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ORIGINAL ARTICLE

Effect of delayed cord clamping on stem cell transfusion and hematological parameters in preterm infants with placental insufficiency: a pilot randomized trial

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Abstract

The feasibility of delayed cord clamping (DCC) in preterm infants with placental insufficiency (PI) is questionable. We aimed to study the effect of DCC on stem cell transfusion, hematological parameters, and clinical outcomes in preterm infants born to mothers with PI. Preterm infants, < 34 weeks' gestation, born to mothers with PI were randomized based on the timing of umbilical cord clamping into delayed clamping for 60 s (DCC group) or immediate cord clamping (ICC group) groups at time of birth. CD34 percentage as a marker of stem cell transfusion, early and late-onset anemia, hypothermia, hypotension, polycythemia, hyperbilirubinemia, duration of oxygen therapy, bronchopulmonary dysplasia, intra-ventricular hemorrhage, necrotizing enterocolitis, sepsis, mortality, and length of hospital stay were compared between studied groups. We found that peripheral blood CD34 percentage was significantly higher in DCC compared with that in the ICC group (median (IQR) of 0.5 (0.40–0.7) versus 0.35 (0.20–0.5), $p = 0.004$). Infants in the DCC group had significantly lower episodes of anemia of prematurity at 2 months, red blood cell transfusion, and shorter duration of oxygen therapy compared with those in the ICC group.

Conclusion: In conclusion, DCC compared with ICC increased stem cell transfusion and decreased early- and late-onset anemia in preterm infants with placental insufficiency.

Trial registration: NCT03731546 www.clinicaltrials.gov

What is Known:
- *Delayed cord clamping has been recommended by the American Academy of Pediatrics as a standard of care practice during delivery of preterm infants.*
- *The feasibility of DCC in preterm infants with placental insufficiency (PI) is uncertain.*

What is New:
- *This randomized controlled trial demonstrated that DCC in the delivery room care of preterm infants born to mothers with placental insufficiency increased stem cell transfusion and decreased early- and late-onset anemia.*

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Keywords Preterm infant · Placental insufficiency · Stem cell · Umbilical cord · Anemia neonatorum

Abbreviations

BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
DCC	Delayed cord clamping
DCC+NP	Delayed cord clamping and normal placenta
DCC+PI	Delayed cord clamping and placental insufficiency
ICC	Immediate cord clamping
ICC+PI	Immediate cord clamping and placental insufficiency
ELBW	Extreme low birth weight infant
IUGR	Intrauterine growth retardation
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
SGA	Small for gestational age

Introduction

Delaying the clamping of the umbilical cord for 30–180 s, after the delivery of the fetus, has been recently recommended [5, 18]. It has been associated with higher Apgar scores [12], less delivery room resuscitation [12], less early- and late-onset anemia [12, 13], less requirement for blood transfusion, better circulatory stability, lower incidence for intra-ventricular hemorrhage, and decreased hospital mortality [7] in preterm infants [4, 19]. The most recent recommendations by the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) have set delayed cord clamping as the standard of care during delivery room management for full-term and preterm infants [5, 18].

The presumed physiologic rationale behind delayed cord clamping benefit is the transfer of residual placental blood and stem cells to the infants [14]. In term infants, delayed cord clamping (DCC) for 60 s after birth added an estimated volume of 80 mL of placental blood to the infant's circulation, which increased to about 100 mL if DCC extended to 180 s [6]. In preterm infants, DCC for 45 s resulted in an increase in blood volume by 2–16 mL/kg and 10–28 mL/kg if delivered by cesarean section and vaginal birth, respectively [2]. However, majority of published studies on the effect of DCC in preterm infants did not include those with IUGR and placental insufficiency. Theoretically, this exclusion was based on the assumption that placental residual blood volume is reduced enough not to be beneficial for potentially unstable infants in whom early initiation of resuscitation may be of priority [1]. The International Liaison Committee on Resuscitation did not state a clear contraindication for DCC in preterm infants with IUGR, infants with abnormal umbilical artery Doppler measurements, and infants with impaired utero-placental perfusion. In the absence of robust evidence, the committee stated that benefits from DCC should be discussed between the neonatal and obstetric providers [25].

The question whether residual placental blood volume could be enough to provide stem cell levels to preterm infants born to mothers with placental insufficiency, should DCC be applied, has yet to be answered. We aimed to study the effect of DCC on stem cell transfusion and hematological parameters of preterm infants born to mothers with placental insufficiency.

Subjects and methods

The study was conducted at the Neonatal Intensive Care Unit (NICU) of Mansoura University Children's Hospital, Mansoura, Egypt, between September 2017 and March 2019. The study protocol was approved by the local Medical Research Ethics Committee under a reference number of MS/17.04.15 and a written informed consent was obtained as soon as the possibility of a preterm birth seemed likely and often well before delivery from parents or guardians of each infant before randomization. This study was registered at www.clinicaltrials.gov (NCT03731546).

Study designs

This was a pilot, prospective, non-blinded, randomized controlled trial.

Participants

Preterm infants, less than 34 weeks' gestation, delivered to mothers with antenatal diagnosis of placental insufficiency were eligible for the study. Placental insufficiency was diagnosed in the presence of fetal growth restriction as evidenced by ultrasound fetal biometry and uterine Doppler studies. An abdominal circumference value below the 10th percentile for gestational age [20], together with an umbilical artery pulsation index above the 95th percentile on umbilical artery Doppler assessment with or without absent end-diastolic flow [10], was considered evidence of fetal growth restriction due to placental insufficiency.

Infants with a congenital anomaly or suspected chromosomal anomaly and infants who required major resuscitation steps at birth in whom delay of resuscitation measures was not possible were excluded from the study.

Intervention

Following parents/guardians' consent, infants were randomized to start on one of two protocols. In the first protocol, DCC practice was performed by keeping the infant 2–3 in. below the level of the maternal introitus or placenta, with caution not to put traction on the cord, for 60 s with an intact umbilical cord followed by ligation of the cord at 2–3 cm from the umbilical stump without cord milking. In the second protocol, the infant's umbilical cord was immediately clamped within 10 s after delivery of the whole body of the infant at 2–3 cm from the umbilical stump without cord milking. A third group of 30 preterm infants with normal feto-placental circulation, routinely managed with DCC, were recruited to act as a reference value for validation of the significance of DCC practice in preterm infants with placental insufficiency. Timing of cord clamping was controlled by special stopwatch present in the delivery room. All infants were handled in warm towels prior to umbilical cord clamping to maintain their temperature. Resuscitation was provided by a senior neonatal specialist who was not part of the research. The decision of immediate resuscitation and ICC in infants born non-vigorous with bradycardia (< 100 bpm) was left to the discretion of the attending neonatologist.

Outcomes

The primary measured outcome was peripheral blood percentage of cluster of differentiation 34 (CD34) in 1 mL of peripheral blood sample taken within the 1st hour of life as a marker of stem cell level. Cluster of differentiation 34 level was measured by three-color flow cytometry with conjugated monoclonal antibodies CD34 (phycoerythrin-texas red ECD, Beckman Coulter Inc., Danaher Corporation company, Pasadena, CA, USA). Secondary outcomes included a complete blood count (LH 450 counter, Beckman Coulter Inc., Danaher Corporation company, Pasadena, CA, USA) which was measured within the first hour of life and at 2 months postnatal age with routine immunization as a marker for late-onset anemia; infants with polycythemia at birth (hematocrit level ≥ 65%); first body temperature reading in the NICU; episodes of hypothermia in the first 24 h of life (defined by body temperature < 36.5 °C); episodes of hypoglycemia in the first 24 h of life (defined by pre-feeding blood glucose level < 45 mg/dL); episodes of hypotension in the first 24 h of life (defined by mean noninvasive arterial blood pressure below the 10th percentile for age); boluses administered for management of hypotension; need for inotrope support during the first 24 h of age; peak serum bilirubin level during NICU admission period; frequency of phototherapy initiation; duration of oxygen therapy; bronchopulmonary dysplasia defined as oxygen more than 30% at 36 weeks' corrected gestation [11]; intra-ventricular hemorrhage greater than grade II; incidence of any stage necrotizing enterocolitis according to modified Bell classification [23]; culture-proven late-onset sepsis; length of hospital stay; and neonatal mortality before hospital discharge. All infants were maintained on prophylactic daily doses of 3 mg/kg of oral iron therapy starting on day 30 of life if full enteral feeding was achieved. Management of preterm infants in the NICU including initiation and duration of phototherapy, initiation and weaning of respiratory support, and neonatal discharge followed fixed unit policy and procedures.

Sample size calculation

As a pilot study, a convenient sample of 30 infants in each group was chosen to test our hypothesis. Previous research has shown that 27% of preterm infants assigned to DCC practice did not receive the intervention because of immediate resuscitation requirement [21]. To achieve our targeted 30 infants into DCC intervention, a total random numbers of 40 were assigned to the DCC+PI group to compensate for the assumed 10 infants in whom resuscitation is a priority.

Randomization

Fetuses were assigned randomly to treatment groups using internet-based random table technique with cards in sequentially numbered, opaque, sealed envelopes kept in the delivery room. The primary investigator approached the parents for consent in the high-risk pregnancy department prior to transferring the mother to the delivery room and allowing enough time for the parents to make a decision. A designated delivery room nurse was responsible for opening the sealed envelopes and randomization of selected fetuses.

Statistical analysis

As CD34 level was our primary measured outcome, statistical analysis was conducted on non-intention to treat base including only infants in whom intervention was applied. Preterm infants who were assigned to the DCC+PI group and did not receive DCC intervention because of resuscitation priority were excluded in the delivery room once a decision for resuscitation priority was made. Statistical analysis was performed using commercially available software (SPSS for Windows Inc. Version 22. Chicago, IL). The Kolmogorov–Smirnov test was performed to examine the distribution of data. Independent Student's t test was used to compare continuous parametric variables to determine the differences between epochs; Mann–Whitney U test was used for continuous non-parametric variables; Chi-square test (χ^2) or Fisher exact test was used for categorical variables when appropriate. Linear and multinomial logistic regression analyses were used to examine the effect of DCC compared with ICC in preterm

infants with placental insufficiency on clinical outcomes after adjustment for gestational age. Spearman rank-order correlation coefficient test was used to correlate between CD34 level and late hemoglobin levels. Significance was defined as a p value of < 0.05. Data are expressed as mean ± standard deviation, median (inter-quartile range), or number (percentage) unless otherwise stated.

Results

Flow of participants through stages of the trial is shown in Fig. 1. In the consented infants into the DCC+PI group, 8 (21%) infants were not included in the analysis because of immediate resuscitation requirement. Infants in the DCC+PI and ICC+PI groups were equivalent to the baseline characteristics as shown in Table 1. Infants in the DCC+PI and ICC+PI groups had significantly lower birth weights, significantly higher percentage of small for gestational age weights, significantly higher maternal diseases, significantly higher use of antenatal magnesium sulfate, and significantly higher cesarean section delivery (particularly maternal hypertension) compared with those in the DCC+NP group (Table 1). Percentage of postnatal confirmed IUGR infants was highly accurate (97%) of the prenatal defined IUGR by ultrasound assessment of estimated fetal weight (Table 1).

Infants in the DCC+PI group had a significantly higher percentage of peripheral blood CD34 compared with infants in the ICC+PI group (median (IQR) of 0.5 (0.40–0.7) versus 0.35 (0.20–0.5) respectively, $p = 0.004$). Both infants of the DCC+PI group and ICC+PI group had significantly lower CD34 percentage compared with infants with normal placental circulation who were routinely managed with DCC (DCC+NP group) (median (IQR) of 0.5 (0.40–0.7) versus 0.75 (0.57–1.0), $p = 0.005$ and 0.35 (0.20–0.5) versus 0.75 (0.57–1.0), $p = 0.001$ respectively) (Fig. 2). Infants in the DCC+PI group had a significantly higher hemoglobin level and a significantly higher hematocrit percentage in the first 24 h of life compared with those in the ICC+PI group (Table 2). At 2 months follow-up, infants in the DCC+PI group had a significantly higher hemoglobin level compared with those the ICC+PI group (mean ± SD of 10.4 ± 0.9 versus 9.5 ± 1.0, $p < 0.001$).

Frequency of packed red blood cell (PRBC) transfusion was not significantly different between the studied groups. However, requirement of more than 3 episodes of PRBC transfusion was significantly lower in the DCC+PI group compared with that in the ICC+PI group (Table 3). Peak serum bilirubin level was significantly higher in the DCC+PI group compared with that in the ICC+PI group.

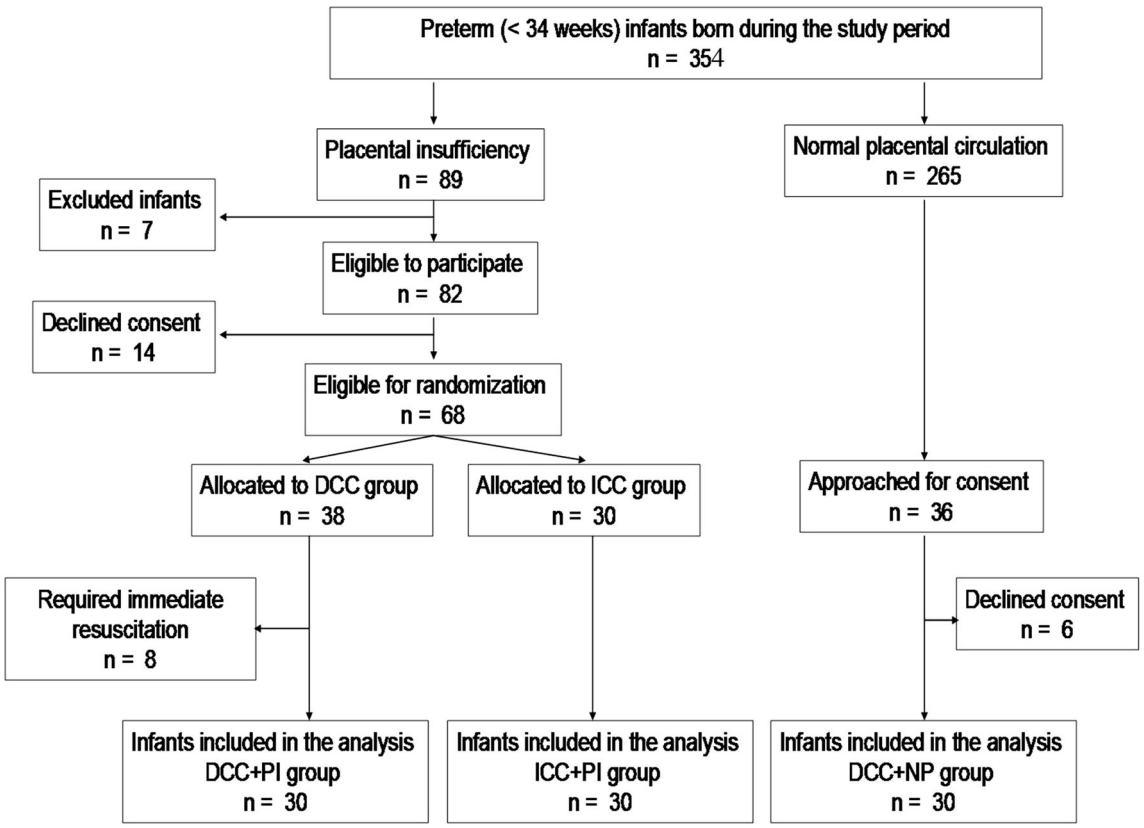

Fig. 1 Diagram showing the flow of participants through stages of the trial. DCC+PI, delayed cord clamping and placental insufficiency; ICC+PI, immediate cord clamping and placental insufficiency; DCC+NP, delayed cord clamping and normal placenta

Table 1 Demographic data and baseline characteristics of included infants

Variable	DCC+PI group $n = 30$	ICC+PI group $n = 30$	DCC+NP group $n = 30$
Gestational age (weeks)	29.7 ± 1.7	30.4 ± 1.2	29.6 ± 1.7
Birth weight (gm)	815.0 ± 196*	893.3 ± 148*	1106.6 ± 246
Birth weight less than the 10th percentile	29 (97%)*	29 (97%)*	2 (7%)
Sex (male)	15 (50%)	16 (53.3%)	15 (50%)
Maternal age (year)	25.10 ± 4.11	23.76 ± 3.56	24.66 ± 4.52
Maternal gravidity	2 [1–3]	2 [1–4]	2 [1–3]
Antenatal magnesium sulfate	25 (83%)*	22 (73%)*	0 (0%)
Antenatal steroid	25 (83%)	26 (87%)	27 (90%)
Maternal diseases	30 (100%)*	30 (100%)*	3 (10%)
Hypertension	25 (83%)*	21 (70%)*	1 (3%)
Diabetes	2 (7%)	3 (10%)	2 (7%)
Renal diseases	2 (7%)	3 (10%)	0 (0%)
Immune diseases	1 (3%)	2 (7%)	0 (0%)
Others	0 (0%)	1 (3%)	0 (0%)
Maternal hemoglobin (gm/dL)	12.10 ± 1.12	12.38 ± 0.77	12.39 ± 0.81
Postpartum hemorrhage	0 (0%)	0 (0%)	0 (0%)
Mode of delivery			
Vaginal	1 (3%)*	2 (7%)*	16 (53%)
Cesarean section	29 (97%)*	28 (93%)*	14 (47%)
Apgar score			
1 min	5 [2–8]	6 [3–8]	7 [4–9]
5 min	7 [5–9]	8 [6–9]	8 [6–9]
Surfactant therapy			
Single dose	11 (37%)	10 (33%)	11 (37%)
Multiple doses	4 (13%)	4 (13%)	4 (13%)

Data expressed as mean ± SD, median [IQR], or number (percentage)

DCC+PI delayed cord clamping and placental insufficiency, *ICC+PI* immediate cord clamping and placental insufficiency, *DCC+NP* delayed cord clamping and normal placenta

* $p < 0.05$ compared with the DCC+NP group

# $p < 0.05$ compared with the ICC+PI group

Infants of the DCC+PI group had a non-significantly different hemoglobin level compared with infants in the DCC+NP group (mean ± SD of 14.7 ± 2.1 versus 15.0 ± 1.5, $p = 0.53$) (Table 2). Infants of the ICC+PI group had a significantly lower hemoglobin level compared with infants of the DCC+NP group (mean ± SD of 13.2 ± 1.2 versus 15.0 ± 1.5, $p < 0.001$) (Table 2). At 2 months follow-up, infants in the DCC+PI group had a non-significantly different level of hemoglobin compared with infants in the DCC+NP group (mean ± SD of 10.4 ± 0.9 versus 10.7 ± 0.8, $p = 0.17$) (Table 2). Peak serum bilirubin level was significantly higher in the DCC+PI group compared with that in the DCC+NP groups. Frequency of initiation of phototherapy was significantly higher in the DCC+PI group compared with that in the DCC+NP group (Table 3).

There was no significant difference between the three groups in regard to culture-proven sepsis, IVH, NEC, BPD, length of hospital stay, or neonatal mortality (Table 3).

Linear and multinomial logistic regression analyses showed that DCC in preterm infants born to mother with placental insufficiency resulted in a significantly higher CD34 percentage, higher hemoglobin level at 1 h of life, higher initial bilirubin level without significant need for phototherapy, higher hemoglobin level at 2 months of age, and shorter duration of oxygen therapy independent of the gestational age (Table 4).

There was a significant positive correlation between peripheral blood CD34 level and hemoglobin level at 2 months postnatal age in preterm infants of the DCC+PI group ($r = 0.49$, $p = 0.008$).

Discussion

The main finding of our study is that DCC increases CD34 percentage as a marker of stem cells in preterm infants who are

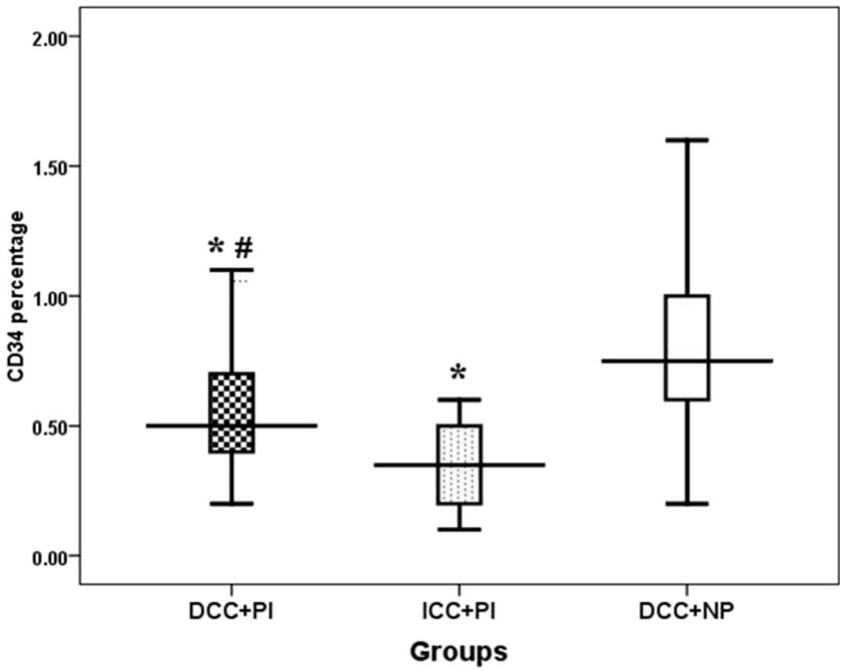

Fig. 2 Box and whisker plot illustrating stem cell (CD34) percentage to total cell count in preterm infants with placental insufficiency comparing DCC and ICC groups in relation to preterm infants with normal placental circulation who were managed with DCC. DCC+PI, delayed cord clamping and placental insufficiency; ICC+PI, immediate cord clamping and placental insufficiency; DCC+NP, delayed cord clamping and normal placenta. Asterisk indicates $p < 0.05$ compared with the DCC+NP group, number sign indicates $p < 0.05$ compared with the ICC+PI group

delivered to mothers with placental insufficiency compared with the same cohort with ICC. Although CD34 percentage was still significantly lower in preterm infants with placental insufficiency who were managed with DCC compared with preterm infants with normal placental circulation who were managed with DCC, hemoglobin levels at birth and 2 months postnatal age were close to and non-significantly lower in the former compared with latter infants.

Allan and colleagues found that delayed umbilical cord clamping for < 60 s, 60–120 s, and > 120 s respectively was associated with progressive reduction in the mean volume of blood and the total number of nucleated cells left in the cord for umbilical cord banking indicating a placental to fetal transfusion proportionate to the time of delay in cord clamping [3]. Primitive hematopoietic stem cells are abundantly present in the cord blood of preterm infants between 24 and 31 weeks' gestation compared with those in the cord blood of term infants [9]. DCC enhances endogenous hematopoietic stem cell transfusion to the newborn which subsequently reduces the need for blood transfusion, increases cerebral oxygenation in preterm infants, and decreases the frequency of iron deficiency anemia in term infants [14]. However, the feasibility of delayed cord clamping in preterm infants delivered to mothers with placental insufficiency particularly those who have intrauterine growth restriction has been questioned by health care practitioners. The main reasons given are (1) physician's assumptions that placental reserve volume may not be enough to transfuse preterm infants in presence of placental insufficiency, (2) there may be a

Table 2 Effect of DCC on stem cell levels and hematological parameters

Variable	DCC+PI group $n = 30$	ICC+PI group $n = 30$	DCC+NP group $n = 30$
Hemoglobin level at 1 h of age (gm/dL)	14.7 ± 2.1#	13.2 ± 1.2*	15.0 ± 1.5
Hematocrit at 1 h of age (%)	45.2 ± 4.2#	40.5 ± 2.4*	45.1 ± 4.4
Infants with polycythemia	0 (0%)	0 (0%)	0 (0%)
Hemoglobin level at 2 months of age (gm/dL)	10.4 ± 0.9#	9.5 ± 1.0*	10.7 ± 0.8
White blood cells at 1 h of age (K/uL)	15.00 (13–23)	15.00 (15–20)	16.50 (15–27)
Platelets at 1 h of age (K/uL)	226.6 ± 77.4	235.10 ± 87.1	227.50 ± 88.

Data expressed as mean ± SD, median [IQR], or number (percentage)

DCC+PI delayed cord clamping and placental insufficiency, *ICC+PI* immediate cord clamping and placental insufficiency, *DCC+NP* delayed cord clamping and normal placenta, *K/uL* thousands per cubic milliliter

* $p < 0.05$ compared with the DCC+NP group

# $p < 0.05$ compared with the ICC+PI group

Table 3 Effect of DCC on clinical outcomes of preterm infants

Variable	DCC+PI group $n = 30$	ICC+PI group $n = 30$	DCC+NP group $n = 30$
Initial body temperature (°C)	36.7 ± 0.5	36.8 ± 0.4	36.8 ± 0.5
Infants with hypothermia in the first 24 h of life			
Single episode	4 (13%)	6 (20%)	3 (10%)
Repeated episodes	9 (30%)	7 (23%)	3 (10%)
Infants with hypoglycemia in the first 24 h			
Single episode	9 (30%)	7 (23%)	7 (23%)
Repeated episodes	2 (7%)	6 (20%)	1 (3%)
Infants with hypotension in the first 24 h			
Single episode	4 (13%)	6 (20%)	4 (13%)
Repeated episodes	2 (7%)	8 (27%)	2 (7%)
Infants who received intravenous saline therapy	2 (7%)	5 (17%)	2 (7%)
Infants who received inotrope support	2 (7%)	3 (10%)	2 (7%)
Frequency of packed red blood cell transfusions			
None	15 (50%)	10 (33%)	20 (67%)
1	5 (17%)	11 (37%)	2 (7%)
2	6 (20%)	1 (3%)	4 (13%)
3	4 (13%)	2 (7%)	3 (10%)
> 3	0 (0%)[#]	6 (20%)	1 (3%)
Peak serum total bilirubin (mg/dL)	9.75 ± 2.90*[#]	6.97 ± 4.40*	5.81 ± 3.95
Episodes of phototherapy	22 (73.3%)*	18 (60%)	14 (46.7%)
Culture-proven sepsis	5 (16%)	8 (26%)	7 (23%)
Duration of oxygen therapy (days)	15.5 (10–30)* [#]	22.5 (15–35)*	8 (5–29)
Intra-ventricular hemorrhage grades III–IV	1 (3%)	2 (7%)	1 (3%)
Necrotizing enterocolitis	1(3%)	2 (7%)	1 (3%)
Bronchopulmonary dysplasia	3 (10%)	4 (13%)	1 (3%)
Length of hospital stay (days)	32 ± 14	29 ± 9	34 ± 17
Mortality	4 (13.3%)	3 (10%)	3 (10%)

Data expressed as mean ± SD, median [IQR], or number (percentage)

DCC+PI delayed cord clamping and placental insufficiency, *ICC+PI* immediate cord clamping and placental insufficiency, *DCC+NP* delayed cord clamping and normal placenta

[*] $p < 0.05$ compared with the DCC+NP group

[#] $p < 0.05$ compared with the ICC+PI group

potential augmentation of polycythemia in IUGR infants should DCC transfuse extra blood volume to the infants, and (3) priority of immediate resuscitation over DCC in preterm IUGR infants. Our results run against the first two assumptions and indicate that even with placental insufficiency, a placental reserve volume exists to provide positive placental to fetal transfusion with DCC as evident by higher CD34. We also found that DCC increases the level of initial hemoglobin, level of initial hematocrit, and level of follow-up hemoglobin at 2 months postnatal age in preterm infants who are delivered to mothers with placental insufficiency compared with the same cohort with ICC without an increase in the risk of polycythemia. Contrary to our findings, Gokman and colleagues found that DCC was associated with lower hematopoietic stem cell count in the peripheral blood of preterm infants compared with ICC. Authors attributed their results to a rapid process of migration, homing, self-renewal, and multi-lineage differentiation of circulating hematopoietic stem cells prior to their proliferation which occurs earlier in preterm compared with term infants [8]. However, the difference between our results and the findings of Gokman's study may be attributed to our longer 60 s of DCC compared with 30–45 s in Gokman's study. Our timing may load the circulation of preterm infants with enough stem cells to overcome the migration and homing process as suggested by Gokman.

We found that DCC did not decrease the need for overall packed red blood cell transfusion but decreased the need for frequent (> 3 times) red blood cell transfusion during the

Table 4 Linear and multinomial logistic regression analysis of DCC versus ICC and outcomes in preterm infants born to mothers with placental insufficiency

Characteristics	β coefficient	Odds ratio (95% CI)	p value
Stem cell (CD34) percentage	0.32		0.02
Hemoglobin level at 1 h of age (gm/dL)	0.48		0.001
Hemoglobin level at 2 months of age (gm/dL)	0.27		0.04
Peak serum total bilirubin (mg/dL)	0.28		0.02
Episodes of phototherapy		1.72 (0.22–3.4)	0.78
Culture-proven sepsis		0.79 (0.37–7.7)	0.86
Duration of oxygen therapy (days)	0.31		0.04
Intra-ventricular hemorrhage grades III–IV		0.86 (0.26–6.2)	0.75
Necrotizing enterocolitis		0.94 (0.14–7.2)	0.95
Bronchopulmonary dysplasia		0.71 (0.21–2.4)	0.58
Length of hospital stay (days)	0.09		0.09
Mortality		1.04 (0.14–7.2)	0.97

Odds ratio adjusted for gestational age

DCC delayed cord clamping

NICU stay compared with the ICC group. In late preterm and term infants, DCC for ≥ 180 s was associated with decreased incidence of low hemoglobin level < 11.0 g/dL at 8 months (relative risk, 0.89; 95% CI, 0.81–0.98; number needed to treat (NNT), 11; 95% CI, 6–54), the risk for iron deficiency at 8 months (relative risk, 0.58; 95% CI, 0.44–0.77; NNT, 6; 95% CI, 4–13), and higher hemoglobin level at 12 months of age compared with the early cord clamping group [13]. In preterm infants less than 32 weeks' gestation, DCC for 30–45 s decreased blood loss, number of infants' required transfusion, amount of packed red blood cell transfusion, and iron stores compared with ICC [15, 17].

Our results revealed that DCC in preterm infants with placental insufficiency was associated with increased peak serum bilirubin level compared with infants who had placental insufficiency with ICC. However, the need for phototherapy was non-significantly different between the two groups. Moreover, none of the included infants in this study required exchange transfusion for either hyperbilirubinemia or polycythemia. In term infants, DCC was associated with significantly higher bilirubin levels and more clinical diagnoses of jaundice without an increase in the incidence of phototherapy [26]. Previous studies reported variable effects for DCC on the incidence of hyperbilirubinemia in preterm infants without a significant increase in the risk of phototherapy [22, 24]. In a meta-analysis of 18 randomized controlled trials, Fogarty and colleagues found that delayed clamping increased peak serum bilirubin by only 4 μmol/L without increasing partial exchange transfusions for polycythemia or exchange transfusions for hyperbilirubinemia and they concluded that its potential risks in low-resource settings seem unlikely [7].

We found that DCC decreased duration of oxygen therapy compared with ICC in preterm infants with placental insufficiency but did not affect other outcomes such as incidence of initial hypotension, hypotension requiring boluses or inotropic therapy, culture-proven sepsis and BPD, NEC, IVH, length of hospital stay, and mortality before hospital discharge. However, our results should be interpreted with caution as our study was not powered to detect differences in clinical outcomes. We did not calculate a proper sample size to test these outcomes and we did not include all eligible infants in an intension to treat design. In a large multicenter trial on 1634 preterm infants < 30 weeks' gestation, death at 36 weeks corrected gestational age was significantly lower (6.4% versus 9%; relative risk, 0.69; 95% CI, 0.49–0.97; $p = 0.03$) in the DCC group compared with that in the ICC group [21].

We found that DCC in preterm infants with placental insufficiency was not associated with decreased Apgar scores or increased episodes of initial hypothermia or initial hypoglycemia compared with ICC. In a secondary analysis of a subset of IUGR infants included in the randomized control trial by Mercer and colleagues [16], Wang et al. found that DCC practice was not harmful to preterm IUGR infants as evident by comparable initial body temperature in the NICU and Apgar scores at 1 and 5 min [24]. However, we cannot make a solid recommendation regarding the safety of DCC in preterm infants born with placental insufficiency since we have selected relatively stable infants who did not need immediate resuscitation in the delivery room in the DCC+PI group.

To the best of our knowledge, this paper is strengthened by being the first study to test the feasibility of DCC practice in preterm, IUGR, infants with placental insufficiency in a prospective randomized control design. We acknowledge that our study is limited by being a pilot trial with a relatively small sample size which lowers the feasibility of finding significant clinical outcomes. The study is also limited by the lack of non-intention to treat analysis which limits the ability of the results to confirm the safety of the practice among all preterm IUGR infants.

In conclusion, DCC appears practicable in preterm, IUGR, infants delivered to mother with placental insufficiency. It resulted in a significant transfusion of stem cells, significantly higher hemoglobin and hematocrit percentage at birth without an increase in the risk of polycythemia, or significant hyperbilirubinemia. Future research with proper power and sample size calculation and intention to treat analyses are warranted to test clinical benefit and safety of DCC in this particular cohort of preterm infants.

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Authors' contributions Mohammed Yunis participated in design of the study, data collection and writing the first draft of the manuscript. Nehad Nasef and Islam Nour participated in formulating the hypothesis, design of the study, data collection, data interpretation, statistical analysis, and writing of the manuscript. Basma Shouman and Mohamed Sarhan participated in design of the study, data collection, and writing of the manuscript. Ahmed Gibreel participated in design of the study, supervising the delayed cord clamping practice, obstetric data collection, data interpretation and writing the manuscript. Mohamad Darwish participated in laboratory analysis, data interpretation, and writing of the manuscript. All authors approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article has been approved by the local Medical Research Ethics Committee of Faculty of Medicine, University of Mansoura, Egypt.

Informed consent Informed consent was obtained from all individual participants included in the study.

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