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Original Article (Pages: 4909-4918)

Is "Delayed Umbilical Cord Clamping" Beneficial for Premature Newborns?

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Abstract

Background: The appropriate moment for clamping the umbilical cord is controversial. Immediate cord clamping (ICC) is an item of active management of the third stage of labor (AMTSL). Unclamped umbilical cord may cause inconvenience in preterm neonates because they commonly need some levels of emergent services. Some studies revealed delayed cord clamping (DCC) of preterm neonates results in better health conditions like lower rates of respiratory distress syndrome (RDS), less morbidities in labor room and lower risk of postpartum hemorrhage. The aim of the present study was to determine the effect of delayed umbilical cord clamping on premature neonatal outcomes.

Materials and Methods: In this single-center randomized control trial study, sixty premature neonates (gestational age ≤ 34 weeks) were randomly assigned to ICC (cord clamped at 5–10 seconds) or DCC (30–45 seconds) groups and followed up in neonatal intensive care unit (NICU). Primary outcomes were 1st and 5th minute Apgar score, average of level of hematocrit after birth, intra ventricle hemorrhage and need some levels of resuscitation.

Results: Differences in demographic characteristics were not statistically significant. After birth, neonates who had delayed clamping had significantly higher mean hematocrit after at 4-hour of birth (49.58±5.15gr/dl vs. 46.58±5.40gr/dl in DCC vs. ICC groups, respectively) (P=0.031). Delayed cord clamping reduced the duration of need to nasal continues positive airway pressure (NCPAP) (86.7% and 60.0% in ICC and DCC groups, respectively, P= 0.039). Attractively, the results showed lower incidence of clinical sepsis in delayed cord clamping neonates (53.3% vs. 23.3% in ICC and DCC groups, respectively, P=0.033).

Conclusion: Prematurity complications might decrease by delay umbilical cord clamping which improve the hematocrit, duration of need to NCPAP and incidence of clinical sepsis. Furthermore, DCC may have no negative impact on neonatal resuscitation.

Key Words: Delayed cord clamping, Premature Infants, Umbilical cord clamping.

*Please cite this article as: Armanian AM, Ghasemi Tehrani H, Ansari M, Ghaemi S. Is "Delayed Umbilical Cord Clamping" Beneficial for Premature Newborns? Int J Pediatr 2017; 5(5): 4909-18. DOI: **10.22038/ijp.2016.7909**

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Received date Feb.15, 2017; Accepted date: Mar. 22, 2017

1- INTRODUCTION

Immediately after birth, during neonatal resuscitation, there are still controversial issues which there are no clear answers for them. One of these issues is the question of when the umbilical cord should be clamped. Clamping the umbilical cord after childbirth, is one of the very early interventions (1) and mainly considers as a part of the third stage of labor (2). Since antiquity, there has been considerable controversies regarding the appropriate moment for clamping the umbilical cord (2-6). Physicians` approach is to clamping the cord 10 to 15 seconds just after birth even now which seems unlike ancient time which was clamping the cord 1 to 3 minutes after birth (7).

In 1960s active management of the third stage of labor (AMTSL) proposed in order to reduce postpartum hemorrhage and retained placenta, and became worldwide instantly(8) and by unknown reasons, clamping the cord immediately, was mentioned as an item of AMTSL(9). Immediate cord clamping (ICC) means clamping the cord and cutting in the first 20 seconds after labor without considering whether the cord has stopped pulsing. Perhaps, this decision was made in order to transfer the newborn to neonatal department faster, or facilitate neonatal resuscitation or accessibility to pediatrician (9, 10). Some experts believe that ICC has no physiological rationales, and is not been proved beneficial neither for infant nor the mother (8, 11, 12).

Furthermore, all of the benefits and harms of delayed cord clamping (DCC) versus ICC in preterm infants remains controversial(1-11, 13-25), thus the appropriate time for clamping the cord is still unclear(26). Preterm infants commonly need some levels of service or even resuscitation and then unclamped umbilical cord may cause inconvenience for additional interventions consequently. Despite having more concerns about occurrence of polycythemia (27) or blood exchange requirement and even the risk of intraventricular hemorrhage (IVH) in preterm infants, these aren`t still confirmed and in some studies preterm infants DCC results in lower rates of respiratory distress syndrome (RDS), improved hematocrit in addition to lower demand for blood transfusion. Mercer JS et al. demonstrated that DCC for a period of 45 seconds after labor in preterm newborns, conveys decline in manifestation of IVH (12). Kaempf et al. concluded that DCC in preterm neonates makes hematocrit improved, lessens neonatal resuscitation requirements and morbidities in labor room (12). However McDonald and Middleton in 2008, observed that DCC doesn`t lead to higher risk of postpartum hemorrhage (28). Based on foregoing, we decided to determine the effect of delayed umbilical cord clamping on premature neonatal outcomes.

2- MATERIALS AND METHODS

2-1. Design of randomized clinical trial

In this single-center randomized control trial (RCT) study, infants who born between Jul 2014 and Feb 2015 with a gestational age of $\leq$ 34 weeks and admitted to the tertiary referral neonatal intensive care units (NICU) of the Isfahan University of Medical Sciences at Alzahra and Shahid Beheshti Hospitals, were eligible for participation in the study. Gestational age was determined by the last menstrual period and ultrasound.

After informed consent was obtained from the parents, generally obtained as soon as the possibility of a preterm birth seemed likely and often well before labor and delivery, preterm neonates ($\leq$ 34 weeks' gestation) were randomly assigned to umbilical cord clamping, with a sterile surgical scissors, at 30-45 seconds after delivery (DCC group) or below 5-10 seconds after delivery (ICC group). Allocated infants

were being entered into the study based on the table of random numbers.

2-2. Clinical observations during the hospitalization

To assess neonatal clinical condition immediately after birth, Apgar scores were measured at 1 and 5 minutes after delivery, with a score of 10 indicating optimal status of heart rate, respiratory effort, muscle tone, response to nasal catheter, and skin color. Apgar score more than seven assigned as normal and interpreted as good health in newborns (29). To interpret neonatal clinical condition during the hospitalization in NICU how many times infants required the insuring and how long infants needed oxygen (days), nasal continues positive airway pressure (NCPAP) and hospitalization had been mentioned.

To investigate neonatal clinical condition patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), clinical sepsis and necrotizing enterocolitis (NEC) were diagnosed by the pediatric. The NEC was divided into three subgroups: proven, advanced and sustained. Diagnosis of NEC was made as shown in **Figure.1** (30 - 32).

Stage	Classification	Clinical Signs	Radiologic Signs
I	Suspected NEC	Abdominal distention Bloody stools Emesis/gastric residuals Apnea/lethargy	Ileus/dilation
II	Proven NEC	As in stage I, plus: Abdominal tenderness ±Metabolic acidosis Thrombocytopenia	Pneumatosis intestinalis and/or portal venous gas
III	Advanced NEC	As in stage II, plus: Hypotension Significant acidosis Thrombocytopenia/disseminated intravascular coagulation Neutropenia	As in stage II, with pneumoperitoneum

Modified from Walsh MC, Kliegman RM: Necrotizing enterocolitis: treatment based on staging criteria, *Pediatr Clin North Am* 33:179, 1986.

Fig.1: Modified bell staging criteria for necrotizing enterocolitis (30-33).

2-3. Laboratory and para-clinical observations

Blood culture was done for infants who had clinical sepsis been diagnosed for. The hematocrit (HCT) was determined within 4 hours of birth by routing sampling. Normal range of HCT intended as normal was 45 to 50 (29). PDA was confirmed by echocardiography which was done by pediatric heart specialist; in addition, IVH was confirmed by brain ultrasonography (33).

2-4. Ethics statement

This paper is derived from a research project no. 292270 in the Isfahan University of Medical Sciences. The study was approved by the regional ethics review board at university. Written informed consents were obtained from parents. This trial was registered at irct.ir as IRCT2015013010026N5.

2-5. Statistical analysis

For data analysis, several statistical tests were used. For the single measurement outcome variables that were normally distributed, the sample t-test was used.

The Chi-square test or Fisher's exact test were used for comparing the categorical outcome variables between the two groups. For the outcome variables that were measured at multiple time points (i.e., time of oxygenation, HCT, time of hospitalization), Mann-Whitney test was used. The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA). P-value less than 0.05 were significant.

3- RESULTS

In our study a total of 113 infants who born with a gestational age of ≤ 34 weeks, were assessed for eligibility during the study period. Of these, 39 were ineligible because of non-admission to the NICU, twin pregnancy or because the attending was not compliant with the study protocol.

There were a total of 74 infants who met the eligibility criteria, and 11 infants who were excluded because of their parents' refusal to participate, major congenital anomalies, asphyxia. 63 infants underwent randomization (32 in the DCC and 31 in the ICC groups) during the study period and completed the study (**Figure.2**).

Baseline characteristics for early and delay clamping groups who were included did not differ significantly from individuals' variables which were including gender, mortality ratio, kinds of delivery, need for corticosteroid, Apgar, IVH and PDA (**Tables.1, 2**).

After birth, neonates who had delayed clamping had significantly higher mean hematocrit after 4- hour of birth (49.58$\pm$5.15gr/dl vs. 46.58$\pm$5.40gr/dl in DCC vs. ICC groups) (P=0.031). There was a significant difference between two groups in level of hematocrit (HCT) in the 4th hour of birth, duration of need to NCPAP and clinical sepsis (**Table.2**).

The effects of delayed cord clamping (DCC) were favourable. Average level of hematocrit (measured at around 4- hour of age) was significantly higher in the DCC group (49.58$\pm$5.15gr/dl vs. 46.58$\pm$5.40 gr/dl in DCC vs. ICC groups; P= 0.031) (**Table.2**).

Blood transfusion needing did not differ significantly between two groups. Length of need to NCPAP was significantly higher in the early clamping group (26$\pm$86.7 vs. 18$\pm$60.0 hours in ICC vs. DCC groups; P= 0.039); however, length of needing oxygen was not differing between groups (**Table.2**).

In addition, the insuring was not significantly affected by kind of clamping. Incidence of PDA, IVH and retinopathy of prematurity (ROP) were not different between groups. 23.3% of the infants in delayed clamping (DCC) group were having clinical sepsis (as diagnosed in the hospital and by symptoms); while 53.3% in early clamping (ICC) group diagnosed as clinical sepsis (P= 0.033; **Table.2**).

The blood cultures of the infants were not significantly different between groups; however, there was significant difference between groups in experience of clinical sepsis during the hospitalization.

NEC which was divided into three subgroups which could happen in premature infants, but the results revealed that any kinds of NEC were not affected by timing of clamping (all of the infants were not diagnosed for advanced NEC).

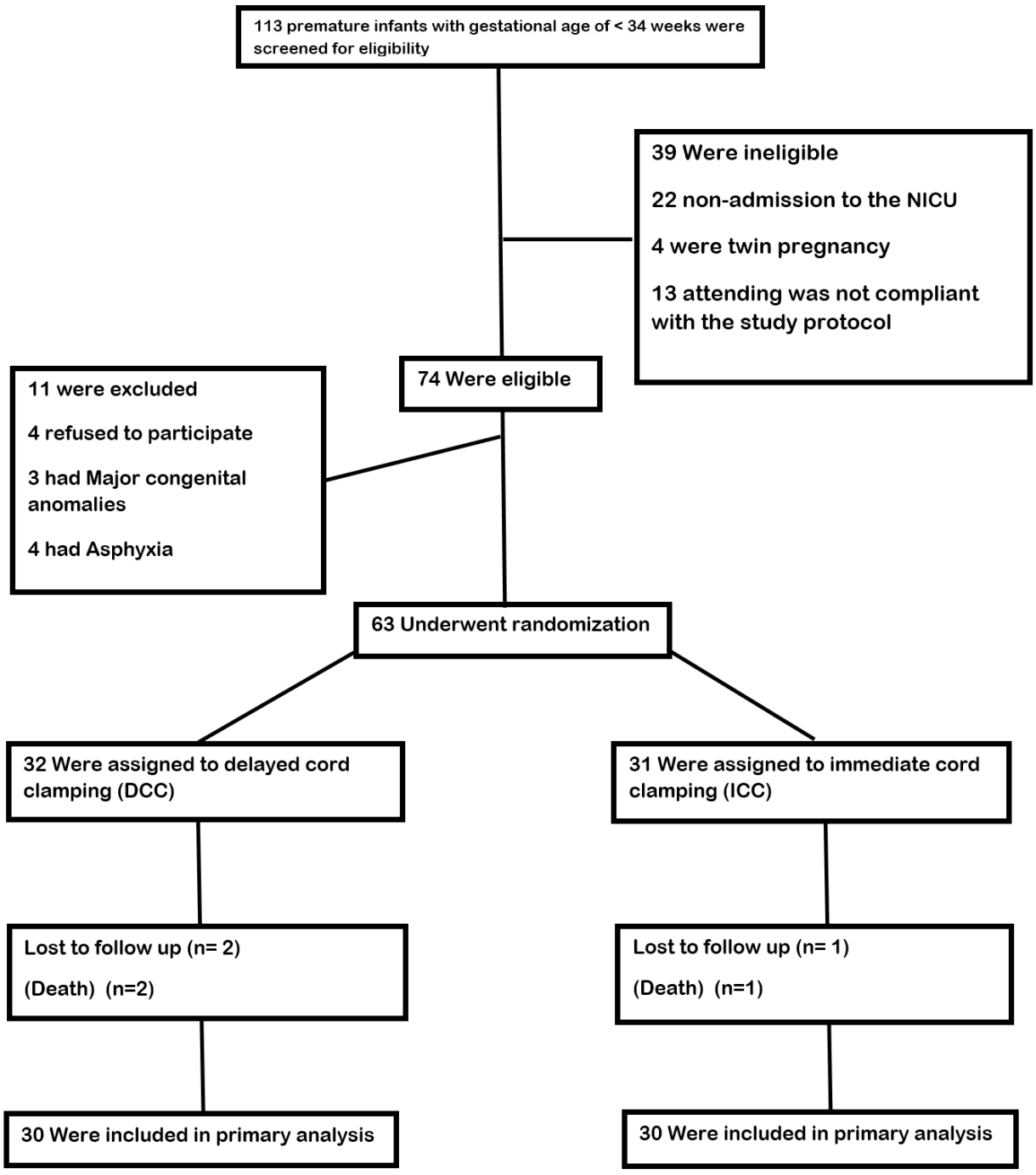

Fig.2: CONSORT diagram showing the flow of subjects through each stage of study

Table-1: Baseline characteristics of infants studied

Variables	ICC (n=30)	DCC (n=30)	P-value
Gender (%male)	13(43.3%)	13(43.3%)	0.603
Gestational age (weeks)* (mean ± SD)	30.95±2.09	31.90±1.58	0.064
Apgar score in the first minute of life ** (mean ± SD)	6.33±1.88	6.43±2.22	0.851
Apgar score in the 5th minute of life ** (mean ± SD)	8.67±1.02	8.63±1.15	0.907
Birth weight (mean ± SD)	1518.33±326.61	1597±281.60	0.327
Type of delivery			
Cesarean sections NVDs	20(66.7%) 10(33.3%)	25(83.3%) 5(16.7%)	0.116
Receive corticosteroid before birth	14(46.7%)	10(33.3%)	0.430
IVH			
Absence Grade I Grade II Grade III	28(93.3%) 1(3.3%) 1(3.3%) 0(0.0%)	27(90.0%) 0(0.0%) 2(6.7%) 1(3.3%)	0.600

Data mentioned as Mean (SD) or N (%) for all of variables; SD: Standard deviation; ICC: Immediate umbilical cord clamping; DCC: Delayed umbilical cord clamping; NVD: Normal vaginal delivery; IVH: Intraventricular hemorrhage. *Maternal report of estimated delivery date, verified with medical chart. **The Apgar reported justified by the mentioned symptoms.

Table-2: Effects of immediate and delayed umbilical cord clamping on neonatal outcomes

Variables	ICC (n=30)	DCC (n=30)	P-value
Neonatal resuscitation			
CPAP, n (%) PPV, n (%)	17(56.7%) 7(23.3%)	14(46.7%) 7(23.3%)	0.606 1.000
PDA, n (%)	7(23.3%)	3(10.0%)	0.299
NEC, n (%)			
Suspected, n (%) Proven, n (%)	11(36.7%) 0(0.0%)	6(20.0%) 1(3.3%)	0.252 1.000
ROP, n (%)	6(20%)	3(10%)	0.472
Clinical sepsis, n (%)	16(53.3%)	7(23.3%)	0.033
Death, n (%)	2(6.7%)	1(3.3%)	1.000
Blood transfusion, n (%)	7(23.3%)	4(13.3%)	0.506
INSURE	17(56.7%)	11(36.7%)	0.195
Duration of need to NCPAP (hours) (mean ± SD)	26±86.7	18±60.0	0.039
Hematocrit in the 4th hours of life (gr/dl) (mean ±SD)	46.58±5.40	49.58±5.15	0.031

Length of hospitalization** (day) (mean ± SD)	13.53±9.09	10.97±11.27	0.336
Oxygen dependency (day) (mean±(SD))	5.33±6.37	5.33±8.84	1.000

Data mentioned as Mean (SD) or N (%) for all of variables; SD: Standard deviation; ICC: Immediate umbilical cord clamping; DCC: Delayed umbilical cord clamping; CPAP: continues positive airway pressure; PPV: positive pressure ventilation; PDA: Patent of ductus arteriosus; NEC: Necrotizing enterocolitis; ROP: Retinopathy of prematurity.

4- DISCUSSION

Previous studies mentioned that DCC results in decline in the requirement of blood transfusion in newborns who are required because of anemia and low blood pressure, while there is not still proved findings which provides confirmed data due to the effects of DCC in occurring of IVH, although there are few studies which have revealed decrease in IVH as a result of DCC (11). In some other studies there had been evidence that demonstrates DCC improves hematocrit in neonates. The relatively large neonates (30-36 weeks` gestation at birth) required very few red blood cell (RBC) transfusions-regardless of whether they were in ICC or DCC groups- precluding meaningful statistical comparison (26).

The current study demonstrates blood transfusion requirement did not have a meaningful difference in both groups, but hematocrit was meaningfully higher in neonates that were in DCC groups; which might improve the blood flow and decreased complications of prematurity. Furthermore, the existence of IVH in newborns is not affected by the timing of clamping the cord after delivery which is the same as the results in a Strauss et al. study and surprisingly not supporting Mercer et al. study (7, 26). In Rabe et al. study there was no explicit contrast between the two groups regarding the rate of mortality (11) which seems to be similar to the outcomes of this study. NEC and sepsis appears decline in DCC group which of course has been observed in few studies. Clinical sepsis in ICC group was pointedly more prevalent while NEC did not meaningfully differ in the groups and there is no clear evidence that Apgar scores are significantly different (11). In this study there were higher rates of sepsis in ICC group and there is a probability that this outcome could be related to more NCPAP days and more requirements for oxygenation, and lower hematocrit in ICC group. In the present study results showed that Apgar scores right after birth did not differ significantly in the two groups, but Apgar score in the minute 5 was higher in DCC group. Surprisingly, as one of the rationales for early clamping is to allow the infant to be transferred to a resuscitative place for respiratory support, there are few data on respiratory outcomes (1). Hutton et al., noted that no significance difference was observed between late and early cord clamping in terms of the risk of developing either tachypnea or respiratory grunting (1).

The number of Continuous Positive Airway Pressure (CPAP) required neonates in both groups was not significantly different in the study, while NCPAP requirement was pointedly higher in ICC group which is suggesting that the newborns in ICC group had more respiratory problems. Although, there is no significant difference in the length of hospitalization (days), but the amount of days was higher in ICC group which is

providing this idea that the ICC group needs more observations due to having more problems. According to increasing of premature births which is one of the most important cause of neonatal morbidity and mortality (34- 38), investigation of different interventions on neonatal outcomes are of great importance. Hence, further investigations are recommended with larger series of participants and longer follow-up to validate the findings reported in this study.

5- CONCLUSION

In current study, delayed umbilical cord clamping had favourable effects on level of hematocrit in the 4th hours of life, duration of need to NCPAP and incidence of clinical sepsis. Delayed cord clamping also had no negative impact on neonatal resuscitation; although had not favourable effect on blood transfusion, Apgar score in the first and 5th minutes of life and IVH. Furthermore incidence of PDA, ROP and NEC were similar in DCC and ICC groups. These findings suggests a possible beneficial effect that should be evaluated in larger studies.

6- CONFLICT OF INTEREST: None.

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