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ORIGINAL RESEARCH

The Short and Long Term Consequences of Delayed Cord Clamping on Late Pre-Term Infants

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Objective: To explore the effect of delayed cord clamping on preterm infants.

Methods: A retrospective analysis was conducted using the clinical data of 163 preterm infants with a gestational age of 34–36 weeks + 6 who were admitted to the neonatology department within 2 hours after birth. The blood routine examination indices within 2 hours and at 3–5 days after birth, the biochemical indices and arterial blood gas (ABG) indices within 2 hours after birth, and the hemoglobin level 5–6 months after birth were compared between the early cord clamping (ECC) group and the delayed cord clamping (DCC) group.

Results: Compared with the ECC group, the DCC group had significantly higher venous blood levels of red blood cells, hemoglobin, and hematocrit within 2 hours and at 3–5 days after birth. The ABG bicarbonate (HCO_3) level within 2 hours after birth was obviously higher in the DCC group than in the ECC group, and the ABG absolute base excess(BE) and lactate levels were lower in the DCC group than in the ECC group ($P < 0.05$). There was no significant difference between the two groups in the incidence of hypothermia, hypoglycemia, respiratory distress, septicemia, feeding intolerance, polycythemia, and hyperbilirubinemia requiring phototherapy during hospitalization ($P > 0.05$). Compared with the ECC group, the DCC group had a significantly higher venous blood hemoglobin level 5–6 months after birth. The incidence of anemia in the DCC group was significantly lower than in the ECC group ($P < 0.05$).

Conclusion: Delayed cord clamping can significantly increase the hemoglobin levels of preterm infants at birth and at 5–6 months after birth and can improve the oxygen circulation supply to the organs of such infants. Therefore, delayed cord clamping can improve the prognosis of preterm infants.

Keywords: preterm infants, delayed cord clamping, hemoglobin, ABG

Introduction

With the development of perinatal medicine and neonatal intensive care technology, the birth and survival rates of preterm infants have been increasing. The global scholars and physicians have been researching how to reduce the incidence of complications and improve the prognosis for preterm infants. Accordingly, the short- and long-term effects of delayed cord clamping on preterm infants have attracted global research attention.

The optimal time for umbilical cord clamping should allow the flow of placental blood to the fetus without affecting fetal resuscitation or interfering with the adaptation and stability of fetal organ functions after birth. There are two perspectives on the optimal timing of cord clamping: ECC, ie, neonatal cord clamping within 15–20 seconds after birth, and DCC, ie, neonatal cord clamping at least 30~60 seconds after birth or after the cessation of cord pulsation.[1,2] Studies have shown[3,4] that if cord clamping is performed 1 minute after birth, neonates can receive about 80 mL of blood from the placenta, although when clamping is performed at 2–3 minutes, the amount received is around 100 mL; Delayed cord clamping can allow neonates to obtain a greater blood volume and additional red blood cells. As the blood contains rich substances, such as immune globulin and stem cells, this supports the physical transformation of neonates from the intrauterine environment to the extrauterine environment. In recent years, studies have indicated[1,5,6] that delayed cord clamping has significant effects on improving blood pressure, reducing neonatal anemia and blood transfusion,

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improving cardiac function, reducing intraventricular hemorrhage, and enhancing immunity; consequently, it can reduce the incidence of complications in preterm infants.

However, the possible adverse effects of DCC in infants have provoked controversies among researchers both at home and abroad. Concern persists about that delayed cord clamping may affect the early care of the neonate after birth and the timely implementation of asphyxia resuscitation. In addition, the likelihood of excessive placental blood transfer due to delayed cord clamping may cause hypervolemia and polycythemia, and the decomposition of erythrocytes may lead to an increased bilirubin load. Consequently, delayed cord clamping may result in a higher incidence of hypothermia, delayed resuscitation, polycythemia, and hyperbilirubinemia requiring phototherapy.[7,8] Therefore, the present study aimed to investigate the benefits and potential harms of delayed cord clamping in preterm infants.

Subjects and Methods

Study Population

A retrospective analysis was performed using the inpatient and outpatient records of preterm infants with a gestational age of 34–36 weeks + 6 who were admitted within 2 hours after birth to the Neonatal department of Suzhou Ninth People's Hospital between July 2015 and July 2017 and between July 2018 and February 2020. As we used the electronic medical record search system of the hospital to collect the inpatient and outpatient records of the subjects for retrospective analysis, informed consent was not required.

Exclusion Criteria

Infants with asphyxia after birth and required resuscitation were excluded from this study. Also excluded were infants with severe congenital malformation or chromosomal disease found in prenatal examination, and infants with incomplete laboratory and clinical data (due to diagnosis/treatment reasons or seasonal discharge, death). Those who failed to attend follow-ups in our child healthcare department 5–6 months after birth were also excluded from this study.

Methods

Clamping Method

According to the recommendations of the American College of Obstetricians and Gynecologists (ACOG)[1,2] and the American guidelines for neonatal asphyxia resuscitation,[9] delayed umbilical cord clamping for at least 30 to 60 seconds in term and preterm infants except when immediate umbilical cord clamping is necessary because of neonatal or maternal indications. Since July 2018, our obstetrics department has performed delayed cord clamping on preterm infants born at a gestational age of >34 weeks and did not require resuscitation after birth asphyxia.

Preterm infants born between July 2018 and February 2020 were subject to DCC. Specifically, after birth, the neonate was placed on the maternal abdomen (a medical worker held the neonate at the placental level after a Cesarean section);[2,10] airway clearing and temperature maintenance measures were performed, and the neonate underwent cord clamping at 2 minutes after birth. Conversely, preterm infants born between July 2015 and July 2017 underwent cord clamping (instead of delayed cord clamping) within 30 seconds after birth. These infants were classified as the ECC group. Preterm infants in both groups received the same intervention measures after cord clamping.

Data Collection

The clinical data of subjects were collected, including delivery mode, gestational age, birth weight, Apgar score, birth resuscitation, and maternal gestation period. The subjects' gestational ages were calculated according to maternal menstrual history, and they were verified by ultrasonography.

For infants within 2 hours after birth, the laboratory data included red and white blood cell counts, platelet counts, hemoglobin level, hematocrit; total, direct, and indirect bilirubin; total protein and globulin of venous blood; pH, HCO_3, BE, ABG lactate, and blood glucose. The data for venous blood 3–5 days after birth included the red blood cell count, hemoglobin level, and hematocrit, while the data at 5–6 months after birth included the hemoglobin level.

Complications

Data on the incidence of the following complications in subjects during hospitalization in the neonatology department were collected: hypothermia: rectal temperature below 35°C;[11] hypoglycemia: blood glucose level < 2.6 mmol/L;[11] polycythemia: Hemoglobin (Hb)> 220 g/L or Hematocrit (HCT) of venous blood ≥ 0.65% within 1 week after birth;[11] Respiratory distress: with respiratory distress manifestations, such as labored breathing, three concave sign, and nasal flaring, or respiratory rate > 60 bpm, or irregular respiratory rhythm, with other manifestations identified as positive,[11] feeding intolerance: gastric residual volume greater than 50% of feeding volume, with abdominal distension and/or vomiting and affecting the implementation of the enteral feeding scheme,[12,13] and neonatal hyperbilirubinemia requiring phototherapy was based on the consensus of the indication of phototherapy and exchange transfusion for neonatal hyperbilirubinemia.[14,15]

Prognosis

The hemoglobin level and anemia (Hb < 100 g/L)[16] of the subjects 5–6 months after birth were analyzed.

Statistical Methods

All data were analyzed using SPSS 19.0 statistical software. All data were subject to a normality test. The measurement data conforming to a normal distribution were expressed in terms of mean ± stand deviation, and comparisons between the groups were made using a *t*-test. The enumeration data were expressed as percentages, and comparisons between the groups were made using a Chi-squared test. The measurement data not conforming to a normal distribution were expressed as median and interquartile ranges, and comparisons between the groups were made using a Mann–Whitney (rank–sum) *U*-test. Continuity correction was performed for the gestational ages of the DCC and ECC groups using an analysis of covariance. A value of $P < 0.05$ was interpreted as a statistically significant difference.

Results

Demographics

A total of 720 preterm infants with a gestational age of 34–36 weeks + 6 were admitted within 2 hours after birth to our neonatology department between July 2015 and July 2017 and between July 2018 and February 2020. The mothers of 10 infants had severe anemia and other hematological diseases, while the mothers of 8 others had placental abruption or pre- or intra-natal bleeding. After searching and summarizing the relevant inpatient and outpatient records, a total of 163 preterm infants were included as subjects in this study. As shown in Table 1, there were no statistical differences in terms of gestational age, birth weight, gender, and delivery mode between the 163 subjects and the 557 excluded preterm infants ($P > 0.05$).

Demographics of the Early Cord Clamping Group vs the Delayed Cord Clamping Group

There were no statistically significant differences in terms of the hemoglobin level of their mothers before delivery, the incidence of hypertension during pregnancy, gestational diabetes in their mothers, the use of oxytocin by their mothers before delivery, birth weight, gender, delivery mode, 1-minute Apgar score, and 5-minute Apgar score between the two

Table 1 Demographics of Subjects vs Excluded Preterm Infants

Item	Subject	Excluded Premature Infant	*P*
Gestational age, w	36.00 (35.10–36.30)	36.00 (35.10–36.30)	0.631
Birth weight, g	2550.00 (2300.00–2750.00)	2500.00 (2290.00–2780.00)	0.312
Gender, F/M	80/83	247/310	0.325
Delivery mode, natural/cesarean	59/104	197/360	0.853

Note: Data were expressed with median (interquartile range) or n.
Abbreviations: w, week; g, gram; F, female; M, male.

Table 2 Demographics of ECC Group vs DCC Group

Item	ECC	DCC	*P*
Maternal hemoglobin levels before delivery, g/L	115.08±11.33	118.37±10.37	0.056
Maternal had gestational hypertension, n (%)	7 (9.21)	8 (9.19)	0.603
Maternal had gestational diabetes mellitus, n (%)	8 (10.53)	10 (11.49)	0.523
Maternal used oxytocin before delivery, n (%)	30 (39.47)	32 (36.78)	0.424
Gestational age (w)	35.50 (35.0–36.20)	36.1 (35.30–36.30)	0.011
Birth weight (g)	2475.00 (2250.00–2750.00)	2550.00 (2400.00–2800.00)	0.098
SGA/AGA/LGA	5/67/4	7/79/1	0.303
Gender, F/M	35/41	44/43	0.638
Delivery mode, natural/cesarean	29/47	31/56	0.748
1-minute Apgar score	10.0 (9.0–10.0)	10.0 (10.0–10.0)	0.052
5-minute Apgar score	10.0 (10.0–10.0)	10.0 (10.0–10.0)	0.180

Note: Data were expressed with median (interquartile range) or n.
Abbreviations: w, week; g, gram; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; F, female; M, male.

groups ($P > 0.05$); however, there was a statistical difference in gestational age between the two groups ($P < 0.05$), as shown in Table 2.

Blood Routine Examination Indices of the Early Cord Clamping Group vs the Delayed Cord Clamping Group

There were no statistically significant differences between the two groups in terms of the white blood cell and platelet counts of venous blood within 2 hours after birth ($P > 0.05$). The red blood cell count, hemoglobin level, and hematocrit of venous blood within 2 hours and at 3–5 days after birth were significantly higher in the DCC group than in the ECC group ($P < 0.05$), as shown in Table 3.

Biochemical and ABG Indices of the Early Cord Clamping Group vs the Delayed Cord Clamping Group

The levels of total bilirubin and direct bilirubin in venous blood within 2 hours after birth were higher in the DCC group than in the ECC group ($P < 0.05$). In the DCC group, the ABG HCO3 level was significantly higher than in the ECC group, and the absolute value of BE and the lactate level were lower in the DCC group than in the ECC group ($P < 0.05$). There were no statistically significant differences between the two groups in terms of the levels of total protein, globulin, indirect bilirubin, blood glucose, and the pH of ABG ($P > 0.05$), as shown in Table 4.

Table 3 Blood Routine Examination Indexes of ECC Group vs DCC Group

Item	ECC	DCC	*P*	Adjusted *P*
WBC within 2h, (10^9 L^{-1})	10.5550 (8.9375–12.970)	10.5500 (9.2000–12.6800)	0.960	0.671
RBC within 2h, (10^{12} L^{-1})	4.6899±0.48907	4.9116±0.53822	0.007	0.009
Hemoglobin within 2h (g/L)	168.250±16.2005	179.517±18.8845	0.000	0.000
Hematocrit within 2h (%)	49.616±4.9091	51.734±5.8909	0.014	0.020
Platelet at 2h, 10^9 L^{-1}	273.645±62.9346	269.057±57.7833	0.628	0.624
RBC 3–5d after birth, (10^{12} L^{-1})	4.3300 (4.0125–4.7450)	4.7400 (4.4700–5.1800)	0.000	0.000
Hemoglobin 3–5d after birth (g/L)	157.000±21.9107	172.517±21.3813	0.000	0.000
Hematocrit 3–5d after birth (%)	43.750 (40.375–48.375)	48.300 (43.900–52.300)	0.000	0.001
Hemoglobin 5–6m after birth (g/L)	114.000 (107.00–120.00)	117.000 (112.000–123.000)	0.005	0.007

Notes: Data were expressed with median (interquartile range) or mean ± stand deviation; Adjusted *P*: Continuity correction was carried out for the gestational age of the DCC and ECC groups using ANCOVA analysis.
Abbreviations: WBC, white blood cell; RBC, red blood cell; h, hour; d, days.

Table 4 Biochemical Indexes and ABG Indexes of ECC Group vs DCC Group

Item	ECC	DCC	*P*	Adjusted *P*
Total bilirubin within 2h, umol L^{-1}	35.050 (30.175–41.200)	37.200 (33.400–44.200)	0.016	0.007
Direct bilirubin within 2h, umol L^{-1}	8.700 (7.500–11.625)	10.000 (8.400–13.200)	0.007	0.014
Indirect bilirubin within 2h, umol L^{-1}	26.050 (18.850–33.125)	27.300 (21.700–34.200)	0.314	0.139
Total protein within 2h, g L^{-1}	48.489±4.493	49.661±3.815	0.074	0.118
Globulin within 2h, g L^{-1}	15.779±2.9172	15.468±2.4076	0.457	0.456
pH of ABG within 2h,	7.3061±0.0534	7.3252±0.0599	0.034	0.060
HCO_3 in ABG within 2h, mmol L^{-1}	21.151±2.375	21.916±2.374	0.042	0.009
BE of ABG within 2h, mmol L^{-1}	−5.1596±1.6973	−3.9667±1.7957	0.000	0.000
Lactate in ABG within 2h, mmol L^{-1}	2.800 (2.100–3.600)	2.100 (1.600–2.900)	0.001	0.002
Blood glucose at 2h, mmol L^{-1}	2.600 (2.200–3.200)	2.500 (2.000–3.200)	0.372	0.217

Notes: Data were expressed with median (interquartile range) or mean ± stand deviation; Adjusted *P*: Continuity correction was carried out for the gestational age of the DCC and ECC groups using ANCOVA analysis.
Abbreviations: HCO3, bicarbonate; BE, absolute base excess.

Complications and Prognosis

There were no significant differences between the two groups in the incidence of hypothermia, hypoglycemia, respiratory distress, septicemia, feeding intolerance, polycythemia, and hyperbilirubinemia requiring phototherapy during hospitalization ($P > 0.05$). There was no statistical difference between the two groups in the duration of oxygen inhalation and the use rate of surfactant after delivery ($P>0.05$), but the use of non-invasive ventilation (CPAP) in the ECC group was significantly higher than that in the DCC group ($P<0.05$). There was no use of invasive ventilator in the two groups. The hemoglobin level in venous blood 5–6 months after birth was obviously higher in the DCC group than in the ECC group, while the incidence of anemia 5–6 months after birth was significantly lower in the DCC group than in the ECC group ($P < 0.05$), as shown in Table 3 and Table 5, respectively.

Discussion

Preterm infants are prone to various complications due to the immature development of their organs, directly affecting both outcomes and prognoses. Such infants are also prone to anemia, which can affect growth, development, behavior, and cognitive ability, even causing multiple organ failure in severe cases.[17,18] Although there is no consensus on the effect of delayed cord clamping on hemoglobin levels in preterm infants,[19] most studies have shown that infants who undergo delayed cord clamping at birth have significantly higher levels of hemoglobin and ferritin than those who undergo early cord clamping. This suggests that delayed cord clamping can effectively increase the stores of hemoglobin

Table 5 Complications and Prognosis of ECC Group vs DCC Group

Item	ECC	DCC	*P*	Adjusted *P*
Hypothermia, n (%)	10 (13.15)	11 (12.64)	1.000	0.766
Hypoglycemia, n (%)	36 (47.37)	45 (51.72)	0.639	0.437
Dyspnea, n (%)	31 (40.79)	21 (24.14)	0.029	0.086
Oxygen inhalation time, days	1.000 (1.000–4.250)	1.000 (1.000–2.000)	0.102	0.061
The use of surfactant, n (%)	5 (6.58)	2 (2.63)	0.253	0.414
The use of non-invasive ventilation, n (%)	7 (9.21)	1 (1.15)	0.026	0.038
Septicemia, n (%)	0 (0)	0 (0)	-	-
Feeding intolerance, n (%)	15 (19.74)	15 (17.24)	0.691	0.956
Polycythemia, n (%)	0 (0.00)	1 (1.15)	1.000	0.494
Hyperbilirubinemia requiring phototherapy, n (%)	41 (53.95)	46 (52.87)	1.000	0.372
Anemia 5–6 months after birth, n (%)	13 (17.11)	4 (4.59)	0.011	0.017

Notes: Data were expressed with median (interquartile range) or n;Adjusted *P*: Continuity correction was carried out for the gestational age of the DCC and ECC groups using ANCOVA analysis.

and iron in full-term and preterm infants, thus reducing the incidence of anemia in infancy.[3,4,20,21] In the present study, the hemoglobin level in venous blood within 2 hours, at 3–5 days, and at 5–6 months after birth was significantly higher in the DCC group than in the ECC group, and the incidence of anemia in the DCC group was significantly lower than in the ECC group. The results are consistent with a recent meta-analysis.[22]

Wiberg et al[23] reported that the intermittent interruption of uteroplacental circulation due to uterine contractions during delivery may cause hypoxia and acidosis in the fetus. In "hidden acidosis", the arterial and venous blood of umbilical cords in infants undergoing delayed cord clamping is characterized by decreased pH and BE values and elevated lactate levels.[6,24] However, some studies have shown that delayed cord clamping only results in elevated levels of PaO2 in ABG and does not affect other indices.[6,25,26] The results of the present study revealed that there was no statistical difference in the pH of ABG between the DCC and ECC groups. It is considered that this finding is associated with the collection of ABG within 2 hours after birth and the compensation by the body to return the pH value of ABG to normal. However, as both the base and HCO_3 are consumed during compensation, and lactate generated by anaerobic glycolysis takes a long time to remove, there were statistical differences in the values of HCO_3, BE, and lactate between the two groups.

Delayed cord clamping can improve circulation in the organs and tissues of neonates to a certain extent by increasing the blood volume at birth, thereby increasing the oxygen supply of tissues and reducing anaerobic glycolysis, the production of acids, and the consumption of HCO3.[24,27] Consequently, the HCO3 level of ABG in the DCC group was significantly higher than in the ECC group, and the absolute value of BE and the lactate level were lower than in the ECC group.

A study[28] reported that a delayed cord clamping group had a significantly decreased incidence of respiratory distress syndrome and a lower usage rate of surfactants than an early cord clamping group. Our study showed that there was no significant difference in the incidence of respiratory distress between the DCC and ECC groups, which is consistent with that reported in the study of Andersson et al.[19] However, the ECC group of preterm infants using non-invasive ventilation (CPAP) was significantly higher than the DCC group ($P<0.05$).

One reason why the timing of delayed cord clamping remains controversial is that it might not allow neonates to remain warm, affecting the performance of prompt and effective asphyxia resuscitation,[29] and it may increase the incidence of neonatal polycythemia, hyperbilirubinemia, and other complications. A study on the effects of delayed cord clamping in preterm infants with a gestational age of <30 weeks showed that in a DCC group, the body temperature on admission was 0.1°C lower than that in an ECC group.[30] In our hospital, as preterm infants undergoing delayed cord clamping received timely and effective post-delivery temperature maintenance, there was no statistically significant difference in the incidence of hypothermia between the DCC and ECC groups.

A previous study[30] revealed that a DCC group had a higher mean peak hematocrit value and polycythemia incidence than an ECC group, and no significant difference in the peak bilirubin level between the two groups was reported. Mercer et al[7] reported that delayed cord clamping did not increase the diagnostic rate of clinical jaundice and resulted in a 2% increase in the number of infants requiring phototherapy compared with early cord clamping. In the present study, the levels of total bilirubin and direct bilirubin in venous blood within 2 hours after birth were higher in the DCC group than in the ECC group. Considering that the excretion mechanism of the fetal liver is immature, and bilirubin is metabolized and cleared by the mother via the umbilical cord and placenta,[31] delayed cord clamping allows the fetal blood containing bilirubin present in the placenta and umbilical cord to flow back to the neonate, thus increasing the blood volume and elevating the bilirubin level within 2 hours after birth. However, in the present study there were no significant differences in the incidence of polycythemia and hyperbilirubinemia requiring phototherapy between the two groups, suggesting that delayed cord clamping did not increase the risk of either polycythemia or hyperbilirubinemia. Indeed, the ACOG Committee's comments on delayed cord clamping after birth state that to date, there has been no evidence that delayed cord clamping leads to an increased risk of polycythemia or hyperbilirubinemia.[1]

After umbilical cord clamping, the newborns faces a metabolic challenge and metabolic adaptation may result in low glucose level in the first few hours after birth, especially in preterm infants. The present study showed that there were no differences between the two groups in terms of the level of blood glucose and the incidence of hypoglycemia. This result is consistent with those reported in studies by Ultee et al and De Bernardo et al[32,33] However, another study suggested that the blood glucose level was significantly lower in a DCC group than in an ECC group.[34]

Feeding intolerance is common in preterm infants due to immature gastrointestinal function and may be associated with the occurrence of necrotizing enterocolitis.[15] Clinical trials have shown that delayed cord clamping reduces the incidence of necrotizing enterocolitis by preventing hypovolemia.[35,36] In the present study, none of the preterm infants developed necrotizing enterocolitis, and there was no difference in the incidence of feeding intolerance between the DCC group and the ECC group.

This study has some limitations. First, it was conducted as a single-center study, larger clinical trials are needed to investigate the effects of delayed cord clamping on infants. Second, preterm infants with a gestational age of <34 weeks and asphyxia after birth were not included. Infants with a lower gestational age are more likely to need resuscitation after birth; therefore, in our hospital, delayed cord clamping is not widely used on infants who require resuscitation immediately after birth and preterm infants with a gestational age of <34 weeks. Further research is needed on the effects of delayed cord clamping on infants with asphyxia and preterm infants of less than 34 weeks gestation.

Conclusion

In conclusion, our results received that delayed cord clamping could improve the short-term and long-term hemoglobin levels of late-preterm infants and reduced the incidence of anemia in 5–6 months after birth. Although the incidence of respiratory distress between the two groups of subjects in this study had no statistical difference, the absolute value of BE and the level of lactic acid in the peripheral arterial blood gas in DCC group were significantly lower than those in ECC group, and HCO_3 was significantly higher than those in ECC group. In addition, the number of preterm infants in DCC group using non-invasive ventilation (CPAP) was significantly lower than that in ECC group, suggesting that delayed core clamping could improve the blood circulation and oxygen supply to the organs of preterm infants. Besides, delayed cord clamping did not increase the incidence of hyperbilirubinemia requiring phototherapy, nor did it increase the incidence of complications such as hypothermia, hypoglycemia, septicemia, feeding intolerance, polycythemia.

The correct method and timing of delayed cord clamping provide benefits for neonates that far outweigh the potential harms, especially for preterm infants, for whom it is recommended. However, further research and follow-ups are needed to determine the effects of delayed cord clamping on preterm infants.

Disclosure

The authors report no conflicts of interest in this work.

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