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Original Article

Delayed cord clamping for prevention of iron deficiency anemia in term infants

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Abstract

Background Iron deficiency anemia (IDA) during infancy and childhood is a concern due to its potentially detrimental effects on development, some of which may be irreversible even after iron treatment. Delayed cord clamping may prevent IDA by increasing an infant's iron reserve at birth.

Objective We aimed to evaluate the effect of delayed umbilical cord clamping at birth on the iron status in newborns at age 24 hours of life.

Methods This randomized, single-blind study was conducted from March to May 2009, at two general hospitals in Medan, North Sumatera Province. Eligible newborn infants were randomly assigned to one of two groups: early cord clamping (ECC) performed 15 seconds after delivery or delayed cord clamping (DCC) performed 2 minutes after delivery. Infants were placed on their mothers' abdomens before the umbilical cords were clamped. Hematologic status was determined from umbilical cord blood.

Results Sixty-three subjects were included in our study, consisting of 31 infants in the ECC group and 32 infants in the DCC group. We found that mean neonatal hemoglobin level was higher in the DCC group than in the ECC group (18.4 g% and 16.2 g%, respectively, P=0.0001). Also, mean ferritin level was higher in the DCC group than in the ECC group (556 mg/dL and 329 mg/dL, respectively, P=0.015). Other hematological status indicators, including mean hematocrit and mean corpuscular volume (MCV) level, were also higher in the DCC group. However, mean red blood cell levels were not significantly different between the two groups. Nor was there a significant difference in mean bilirubin level between the DCC and ECC groups.

Conclusion Delayed cord clamping may improve iron status and prevent IDA in term infants. **[Paediatr Indones. 2012;52:223-8]**.

Keywords: *delayed cord clamping, iron deficiency anemia, term infants*

Approximately 30% of the world population is anemic and half of these people have iron deficiency anemia (IDA).[1] In Southeast Asia, the prevalence of IDA has been reported to be 60 - 70%.[1] In Indonesia, there are an estimated 50 - 70 million people with IDA.[1] The 1992 Household Health Data Survey reported that 55% of toddlers had IDA.[2] The prevalence of IDA in Indonesian infants (aged 3 - 5 months) was reported to be 71%.[2]

Iron deficiency anemia during infancy and childhood is concerning due to its potentially detrimental effects on development. Some effects may be irreversible even with subsequent iron treatment.[3] Maternal iron status, infant birth weight and gestational age, as well as the timing of umbilical cord clamping at birth contribute to the establishment of adequate total body iron at birth.[4]

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The prevalence of IDA was reported to be 3 times more frequent in infants who underwent early cord clamping.[5] Delayed cord clamping may prevent IDA by increasing an infant's iron endowment at birth.[6,7] As such, we aimed to compare the iron status of infants at the age of 24 hours of life who underwent delayed cord clamping or early cord clamping. Delayed umbilical cord clamping has the potential to improve the iron status of newborns.

Methods

A randomized, single-blind study was conducted on March to May 2009, at two general hospitals (H. Adam Malik and Dr. Pirngadi) in Medan, North Sumatera. This study was approved by Ethics Committee of the University of Sumatera Utara Medical School. In our study, we enrolled spontaneously born, singleton newborn infants with gestational age of 38 to 42 weeks, birth weight of 2500 - 4000 g, and APGAR score of ≥ 7 in the first minute. Parental informed consent was obtained for all subejcts. Gestational age was estimated based on the Naegel formula or new Ballard score of newborn infants. Newborns with major congenital anomalies, birth trauma (subaponeurotic bleeding, caput succedaneum, or hematoma), history of maternal pregnancy/delivery complications or clinical conditions (placenta previa, preeclampsia, eclampsia, diabetes, or hypertension), or who had received diazepam were excluded.

Subjects were randomly assigned into one of the two groups through the use of uniform and sealed envelopes, immediately before the vaginal delivery. ECC was performed in the first group 15 seconds after delivery. DCC was performed in the second group 2 minutes after delivery. We worked along with an obstetrician from the Obstetric and Gynecology Department, University Sumatera Utara Medical School. Given the nature of the intervention, the obstetrician could not be blinded, but mothers were not informed as to the timing of cord clamping. At the time of delivery, an observer used a stopwatch to record the time elapsed. The obstetrician placed the newborn infant on the mother's abdomen, then clamped and cut the umbilical cord.

Ferritin levels were measured using electronic blood counting equipment (Cobas) from the umbilical cord venous blood. As much as 2 ml was drawn at 24 hours of age.

Data was analyzed with SPSS for Windows 14.0. Independent t-test was used to analyze the difference in ferritin values between the ECC and DCC groups. Statistical significance was determined to be $P < 0.05$ with a 95% confidence interval.

Results

During the study, 272 pregnant women had planned to undergo vaginal delivery, but only 68 were eligible for

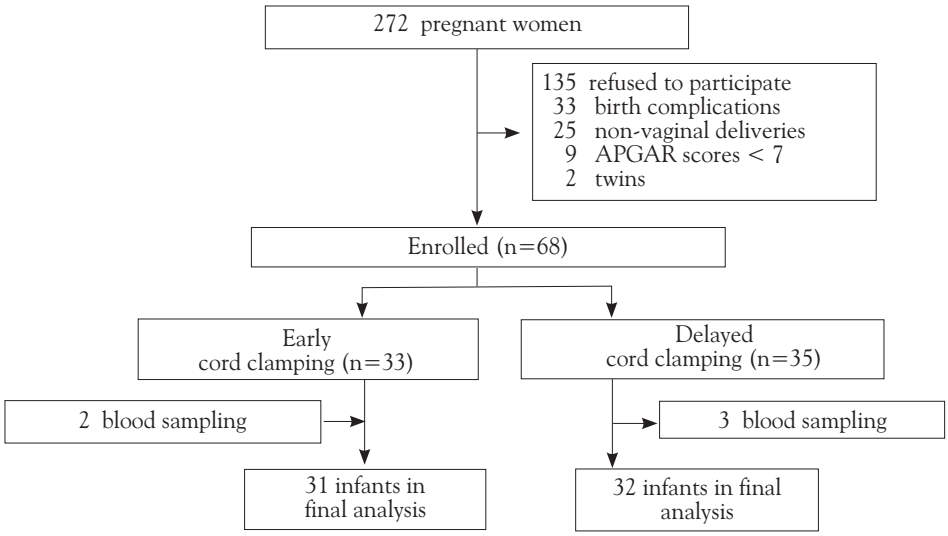

Figure 1. Study profile

inclusion to the study. As shown in the study profile in **Figure 1**, there were 31 subjects in the ECC group and 32 subjects in the DCC group.

Subjects' baseline characteristics are shown in **Table 1.** Mean maternal and infant hemoglobin and hematocrit levels are shown in **Table 2**. Mean red cell indices are shown in **Table 3**.

There was a significant difference in mean ferritin level between the ECC and DCC groups. In the ECC group, the mean ferritin level was 329 (SD

Table 1. Baseline characteristics of subjects

Characteristics	ECC (n=31)	DCC (n=32)
Sex, n, (%)		
Male	13 (41.9)	20 (62.5)
Female	18 (58.1)	12 (37.5)
Mean birth weight, g (SD)	3040 (0.28)	3142 (0.31)
Mean body length, cm (SD)	49.03 (1.23)	49.10 (1.26)
Mean length of hospital stay, days (SD)	2.75 (0.50)	3.06 (0.35
Mean maternal age, years (SD)	26.13 (2.90)	25.65 (2.67)
Median gravida	2	2
Mean gestational age, weeks (SD)	38.66 (0.82)	38.61 (0.84)
Median 1 minute Apgar Score	7	7
Median 5 minute Apgar Score	9	9
Diet, n (%)		
Breast milk	19 (61.3)	21 (65.6)
Breast milk and formula	4 (12.5)	4 (12.5)
Formula	8 (25.8)	7 (21.9)
Maternal educational level attained, n (%)		
Graduate school	0 (0)	2 (6.2)
Bachelor degree	1 (3.2)	0 (0)
Senior high	18 (58.1)	23 (71.9)
Junior high	9 (29.0)	7 (21.9)
Elementary	3 (9.7)	0 (0)

Table 2. Mean maternal and infant hemoglobin (Hb), hematocrit (Ht) and red blood cell (RBC) levels

	ECC (n=31)	DCC (n=32)	95% CI	P
Mean maternal Hb, g% (SD)	11.4 (1.10)	11.8 (1.27)	0.20 to 0.99	0.194
Mean maternal Ht, % (SD)	34.2 (3.08)	35.1 (3.60)	0.86 to 2.48	0.339
Mean infant Hb, g% (SD)	16.2 (1.03)	18.4 (1.06)	1.61 to 2.67	0.0001
Mean infant Ht, % (SD)	34.2 (3.08)	35.1 (3.60)	4.06 to 7.27	0.0001
Mean infant RBC, $10^6/mm^3$ (SD)	4.6 (0.56)	4.7 (0.60)	0.28 to 0.30	0.935

Table 3. Red cell indices in infants

	ECC (n = 31)	DCC (n = 32)	95% CI	P
Mean MCV, fL (SD)	101.8 (4.03)	103.9 (4.27)	-4.293 to 0.127	0.046
Mean MCH, pg (SD)	35.0 (1.52)	35.2 (1.61)	-1.000 to 0.616	0.399
Mean MCHC, g/dL (SD)	34.2 (0.93)	34.5 (0.79)	0.013 to 1.086	0.093
Mean RDW, % (SD)	16.5 (0.92)	16.3 (0.85)	0.338 to 0.578	0.695

MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red cell distribution width

181.3) mg/dL while in the DCC group, it was 556 (SD 463) mg/dL; (95% CI 45.1 to 409.2; P=0.015).

We did not observe a significant difference in mean billirubin levels between the ECC and DCC groups. Mean bilirubin was 4.1 (SD 1.14) mg/dL in the ECC group and 4.8 (SD 1.71) mg/dL in the DCC group (95% CI 0.041 to 1.425; P=0.064).

Discussion

Our results indicated that delayed cord clamping may improve newborns' hematologic status with no cases of polycythemia. At the age of 24 hours, neonatal mean hematocrit and hemoglobin levels were significantly higher in the DCC group than in the ECC group. However, mean RBC levels were not significantly different.

Similarly, Hutton *et al*. in a meta-analysis of 15 controlled trials (1,912 newborns), reported that delayed clamping of the umbilical cord in full-term neonates for a minimum of 2 minutes following birth is beneficial for hematologic status of newborns. The DCC group showed greater levels of hemoglobin, hematocrit, blood volume, and iron status, as well as decreased risk of anemia.[8]

Previous studies found significantly higher neonatal hematocrit levels at 24 – 48 hours after delivery in infants who underwent DCC.[9-11] This higher neonatal hematocrit level was also found at the ages of 5 days,[11-13] and 2 months.[14] However, no difference was observed at the age of 6 months.[15] Mean neonatal hemoglobin measured at 4 and 7 hours after birth in capillary blood was found to be higher in newborns who underwent DCC,[15,16] but no significant difference was observed at the ages of 2 - 3 months,[14,17,18] or 6 months.[15] The risk of polycythemia after birth was reportedly more common in neonates allocated to the DCC group rather than the ECC group at 7 hours,[9,16] and at 24 to 48 hours.[9,10,11-14,17]

Previous studies have shown that 6-month-old infants who underwent DCC at birth had significantly higher mean corpuscular volume (MCV), but no significant differences in mean corpuscular hemoglobin (MCH) or mean corpuscular hemoglobin concentration (MCHC) values.[17] Low MCV or MCH values may be found in cases of chronic fetal anemia, fetomaternal hemorrhage, and α or β thalassemia.[19] No results were reported on MCV, MCH, and MCHC values before at the age of 24 hours. We found that mean MCV was lower in the ECC group than in the DCC group. However, further evaluation needs to be done.

The red cell distribution width (RDW) value expresses differences in erythrocyte size in an individual specimen and may be used to detect anisocytosis where red blood cells have variable and abnormal sizes. Also, RDW can be used as an indicator of iron deficiency anemia.[,] Higher RDW values indicate greater differences in erythrocyte size and may be found in patients with certain conditions, such as hemolytic anemia.[20,21] However, mean RDW values in our study, indicated less variability in infants' erythrocyte size.

Iron level can be defined using ferritin levels, since besides hemosiderin, ferritin is an iron reservoir.[22] Plasma ferritin concentration alone provides a good approximation of total body iron.[23] Previous research has shown that before 6 months of age, the mechanisms present in adults for regulating iron absorption might not yet be mature, thus both hemoglobin and ferritin increase with increased iron intake, even in the presence of adequate iron stores.[24] In developing countries where fetal anemia is common, the advantages of delayed cord clamping might be especially beneficial.[25] Similar iron levels in newborns and 6 – 12 months old age children have been reported in newborns who underwent DCC.[25] Infants from anemic mothers reportedly have lower ferritin levels in early days.[26,27] Ferritin levels at the age of 2 to 3 months were higher for infants allocated to the delayed vs early cord clamping group.[14,17]

Our findings also demonstrated that DCC coincides with an increased ferritin level 24 hours after delivery. Similarly, in two trials comparing the effects of delayed vs early clamping on ferritin levels of less than 50 μg/L at the age of 3 months as an indicator for deficient iron stores, delayed cord clamping showed increased ferritin levels.[17,18] At age 6 months, ferritin levels were also higher with delayed clamping.[16]

We found no jaundiced infants in either group. Similarly, there was no significant difference in mean serum bilirubin levels in the first 24 hours of life. Several limitations of our study should be considered. We did not measure maternal ferritin levels, as we had access to limited maternal specimen quantities. We also did not assess other infant hematologic status

indicators nor did we perform long-term follow up of patients. A prospective cohort study is needed to understand the relationship of the timing of umbilical cord clamping to hematologic status in neonates. In conclusion, DCC may improve iron status in term infants and prevent IDA.

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