]
Secondary outcomes					
Admission	256/1418 (18.1)	237/1419 (16.7)	RR	1.08 [0.92, 1.27]	1.10 [0.96, 1.28]
Hospital stay, d	5.9 ± 4.2	6.2 ± 4.5	MD	−0.3 [−0.5, 1.1]	−0.3 [−0.5, 1.1]
Hyperbilirubinemia	204/1418 (14.4)	188/1419 (13.3)	RR	1.09 [0.90, 1.31]	1.10 [0.93, 1.31]
Haemoglobin, g/dL	22.7 ± 2.7	21.6 ± 2.8	MD	1.1 [0.9, 1.3]	1.2 [1.0, 1.4]
Hematocrit, %	69.5 ± 8.0	66.0 ± 8.4	MD	3.4 [2.8, 4.0]	3.5 [2.9,4.1]
Exploratory outcomes					
Neonatal anaemia	5/1418 (0.4)	17/1419 (1.2)	RR	0.29 [0.11, 0.80]	0.30 [0.11, 0.80]
Apgar <7 @ 1 min	6/1418 (0.4)	9/1419 (0.6)	RR	0.67 [0.24, 1.87]	0.74 [0.25, 2.19]
Hypothermia	437/1418 (30.8)	437/1419 (30.8)	RR	1.00 [0.90, 1.12]	1.00 [0.89, 1.12]
Temperature <36 °C	11/1418 (0.8)	18/1419 (1.3)	RR	0.61 [0.29, 1.29]	0.61 [0.29, 1.28]
Hypoglycemia	86/1355 (6.4)	83/1372 (6.1)	RR	1.05 [0.78,1.41]	1.04 [0.77, 1.38]
Maternal bleeding, mL	398 ± 87	407 ± 128	MD	−9 [−17, 1]	−9 [−16, 0]
Maternal bleeding >500 mL	134/1418 (9.5)	144/1419 (10.2)	RR	0.93 [0.74, 1.16]	0.96 [0.76, 1.19]
Maternal Haemoglobin post-delivery, g/dL	11.3 ± 1.2	11.3 ± 1.2	MD	0 [0, −0.1]	0 [0, 0.1]
Maternal transfusion	4/1418 (0.3)	11/1419 (0.8)	RR	0.36 [0.12, 1.14]	0.34 [0.10, 1.15]

DCC: Delayed Cord Clamping; ICC: Immediate Cord Clamping; RR: relative risk; MD: mean difference. [a]Data are n/N (%) or mean (SD). [b]Adjusted gestational age, small for gestational age, twin, antenatal corticosteroid, gestational diabetes mellitus, pregnancy-induced hypertension.

Table 3: **Outcomes in delayed cord clamping and immediate cord clamping groups by intention-to-treat analyses.**

Subgroup	DCC[a] *no. of events/total no. (%)*	ICC[a] *no. of events/total no. (%)*	RR [95% CI]	aRR [95% CI] of Neonatal Respiratory Distress [b]	P for interaction
Gestational age					0.980
Preterm	52/138 (37.7)	60/137 (43.8)	0.86 [0.65, 1.15]	0.92 [0.72,1.17]	
Term	67/1280 (5.2)	75/1282 (5.9)	0.89 [0.65, 1.23]	0.91 [0.66,1.25]	
Sex					0.443
Male	73/732 (10.0)	81/724 (11.2)	0.89 [0.66, 1.20]	0.99 [0.75,1.29]	
Female	46/686 (6.7)	54/695 (7.8)	0.86 [0.59, 1.26]	0.83 [0.59,1.15]	
SGA					0.464
Yes	10/66 (15.2)	10/85 (11.8)	1.29 [0.57, 2.92]	1.28 [0.60,2.76]	
No	109/1352 (8.1)	125/1334 (9.4)	0.86 [0.67, 1.10]	0.90 [0.73,1.12]	
Birth status					0.215
Singletons	39/206 (18.9)	40/254 (15.8)	1.20 [0.80, 1.80]	1.23 [0.86,1.76]	
Twins	80/1212 (6.6)	95/1165 (8.2)	0.81 [0.61, 1.08]	0.84 [0.65,1.10]	
GDM					0.289
Yes	10/183 (5.5)	17/191 (8.9)	0.61 [0.29, 1.31]	0.68 [0.30,1.55]	
No	109/1235 (8.8)	118/1228 (9.6)	0.92 [0.72, 1.18]	0.96 [0.77,1.20]	
PIH					0.462
Yes	19/129 (14.7)	18/113 (15.9)	0.92 [0.51, 1.68]	0.83 [0.51,1.34]	
No	100/1289 (7.8)	117/1306 (9.0)	0.87 [0.67, 1.12]	0.96 [0.76,1.21]	



DCC: Delayed Cord Clamping; ICC: Immediate Cord Clamping; SGA, small for gestational age; GDM, gestational diabetes mellitus; PIH, pregnancy-induced hypertension. [a]Data are n/N (%) or mean (SD). RR: relative risk; aRR: adjusted relative risk. [b]Adjusted gestational age, small for gestational age, twin, antenatal corticosteroid, gestational diabetes mellitus, pregnancy-induced hypertension, when the specific factor used for subgrouping is excluded.

Table 4: **Subgroup analysis for primary outcome by intention-to-treat analyses.**

Outcomes	DCC[a] (N = 1296)	ICC[a] (N = 1418)	Effect Variables	Effect (95% CI)	Adjusted Effect (95% CI)[b]
Primary outcome					
Neonatal respiratory distress	101/1296 (7.8)	135/1419 (9.5)	RR	0.82 [0.64, 1.05]	0.88 [0.70, 1.10]
Noninvasive ventilation or Mechanical ventilation	38/1296 (2.93)	42/1419 (3.0)	RR	0.99 [0.64, 1.53]	1.07 [0.74, 1.55]
Mechanical ventilation	25/1296 (1.9)	21/1419 (1.5)	RR	1.30 [0.73, 2.32]	1.40 [0.80, 2.43]
Secondary outcomes					
Admission	228/1296 (17.6)	237/1419 (16.7)	RR	1.05 [0.89, 1.24]	1.09 [0.93, 1.26]
Hospital stay, day	5.9 ± 4.1	6.2 ± 4.5	MD	−0.3 [−1.1, 0.5]	−0.2 [−0.9, 0.5]
Hyperbilirubinemia	185/1296 (14.3)	188/1419 (13.3)	RR	1.08 [0.89, 1.30]	1.10 [0.93, 1.32]
Haemoglobin, g/dL	22.8 ± 2.6	21.6 ± 2.8	MD	1.2 [1.0, 1.5]	1.3 [1.1, 1.5]
Hematocrit, %	69.8 ± 8.0	66.0 ± 8.4	MD	3.8 [3.2, 4.4]	3.8 [3.2, 4.5]
Exploratory outcomes					
Neonatal anaemia	5/1296 (0.4)	17/1419 (1.2)	RR	0.32 [0.12, 0.87]	0.33 [0.13, 0.88]
Apgar < 7 @ 1 min	3/1296 (0.2)	9/1419 (0.6)	RR	0.36 [0.10, 1.35]	0.41 [0.10, 1.69]
Hypothermia	389/1296 (30.0)	437/1419 (30.8)	RR	0.97 [0.87, 1.09]	0.97 [0.87, 1.09]
Temperature <36 °C	9/1296 (0.7)	18/1419 (1.3)	RR	0.55 [0.25, 1.21]	0.55 [0.25, 1.22]
Hypoglycemia	80/1246 (6.4)	83/1372 (6.1)	RR	1.06 [0.79, 1.43]	1.05 [0.78, 1.41]
Maternal bleeding, mL	397 ± 85	407 ± 128	MD	−10 [−19, −2]	−10 [−18, −1]
Maternal bleeding >500 mL	117/1296 (9.0)	144/1419 (10.2)	RR	0.89 [0.71, 1.12]	0.91 [0.72, 1.15]
Maternal Haemoglobin post-delivery, g/dL	11.3 ± 1.2	11.3 ± 1.2	MD	0 [0, 0.1]	0 [−0.1, 0.1]
Maternal transfusion	4/1296 (0.3)	11/1419 (0.8)	RR	0.40 [0.13, 1.25]	0.38 [0.11, 1.30]

[a]Data are n/N (%) or mean (SD). RR, relative risk; MD, mean difference. [b]Adjusted gestational age, small for gestational age, twin, antenatal corticosteroid, gestational diabetes mellitus, pregnancy-induced hypertension.
DCC: Delayed Cord Clamping; ICC: Immediate Cord Clamping.

Table 5: **Per-protocol analysis: For primary and secondary outcomes.**

CS for late preterm and early term populations. It demonstrated no increased risk of maternal complications, including postpartum bleeding, massive hemorrhage, or the need for transfusions. Furthermore, performing DCC for 1 min did not elevate the risk of neonatal low Apgar score or hypothermia. This is consistent with animal studies, which showed that DCC better stabilized core temperatures at delivery compared to ICC in term lambs.[33]

This study has several strengths. It is one of the largest randomised controlled trials focusing on DCC in the context of elective CS, providing robust data on a significant sample size. The stratification by gestational age adds depth to the analysis, allowing for more nuanced insights into the effects of DCC across different maturity levels. The comprehensive range of secondary outcomes, including haematological and metabolic parameters, provides a holistic view of the neonatal health impacts of DCC. In addition, since studies have demonstrated that DCC could be safely implemented in twin pregnancy,[34] this population was included in the study, which provided more comprehensive evidence in certain populations.

Certainly, this study has several limitations. The single-centre design, predominantly Han population enrolled may limit the generalizability of the findings to other settings or populations. Furthermore, the number of recruited late preterm infants was small, potentially not powerful enough to detect differences among groups. Especially, given that late preterm infants have a much higher incidence of respiratory morbidities than early term infants,[13,14] the low number of late preterm infants could have resulted in a lower average incidence of respiratory disease, affecting the necessary sample size to detect significant differences. Thirdly, in our study, haemoglobin levels were higher than in other reports,[7,8] but the significant difference in haemoglobin between DCC and ICC was consistent. The main reason is that we use trace amounts of peripheral blood for blood gas and haemoglobin detection, which is feasible to implement in such a large sample size. Lastly, the long-term effects of the intervention were not detected. In addition, we used sex to identify the external anatomy of a newborn according to the SAGER guidelines in this study. Since the psychological identity is not applicable to newborns, this study did not discuss the impact of individual gender on the study variables.

In the future, studies should explore the potential benefits of varying the duration of DCC, especially in different delivery contexts such as emergency CS. Longer follow-up studies are necessary to evaluate the sustained effects of DCC on respiratory health and other developmental outcomes. Investigating the underlying mechanisms through which DCC might influence neonatal respiratory outcomes could provide valuable insights and guide more effective clinical practices. In addition, integrating advanced monitoring techniques and more detailed stratification of risk factors may help

to identify subgroups of newborns who could benefit most from DCC. Finally, studies have demonstrated that umbilical cord milking potentially brings more benefits[35] without increasing the risks of adverse events in infants with higher gestational age.[36] For instance, in our target population of late preterm and early term infants, umbilical cord milking without delaying resuscitation could even be considered for infants with perinatal asphyxia who need resuscitation in the delivery room.

In conclusion, delayed cord clamping in late preterm and early term infants delivered by elective CS significantly improves neonatal haematological parameters without increasing maternal or neonatal risks. Delayed cord clamping did not reduce the risk of early respiratory disease in this population.

Contributors

TW coordinated data collection, drafted the initial manuscript. LP and WC recruited the patients. MZ, SW supervised data collection. YD recruited the patients and responded to the randomisation. ZL supervised the statistical analysis. JZ conducted the statistical analysis and drafted the initial manuscript. JQL conceptualized and designed the study, revised and submitted the manuscript. TW, JZ and JQL have full access and verified the data. All authors contributed in interpretation of data, critically revised the manuscript and agreed on the final version.

Data sharing statement

De-identified data and related documents are available from July 1st, 2024 and requests can be made to the corresponding authors.

Declaration of interests

All authors report no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103126.

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