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Effect of delayed cord clamping on cerebral hemodynamics in preterm infants

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ABSTRACT

Background: Unstable cerebral hemodynamics is an important cause of intracranial hemorrhage in premature infants. The increased blood flow of delayed cord clamping (DCC) compared to immediate cord clamping (ICC) is equivalent to 1/3-1/4 of newborn blood volume. Our objective was to assess whether the increased blood flow causes fluctuations in cerebral blood flow and how.

Methods: This experiment was a prospective, observational study. Neonatologists selected preterm infants eligible for inclusion and exclusion, and divided them into DCC group and ICC group according to the way of umbilical cord ligation performed by obstetrics department, and matched them 1:1 according to gestational age. The peak systolic velocity (PSV) , end diastolic velocity (EDV) , and resistance index (RI) of middle cerebral artery was measured by Mindray M9 color ultrasonic diagnostic instrument within 1 h, 24±1 h, 48±1 h, 72±1 h, respectively.

Results: There was no significant difference in PSV, EDV and RI in middle cerebral artery between DCC group and ICC group ($P > 0.05$). There were no significant differences between groups and time ($P > 0.05$). The hemoglobin and hematocrit in DCC group were higher than those in ICC group within 2 h after birth ($P < 0.05$). ($P > 0.05$).

Conclusion: DCC can increase hemoglobin and hematocrit in preterm infants, but does not cause cerebral blood flow fluctuation within a certain range. DCC is a safe method of placental transfusion.

1. Introduction

Intracranial hemorrhage is a common serious disease in preterm infants, and it is also one of the important causes of death and neurological disorders in preterm infants. Periventricular subependymal intraventricular hemorrhage is the most common in preterm infants [1,2]. Cerebral hemodynamic instability is an important cause of intracranial hemorrhage in preterm infants.

Delayed cord clamping (DCC), that is, clamping the umbilical cord after the fetus is delivered for more than 30 s, is the most popular method of cord clamping in the world [3–6]. It has attracted attention because it can reduce the mortality rate of premature infants and the incidence of intracranial hemorrhage [5,7], and the advantages of simple operation, convenience, and no additional cost. Compared with immediate cord clamping (ICC), DCC increases blood flow by 25–35 ml Per kilogram [8,9], which is equivalent to one third to one quarter of neonatal blood volume. Preterm infants have immature brain development and imperfect regulatory mechanisms. It is not clear whether and how increased blood flow causes fluctuations in cerebral blood flow. At the time, guidelines began

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recommending delayed cord ligation for premature infants, so randomized controlled studies do not conform to medical ethics. We designed a prospective observational protocol to monitor the effects of DCC and ICC on cerebral hemodynamics in preterm infants using ultrasound doppler. This is of significance for clarifying the mechanism by which DCC reduces the occurrence of early postnatal intracranial hemorrhage in preterm infants.

2. Materials and methods

2.1. Patient selection

This study was a prospective observational study. Neonates who admitted to our hospital from September 2020 to September 2021 and met the inclusion and exclusion criteria were enrolled. This study complied with the declaration of Helsinki and has been approved by the ethics committee of Suining Central Hospital. Ethics approval No: LLSLH20200017. Eligible infants whose gestational age at birth <37 W were born in the Department of Obstetrics of Suining Central Hospital, performed immediately (within 20s) or delayed (waiting 30–90s) cord clamping and transferred to the department of neonatology within 1 h after birth. Exclusion criteria for infants were informed consents were not obtained from the family members, twin-twin transfusion syndrome diagnosed prenatally, prenatal diagnosis of ABO or Rh hemolysis, congenital abnormality, positive pressure ventilation or tracheal intubation in obstetrics, see Fig. 1.

2.2. Interventions and care

The obstetrician of our hospital decides whether to delay cord ligation of premature infants according to the mother's will and the condition of the baby at birth. ICC refers to the clamping of the umbilical cord within 20s after fetal delivery. The DCC operation is as follows: Taking the trunk of the premature infant from the mother as the starting point, the midwife timed according to the timer in the operating room. The baby was placed on the mother's chest and abdomen, and the delay was more than 30 s. When the delay was 30 s, the chief surgeon was told that the umbilical cord could be clamped and cut with hemostatic forceps. The chief surgeon decided whether to delay to 90s according to the condition at the time. Other management of the newborn in the obstetric department,

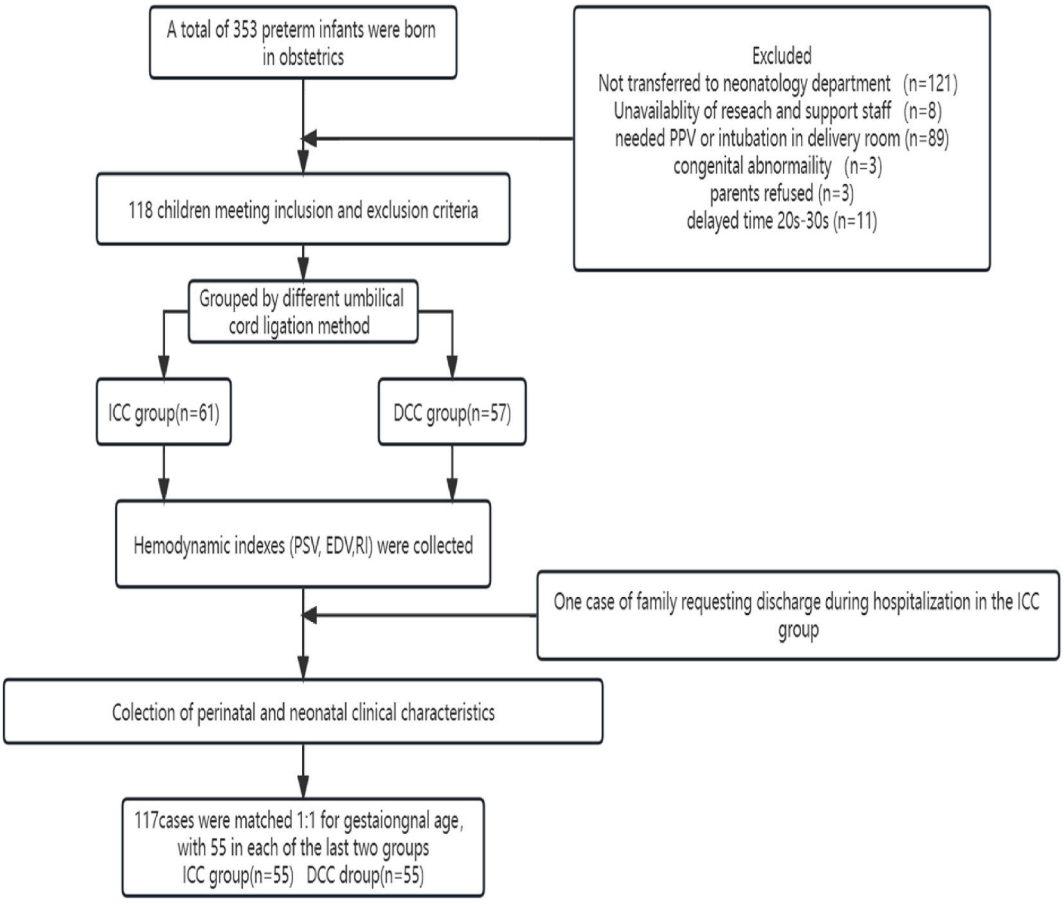

Fig. 1. Study subjects' flowchart diagram.

including resuscitation, is determined by the neonatologist. Whether the baby needs to be transferred to the neonatology department depends on the neonatologist's assessment of the baby. The main admission criteria include gestational age less than 32 weeks or newborns with tachypnea, groaning, cyanosis and other conditions requiring hospitalization and monitor. If the baby required immediate resuscitation such as tracheal intubation or chest compressions, the umbilical cord was clamped and cut immediately, and the baby was taken to the resuscitation table for further processing. This patient was not included in the study.

When the baby was transferred to the neonatology department, neonatologists recruited subjects based on inclusion and exclusion criteria. The neonatologist signed informed consent with the guardians who were willing to enroll their newborn for continued data collection before any study-related procedure (e.g., ultrasounds, additional monitoring) and divided baby into groups by different umbilical cord ligation method. If a parent did not want to enroll their baby in the study, we removed the subject from our study and destroyed all data that had been collected. All other aspects of neonatal care and management will be managed according to standard hospital practice.

3. Outcomes

Our primary study outcomes were hemodynamic parameters of middle cerebral artery: peak systolic velocity (PSV), end diastolic velocity (EDV), and resistance index (RI). Complete blood cell count within 2 h after birth and head ultrasounds on the second or third day of life were part of routine care. All other relevant prenatal and neonatal data were also collected from the medical records of mother and infant.

3.1. Measurements and diagnoses

PSV, EDV, and RI were collected by Mindray M9 color Doppler ultrasound, C11–3S probe, frequency 3–11 MHZ within 1 h, 24±1 h, 48±1 h, 72±1 h after birth. The children were placed in a warm box or radiation table, and ultrasound was performed under their quiet state. The color Doppler ultrasound diagnostic instrument was used for horizontal scanning through the temporal window, and the Wills artery ring was displayed through the temporal window by color Doppler blood flow. During the measurement, the Angle between the Doppler sampling line and the middle cerebral artery was reduced between 0° and 10° as far as possible. After the spectrum stabilized, three blood flow patterns with similar peak values were taken for measurement, and PSV, EDV, RI were measured, and the average value was taken. Data acquisition was performed by professional sonographers.

The diagnostic criteria of intraventricular hemorrhage according to the "Practical Neonatology" 5th edition [10]: grade I: hemorrhage confined to the germinal matrix; Grade II: the volume of blood in the lateral ventricle was ≤50 %; Grade III: the volume of blood in the lateral ventricle was >50 %; Grade IV: hemorrhagic infarction occurred near the lateral ventricle on the same side of the hemorrhage.

3.2. Statistical analysis

The experimental group was the delayed cord clamping group, and the control group was the immediate cord clamping group. Preterm infants eligible for inclusion and exclusion were divided into DCC and ICC groups and matched 1:1 for gestational age. The cerebral hemodynamic parameter PSV was used as the primary outcome. Statistical analysis was a two-way repeated measures analysis of variance. The sample size required for the two-factor repeated measures ANOVA was estimated using the following formula:

$$n = \frac{2\sigma^2(\mu_a + \mu_\beta)}{\delta^2}\left\{\left[\frac{1}{\gamma} + \left(1 - \frac{1}{\gamma}\right)\rho\right] - \frac{\rho}{1\Big/\rho + \left(1 - 1/\rho\right)_\rho}\right\}$$

P = number of observations before treatment; ϒ = number of observations after processing; σ = population standard deviation, estimated by sample standard deviation S; ρ = 0.65; δ is the difference between the peak systolic values with clinical significance, which was derived from previous literature [11]; α = 0.05 (bilateral); β = 0.10; P = 0 , ϒ = 4; σ = 7.0; ρ = 0.65; δ = 1.68; $\mu_\alpha = 1.96$; $\mu_\beta = 1.28$; Therefore, according to the above formula, the sample size of each group was calculated to be at least 32 cases, and it was estimated that 20 % of the children could not be included in the statistical analysis due to various reasons. In order to ensure adequate sample size, at least 40 cases were required to be included in each group.

SPSS 26.0 software was used for statistical analysis. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD), two independent sample *t*-test was used for comparison between groups. Non-normal variables was expressed as median (interquartile range (IQR)), and non-parametric test was used for comparison between groups. Two-way repeated measures analysis of variance was used to compare the differences of PSV, EDV, RI between groups, different time points and the interaction between time and group. Categorical variables were expressed as frequencies (%), and the rate was compared between the two groups using χ^2 test or Fisher exact probability method, and the test level was α = 0.05.

4. Results

A total of 353 premature infants were born in the Department of Obstetrics of Suining Central Hospital from September 2020 to September 2021, 118 of them met the inclusion and exclusion criteria, and 1 case was discharged at the request of family members during hospitalization. A total of 117 patients were included and matched 1:1 according to gestational age, with 55 in the DCC group and 55 in the ICC group. Under 32 weeks, there were 18 cases in each group, and 32 to 36 + 6 weeks, 37 cases in each group. There was no significant difference ($p > 0.05$) between the two groups in terms of perinatal outcomes and delivery room outcomes (Table 1). Postnatal hemoglobin and hematocrit in DCC group were higher than those in ICC group ($p < 0.05$), but there was no statistical difference in other neonatal outcome indexes. ($p > 0.05$, Table 1).

There were no significant differences in PSV, EDV, RI of middle cerebral artery between the two groups. There was no significant difference in the interaction between group and time. PSV and EDV increased with the increase of premature infants' day age (Tables 2–4).

5. Discussion

This study found that the PSV and EDV of cerebral blood flow in DCC group and ICC group increased with postnatal time, same as other studies have shown [12]. Neonatal cerebral hemodynamic indexes after birth are related to gestational age at birth [13], so we matched the DCC and ICC patients according to gestational age. We also excluded cases requiring positive pressure ventilation or tracheal intubation in the delivery room that might have affected cerebral blood flow. This study found that hemoglobin and hematocrit in the DCC group were both higher than those in ICC, indirectly proving an increase in blood volume in the DCC group. However, compared with the ICC group, the DCC group had no statistically significant effect on the PSV and EDV of the middle cerebral artery in premature infants. Considering the autonomic regulatory function of cerebral vessels may be an important reason. When cerebrovascular autoregulation function is normal, fluctuations in systemic pressure within a certain range would not lead to fluctuations in cerebral blood flow. Some studies have suggested that RI may be related to cerebrovascular autoregulation [14]. In this study, RI was in the normal range and the amount of placental transfusion in this study may be within the regulatory capacity of cerebral vessels. Many studies have confirmed that DCC can reduce the occurrence of intracranial hemorrhage compared with ICC [15–17]. Therefore, the mechanism of DCC reducing intracranial hemorrhage may be related to the placental transfusion increasing the stability of systemic circulation and improving the autonomic regulation of cerebral blood vessels, thus reducing the fluctuation of cerebral blood flow in premature infants after birth [18,19]. But the increased blood volume after DCC occurs within a few minutes after birth, so PSV and EDV may be affected in a short time. Since ultrasound cannot be continuously monitored, in this study, the starting time point of our monitoring was delayed, and we may not be able to detect such fluctuations. In addition, in order to understand how much the increase in blood volume of the systemic circulation will exceed the autonomous regulation ability of cerebral blood vessels, it is necessary to design continuous monitoring in future research, try to advance the initial monitoring time point as much as possible, and conduct hierarchical analysis of the delayed time.

Previous studies have suggested that DCC does not increase pathological jaundice [20]. This study was consistent with that. No significant differences were found between the DCC and ICC groups in terms of the rate of intracranial hemorrhage after birth and the rate of need for blood transfusion, unlike some previous results. This is also one of the limitations of this study. To ensure an adequate sample size, we included all preterm infants younger than 37 weeks, but there are fewer premature infants less than 32 weeks prone to intracranial hemorrhage than other studies. It is also related to the insufficient sample size in this study to analyze nominal variable such as intracranial hemorrhage and the need for postpartum transfusion.

Table 1
Perinatal and delivery room and neonatal outcomes.

Characteristics	ICC(N = 55)	DCC(N = 55)	*P*
Perinatal and Delivery Room outcomes			
Gestational Age, mean ± SD, weeks,	33.18 ± 2.08	33.17 ± 2.11	0.167
Birth wt., mean ± SD, g	2097.42 ± 502.53	2081.22 ± 470.05	0.835
Male, N (%)	31 (56.4)	30 (54.5)	0.848
Cesarean Delivery, N (%)	35 (63.6)	33 (60.0)	0.695
Apgar score at 1 min, median (IQR)	10.00 (9.00, 10.00)	10.00 (9.00, 10.00)	0.068
Apgar score at 5 min median (IQR)	10.00 (9.00, 10.00)	10.00 (9.00, 10.00)	0.146
Neonatal outcomes			
Birth Hb, mean ± SD, g/DL	168.00 ± 17.40	186.23 ± 17.57	<0.001*
Hematocrit (%), mean ± SD	49.27 ± 4.75	54.27 ± 5.07	<0.001*
Peak Bilirubin, mean ± SD, μmol/L	139.83 ± 41.62	149.57 ± 48.59	0.15
Need for transfusion, N (%)	9 (16.4)	3 (5.5)	0.067
Continuous positive airway pressure, N (%)	43 (78.2)	39 (70.9)	0.381
Invasive ventilation, N (%)	8 (14.5)	5 (9.1)	0.376
Mild IVH (grade 1 or 2), N (%)	13 (23.6)	8 (14.5)	0.225
Severe IVH(≧grade 3), N (%)	0 (0)	1 (1.8)	0.979
Death, N (%)	0 (0)	0 (0)	/
Length of hospital stay, mean ± SD, day	17.92 ± 12.62	17.52 ± 12.80	0.284

note：*$P < 0.01$。.

Table 2
Comparison and change of PSV of middle cerebral artery between two groups (mean ± SD, cm/s).

	Sample Size (%)	Within 1 h	24±1 h	48±1 h	72±1 h
Overall					
ICC	55	36.68 ± 6.75	42.03 ± 7.03	47.42 ± 6.80	52.15 ± 6.89
DCC	55	36.63 ± 6.56	42.70 ± 6.15	46.84 ± 6.66	52.04 ± 8.30
F	$F_{\text{between groups}} = 0.023$ $F_{\text{interaction}} = 0.872$ $F_{\text{time}} = 218.578$				
P	$P_{\text{between groups}} = 0.988$ $P_{\text{interaction}} = 0.453$ $P_{\text{time}}<0.001$*				

note：*$P < 0.05$。.

Table 3
Comparison and change of EDV of middle cerebral artery between two groups (mean ± SD, cm/s).

	Sample Size (%)	Within 1 h	24±1 h	48±1 h	72±1 h
Overall					
ICC	55	13.51 ± 3.46	15.27 ± 3.77	17.44 ± 4.35	17.94 ± 4.05
DCC	55	13.03 ± 2.98	15.54 ± 3.4	16.2 ± 3.74	17.72 ± 4.44
F	$F_{\text{between groups}} = 0.720$ $F_{\text{interraction}} = 1.173$ $F_{\text{time}} = 46.306$				
P	$P_{\text{between groups}} = 0.404$ $P_{\text{interaction}} = 0.309$ $P_{\text{time}}<0.001$*				

note：*P < 0.05。.

Table 4
Comparison and change of RI of middle cerebral artery between two groups (mean ± SD).

	Sample Size (%)	With 1 h	24±1 h	48±1 h	72±1 h
Overall					
ICC	55	0.63 ± 0.08	0.64 ± 0.07	0.63 ± 0.08	0.65 ± 0.07
DCC	55	0.64 ± 0.07	0.63 ± 0.07	0.66 ± 0.07	0.66 ± 0.07
F	$F_{\text{between groups}} = 1.413$ $F_{\text{interaction}} = 1.126$ $F_{\text{time}} = 2.573$				
P	$P_{\text{between groups}} = 0.213$ $P_{\text{interaction}} = 0.335$ $P_{\text{time}} = 0.059$				

note：*P < 0.05.

In conclusion, DCC can increase hemoglobin and hematocrit in preterm infants, but does not cause cerebral blood flow fluctuation within a certain range. DCC is a safe method of placental transfusion.

Declarations

This study complied with the declaration of Helsinki and has been approved by the ethics committee of Suining Central Hospital. Ethics approval No: LLSLH20200017.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Hui Wang: Conceptualization, Writing – original draft. **Jiu-lang Huang:** Data curation, Software. **Hao Peng:** Conceptualization, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

None.

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