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ARTICLE

The Effect of Timing of Cord Clamping on Neonatal Venous Hematocrit Values and Clinical Outcome at Term: A Randomized, Controlled Trial

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ABSTRACT

BACKGROUND. The umbilical cord is usually clamped immediately after birth. There is no sound evidence to support this approach, which might deprive the newborn of some benefits such as an increase in iron storage.

OBJECTIVES. We sought to determine the effect of timing of cord clamping on neonatal venous hematocrit and clinical outcome in term newborns and maternal postpartum hemorrhage.

METHODS. This was a randomized, controlled trial performed in 2 obstetrical units in Argentina on neonates born at term without complications to mothers with uneventful pregnancies. After written parental consents were obtained, newborns were randomly assigned to cord clamping within the first 15 seconds (group 1), at 1 minute (group 2), or at 3 minutes (group 3) after birth. The infants' venous hematocrit value was measured 6 hours after birth.

RESULTS. Two hundred seventy-six newborns were recruited. Mean venous hematocrit values at 6 hours of life were 53.5% (group 1), 57.0% (group 2), and 59.4% (group 3). Statistical analyses were performed, and results were equivalent among groups because the hematocrit increase in neonates with late clamping was within the prespecified physiologic range. The prevalence of hematocrit at <45% (anemia) was significantly lower in groups 2 and 3 than in group 1. The prevalence of hematocrit at >65% was similar in groups 1 and 2 (4.4% and 5.9%, respectively) but significantly higher in group 3 (14.1%) versus group 1 (4.4%). There were no significant differences in other neonatal outcomes and in maternal postpartum hemorrhage.

CONCLUSIONS. Delayed cord clamping at birth increases neonatal mean venous hematocrit within a physiologic range. Neither significant differences nor harmful effects were observed among groups. Furthermore, this intervention seems to reduce the rate of neonatal anemia. This practice has been shown to be safe and should be implemented to increase neonatal iron storage at birth.

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Dr Ceriani Cernadas had the original idea; Drs Carroli, Ceriani Cernadas, and Lardizábal developed the protocol, conducted the trial, performed the analysis, and wrote the final article; Mr Giordano performed the analysis and data management; and Drs Pellegrini, Otaño, Ferreira, Ricci, and Casas conducted the trial and discussed the results.

Key Words
anemia, cord blood, delivery of care, newborn, full term, perinatal medicine

Abbreviations
CI—confidence interval
RR—relative risk

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TIMING OF UMBILICAL cord clamping has been and still is a highly controversial issue.[1–4] The current obstetric approach in Western medicine is to clamp the cord within the first 10 to 15 seconds after birth. However, there has been no sound evidence in favor of this approach in comparison to the millennial practice of clamping the cord between 1 and 3 minutes after birth.[5,6]

In some studies,[7–9] it was observed that delayed cord clamping could contribute to preventing iron-deficiency anemia in the first year of life. A recent systematic review confirms the benefit of delayed cord clamping.[10] The reason for this effect is based on the fact that after birth the newborn is delivered with a placental transfusion of ~80 mL of blood at 1 minute after birth and 100 mL at 3 minutes after birth.[6,11–17] This volume will supply 40 to 50 mg/kg of extra iron to the ~75 mg/kg of body iron that newborn term infants have, reaching a total of 115 to 120 mg/kg, which might prevent iron deficiency in the first year of life.[4,8] Iron deficiency early in life may have pronounced central nervous system effects such as cognitive impairment[18]; iron deficiency is also the main cause of anemia, one of the most serious conditions in childhood, especially in developing countries.[19]

Conversely, some observational studies suggest that delayed umbilical cord clamping puts newborns at higher risk of suffering from polycythemia, respiratory symptoms, hyperbilirubinemia, and other neonatal disorders.[14,20–24] However, there have been no randomized, controlled trials showing the risk of these harmful effects on the newborn.

In view of the above considerations, we performed a prospective randomized, controlled clinical trial to determine the benefits and risks of delayed cord clamping.

Our hypothesis was that delayed cord clamping (at 1 or 3 minutes after birth) in healthy term newborns increases hematocrit within physiologic ranges without causing any harmful effects. Umbilical cord clamping at 1 minute of life increases hematocrit in no more than 8 points compared with cord clamping in the first 15 seconds after birth. Cord clamping at 3 minutes increases neonatal hematocrit to a level no more than 8 points compared with cord clamping at 1 minute after birth.

Our primary objective of the study was to determine the effect of timing of umbilical cord clamping on venous hematocrit in term neonates 6 hours after birth. Our secondary objectives were to assess the effect of timing of umbilical cord clamping on neonatal outcomes and on the presence of unwanted effects in the newborn while in the maternity ward and during the first month of life. Venous hematocrit and plasma bilirubin levels at 24 to 48 hours of life and maternal postpartum blood loss were measured also.

METHODS

This was a randomized, controlled trial performed in the Hospital Italiano of Buenos Aires and Maternidad Martin of Rosario; Centro Rosarino de Estudios Perinatales was the coordinating center. The trial was approved by the ethics committees of both hospitals (Hospital Italiano de Buenos Aires, protocol number: 681/2002).

Women were eligible if they had uneventful cephalic vaginal or cesarean section delivery with the following characteristics: singleton pregnancy at term; no evidence of clinical disease (diabetes, preeclampsia, hypertension) or any other complications; and no evidence of congenital malformations or intrauterine growth restriction (estimated fetal weight <10th percentile).

Interventions

Three interventions for the newborns were compared: early umbilical cord clamping (within the first 15 seconds after birth), umbilical cord clamping at 1 minute after birth, and at 3 minutes after birth. The latter 2 groups were regarded as delayed cord clamping. The cord-clamping technique used in the 3 groups was similar.

The assigned intervention was considered as accomplished if early cord clamping was performed within the first 20 seconds after birth, delayed 1-minute cord clamping at 45 to 75 seconds of life, and delayed 3-minute cord clamping at ≥150 seconds after birth.

For vaginal deliveries, newborns assigned to delayed cord clamping were held by mothers in their arms while waiting for the cord to be clamped. In the case of cesarean sections, newborns were placed on their mother's laps and swaddled to prevent heat loss. No additional interventions were performed.

Newborns without spontaneous breathing during the first 10 seconds of life, with major congenital malformations diagnosed at birth, with estimated neonatal birth weight <10th percentile, and/or with tight nuchal cord were subjected to early cord clamping based on physician discretion regardless of the assigned intervention.

Outcome Measures

The primary outcome measure was the newborn venous hematocrit value 6 hours after birth. Secondary outcome measures were neonatal hematocrit at 24 to 48 hours of age, plasma bilirubin level at 24 to 48 hours of age, early neonatal morbidity and mortality (tachypnea, respiratory grunting, respiratory distress, jaundice, seizures, sepsis, necrotizing enterocolitis, neonatal death), admission to the NICU, newborn length of hospital stay, any neonatal disease that occurred between birth and 1 month of age, weight and type of feeding at 1 month of age, postpartum maternal blood-loss volume, and maternal hematocrit value 24 hours after delivery. Pediatricians assessing the outcomes were unaware of the assigned interventions.

There is a general consensus that a venous hematocrit level of <3.5 g/dL or 40% in the umbilical cord blood is

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a synonym of anemia.[25,26] However, taking into account that in the first hours of life venous hematocrit and hemoglobin values increase ~10%, it was considered clinically appropriate to define anemia as a venous hematocrit level of <45% at 6 hours after birth. Polycythemia in the newborn is defined as a venous hematocrit of >65%.[27]

Procedures

Venous hematocrit in the newborn was measured in blood drawn from the antecubital vein. Blood was collected in 2 tubes sealed at one end with modeling clay. Both tubes were filled up and centrifuged for 5 minutes. Hematocrit was measured in an "ad hoc" graded scale provided by the centrifuge manufacturer. Bilirubin was measured following the Malloy and Evelyn technique.[28]

Every newborn included in the study was scheduled to be followed up at 7, 14, and 28 days of life. During these visits, neonates were followed up based on the standard clinical approach; growth and development were evaluated, and feeding patterns were recorded also.

For the measurement of maternal blood loss, all vaginal blood was collected immediately after the infant's delivery by placing a pan and pad under the woman's buttocks until she was transferred to the postpartum ward. Collected blood was poured in a graded jar, and blood volume was determined.

Sample Size

The average neonatal hematocrit level at 6 hours is known to be ~50% (SD: 7%) when the cord is clamped early after birth and ~55% (SD: 7%) when the cord is clamped at 1 minute after birth. Sample sizes were calculated to show that the hematocrit level when cord clamping at 1 minute of life is within 8 U of the hematocrit level obtained with early clamping. In that case, the 2 groups will be considered as equivalent. Similar calculations were made assuming a mean neonatal hematocrit level at 6 hours of ~60% (SD: 7%) when the cord is clamped at 3 minutes after birth, an equivalent limit of 8 U was used for the comparison with the group assigned to cord clamping at 1 minute after birth. Using an α error of 5% and a statistical power ($1 - \beta$) of 80%, the number of patients to be studied is 70 in each group, for a total of 210 newborn infants.

Statistical Analysis

The information collected through the data forms was entered in a database by different operators using the double-entry technique. These operators also checked for and validated inconsistencies. Case charts were reviewed whenever a flaw was detected. Means and SDs were used as descriptive measures for continuous variables with normal distributions, and medians and quartiles were used when the normality assumption was not acceptable. Frequencies and percentages were reported for categorical variables. Hematocrit levels were compared among groups by using confidence intervals (CIs) for differences in averages.[29] The Bonferroni method was used for multiple comparison adjustments. The normality assumption for the distribution of hematocrit levels within groups was checked by using the Shapiro-Wilk test.[30] Categorical variables were compared among groups by using relative risks (RRs), and the Fisher's exact test was used to assess that statistical significance of comparisons. Continuous secondary outcomes were compared among groups by using the Kruskal-Wallis test.[31] SAS 8 (SAS Institute, Inc, Cary, NC) was used to perform all calculations.

Analyses were made on an intention-to-treat basis.

Assignment

Randomization

Randomization was conducted by Centro Rosarino de Estudios Perinatales (the center responsible for the study coordination) through a sequence of computer-generated random numbers (SAS 8). The randomization was stratified by hospital, and in turn, in each institution stratification was based on the mode of delivery (vaginal or cesarean section). Variable-length blocks were used for the randomization process. Sealed opaque sequentially numbered envelopes that contained the assigned intervention were used to conceal the allocation. The envelopes were placed in a box from which only 1 envelope could be drawn at a time. The staff responsible for the random generation and the allocation-concealment process was not involved in the recruitment phase of the trial.

Implementation

At 36 weeks of gestational age, eligible women were invited to take part in the trial by the physician in charge of antenatal care. If they agreed to participate, both parents signed an informed consent during the following visit. If at the time of delivery the woman was still considered eligible for the trial, enrollment took place, and an envelope was drawn and opened accordingly in the delivery room. Enrollment was made by a physician of the trial (working in this area but not in charge of the delivery), who read to the obstetrician assisting the delivery the assigned intervention. After completion of these procedures, a third physician used a timekeeper to check the time at which clamping was effectively accomplished. Labor and delivery were performed following the standard practice of care.

Masking

Given the characteristics of the intervention, the physician in charge of the intervention (umbilical cord clamping) could not be blinded. However, health professionals

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who made the neonatal evaluations after birth were not the ones present when infants were delivered and were not aware of the approach to which the delivery had been assigned. The personnel in charge of biochemical tests also were not aware of the approach used.

RESULTS

Recruitment was conducted from November 2, 2002, to April 28, 2003. Invited to take part in the study were 312 eligible women. At the time of random assignment, 21 of the total number of women did not meet the inclusion criteria. Fifteen of the remaining 291 eligible women either did not agree to participate or were not enrolled in the trial for operative reasons. The remaining 276 patients were randomly assigned to the 3 approaches described for umbilical cord clamping (Fig 1).

Compliance with the allocated intervention was 94.6% (88 of 93) in the early-cord-clamping group, 91.2% (83 of 91) in the 1-minute cord-clamping group, and 90.2% (83 of 92) in the 3-minute cord-clamping group. Cases and reasons for protocol deviations are shown on Fig 1.

Average clamping time for each group was 12.7 seconds in the early-cord-clamping group, 59.8 seconds in the 1-minute cord-clamping group, and 169.5 seconds in the 3-minute cord-clamping group.

Study groups were similar with respect to demographic and clinical variables (Table 1).

Compliance with evaluation standards of the first and second neonatal hematocrit determinations and bilirubin level was checked. No differences were found among groups when these tests were performed.

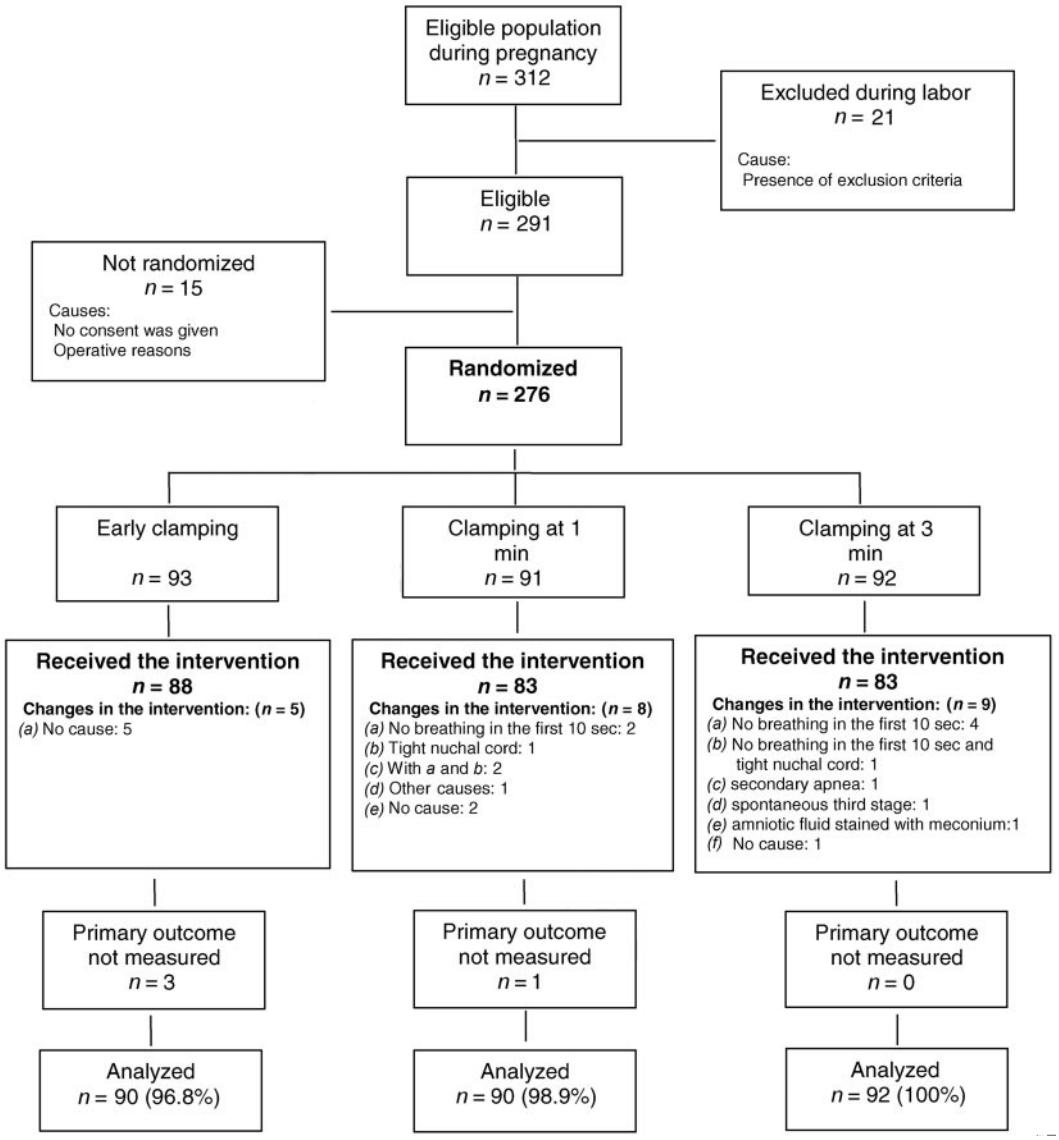

FIGURE 1
Flowchart of the study population.

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TABLE 1 **Baseline Characteristics of the Study Groups**

	Early Clamping ($N = 93$)	Clamping at 1 min ($N = 91$)	Clamping at 3 min ($N = 92$)
Mother's age, mean ± SD, y	28.8 (5.7)	28.6 (6.1)	27.9 (6.2)
Parity, mean ± SD	1.9 (1.8)	1.7 (1.7)	1.6 (1.7)
Gestational age at birth, mean ± SD, wk	39.3 (1.4)	39.1 (1.2)	39.3 (1.1)
Antenatal visits, mean ± SD, *n*	8.0 (2.3)	8.2 (2.2)	8.4 (2.5)
Maternal anemia, *n/N* (%)	15/92 (16.3)	10/90 (11.1)	13/92 (14.1)
Cesarean section, *n/N* (%)	26/92 (28.3)	27/90 (30.0)	26/92 (28.3)
Third-stage active management, *n/N* (%)[a]	52/93 (55.9)	45/88 (51.1)	46/91 (50.6)
Maternal hematocrit before birth, mean ± SD, %	33.9 (3.5)	34.8 (3.6)	34.0 (3.5)
Newborn weight, mean ± SD, g	3390.2 (395.0)	3424.8 (382.8)	3420.7 (360.7)

[a] Third-stage active management: oxytocin administration after delivery of the baby plus cord traction.

Neonatal hematocrit at 6 hours of age was 53.5% (SD: 7.0) in the early-cord-clamping group, 57.0% (SD: 5.8) in the 1-minute cord-clamping group, and 59.4% (SD: 6.1) in the 3-minute cord-clamping group (Table 2).

Statistical analyses among groups showed equivalence within the prespecified ranges, because hematocrit increase in neonates assigned to cord clamping at 1 minute was not higher than 8 points compared with the hematocrit value recorded in the group with early cord clamping (mean difference: −3.52; 95% CI: −5.79 to −1.26). Also, equivalence is shown in the comparison between cord-clamping groups at 1 and 3 minutes, respectively (mean difference: −2.39; 95%CI: −4.64 to −0.13) (Fig 2).

The prevalence of newborn infants with a hematocrit level of <45% at 6 hours was significantly higher in the early-cord-clamping group (8.9%) versus groups with cord clamping at 1 or 3 minutes (1% and 0%, respectively) (Table 3).

There were no differences regarding the percentage of neonates with a hematocrit level of >65% (polycythemia) between groups 1 and 2 (4.4% and 5.5%, respectively), but this was significantly higher in group 3 than in group 1 (14.1% vs 4.4%) (Table 3). None of the polycythemic newborns developed symptoms; hence, partial exchange transfusion was not required.

Venous hematocrit values at 24 to 48 hours were 51.14% in the early-cord-clamping group, 53.62% in the 1-minute cord-clamping group, and 56.41% in the 3-minute cord-clamping group (Table 4).

The prevalence of newborn infants with a hematocrit level of <45% at 24 to 48 hours was significantly higher in the early-cord-clamping group (16.8%) compared with groups assigned to cord clamping at 1 minute (2.2%) and 3 minutes (3.3%), respectively (Table 4).

TABLE 2 **Neonatal Hematocrit at 6 Hours**

	Early Clamping ($n = 90$)	Clamping at 1 min ($n = 90$)	Clamping at 3 min ($n = 92$)
Mean (SD), %	53.5 (7.0)	57.0 (5.8)	59.4 (6.1)
Minimum–maximum, %	39.7–68.0	43.5–71.0	45.0–75.0

No significant differences were observed in the groups concerning the rate of neonates with a hematocrit level of >65% at 24 to 48 hours (Table 4).

Plasma bilirubin values at 24 to 48 hours of age were similar among the 3 groups. No significant differences were observed in neonatal adverse-event rates. There were no cases of necrotizing enterocolitis or seizures. Only 1 case of neonatal sepsis was found in the group subjected to cord clamping at 1 minute. There was only a slight and statistically not significant increase in respiratory distress, tachypnea, and grunting rates in the groups subjected to clamping at 1 or 3 minutes after birth in comparison to the group assigned to early cord clamping (Table 5). No significant differences were found in the admission rate to the NICU (Table 5) or length of hospital stay (Table 5).

The clinical course after discharge during the first month of life was similar in the 3 groups, and at 30 days no differences in relation to the infant's weight or frequency of exclusive breastfeeding were observed (Table 5). No neonatal deaths were observed in the population under study.

Regarding maternal outcomes, no differences were observed among the groups with respect to postpartum blood-loss volume, postpartum hemorrhage, and maternal hematocrit level 24 hours after birth. The median maternal blood loss was 265 mL (first-third quartiles: 150–510 mL) in the early-cord-clamping group, 250 mL (first-third quartiles: 150–400 mL) in the 1-minute cord-clamping group, and 300 mL (first-third quartiles: 200–500 mL) in the 3-minute cord-clamping group.

Postpartum hemorrhage (blood loss >500 mL) was 26.8% in the early-cord-clamping group, 22.2% in the 1-minute cord-clamping group, and 25.4% in the 3-minute cord-clamping group. Severe postpartum hemorrhage (blood loss >1000 mL) was 3.6%, 5.6%, and 3.2% in each group, respectively. The maternal hematocrit at 24 hours postpartum was 29.9% (SD: 3.5) in group 1, 30.9% (SD: 4.5) in group 2, and 30.6% (SD: 3.6) in group 3.

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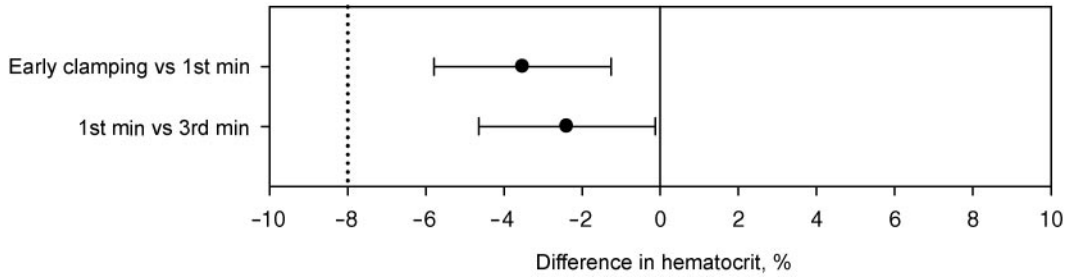

FIGURE 2
Neonatal hematocrit at 6 hours. The vertical dotted line represents the margin of clinical equivalence that was determined a priori.

TABLE 3 **Neonatal Polycythemia and Anemia at 6 Hours of Life**

	Early Clamping ($n = 90$)	Clamping at 1 min ($n = 90$)	Clamping at 3 min ($n = 92$)
Polycythemia (hematocrit > 65%), *n* (%)	4 (4.4)[a]	5 (5.6)	13 (14.1)[a]
Anemia (hematocrit < 45%), *n* (%)	8 (8.9)[b,c]	1 (1.1)[b]	0 (0.0)[c]

[a] Clamping at 3 minutes versus early clamping: RR: 3.2 (95% CI: 1.1 to 9.0); $P = .039$.
[b] Clamping at 1 minute versus early clamping: RR: 0.3 (95% CI: 0.02 to 0.8); $P = .034$.
[c] Clamping at 3 minutes versus early clamping: RR: 0.06 (95% CI: 0.006 to 0.6); $P = .003$.

TABLE 4 **Neonatal Hematocrit at 24 to 48 Hours**

	Early Clamping ($n = 89$)	Clamping at 1 min ($n = 89$)	Clamping at 3 min ($n = 90$)
Neonatal hematocrit at 24–48 h, mean (SD), %	51.1 (6.9)	53.6 (5.5)	56.4 (7.4)
Polycythemia, *n* (%)	2 (2.3)	3 (3.4)	7 (7.8)
Anemia, *n* (%)	15 (16.9)[a,b]	2 (2.3)[a]	3 (3.3)[b]

[a] Clamping at 1 minute versus early clamping: RR: 0.13 (95% CI: 0.035 to 0.50); $P = .0014$.
[b] Clamping at 3 minutes versus early clamping: RR: 0.20 (95% CI: 0.06 to 0.61); $P = .0027$.

DISCUSSION

Although well-designed randomized, controlled trials have not shown any harmful effects related to delayed cord clamping, immediate clamping is still the common practice. However, its value is highly controversial, especially because the newborn is deprived from a large quantity of blood, iron, and other benefits. Iron stores at birth are variable and are correlated to each infant with stores at 6, 9, and 12 months of age.[8] Iron content in the diet is only one of the factors influencing the "iron status" during the first year of life.[32] These considerations have led to the question that, if an elevated iron deposit at birth is associated with an adequate iron status at 12 months of age, then why not attempt to increase iron content in the newborn?[4]

This prospective randomized, controlled study evaluated the potential placental transfusion effects on the newborn and the mother at 3 different cord-clamping time intervals. This study was designed to demonstrate that in late cord clamping (at 1 or 3 minutes after birth) there is an increase in venous hematocrit within physiologic ranges and without harmful effects in comparison to early cord clamping. We found that the mean venous hematocrit of the newborn at 6 hours of life, the primary outcome of this study, remained within physiologic ranges without significant differences among groups, thereby confirming our hypothesis and previous observations.[13,33] There is a correlation between cord-clamping time and the slight increase observed in the hematocrit value.

As described in other studies,[10,13,34] no polycythemia-related harmful effects were observed, and all polycythemic newborns were free of symptoms. Furthermore, we observed a remarkable increase of anemia in the group with early cord clamping, both at 6 and 24 to 48 hours of life. This finding, also reported by others, is significant, especially considering its likely impact on the prevalence of anemia in the first months of life.[34] In the other neonatal variables evaluated in our study, no differences were found among the 3 groups. Respiratory disorders were transient, and there was no need to supplement oxygen beyond 24 hours of life. Plasma bilirubin values as well as hyperbilirubinemia rates were similar in the 3 groups, which goes along with other authors' observations.[10,34,35]

Likewise, another benefit of delayed clamping would be the increase of hematopoietic stem cells transfused to the newborn, which might play a role on different blood disorders and immune conditions.[36]

With respect to maternal variables, no harmful effects were observed. Blood loss after delivery and hematocrit variations between delivery and at 24 hours after birth were similar among the 3 groups. These data are in agreement with what other authors have reported[35,37] and in disagreement with the belief that late clamping is associated with greater postpartum bleeding.[38]

CONCLUSIONS

In term newborn infants, cord clamping at 1 or 3 minutes after birth resulted in an increase of venous hematocrit levels measured at 6 hours, within physiologic ranges, and a decreased prevalence of neonatal anemia without any harmful effect in newborns or mothers. Thus, this intervention seems to be safe and effective and

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TABLE 5 **Neonatal Secondary Outcomes**

Outcome	Early Clamping[a]	Clamping at 1 min[a]	Clamping at 3 min[a]
Bilirubin levels, median (first quartile–third quartile), mg/dL	7.3 (5.6–9.0)	7.7 (6.1–9.0)	7.2 (5.0–9.0)
Bilirubin (≥16 mg/dL), *n/N* (%)	2/91 (2.2)	1/85 (1.2)	0/90 (0.0)
Respiratory status (tachypnea + distress + grunting), *n/N* (%)[b]	2/93 (2.2)	6/91 (6.6)	6/92 (6.5)
Infant feeding at 1 mo, *n/N* (%)			
Exclusive breastfeeding, *n/N* (%)	82/90 (91.1)	70/87 (80.5)	78/91 (85.7)
Partial breastfeeding, *n/N* (%)	6/90 (6.7)	16/87 (18.4)	13/91 (14.3)
Formula, *n/N* (%)	2/90 (2.2)	1/87 (1.2)	0/91 (0.0)
Abnormal neonatal outcome after discharge, *n/N* (%)[c]	4/90 (4.4)	2/89 (2.3)	2/91 (2.2)
NICU admission, *n/N* (%)	4/93 (4.3)	5/91 (5.5)	8/92 (8.7)
Length of hospital stay, median (first quartile–third quartile), d	5.5 (3.0–7.0)	7.0 (5.0–10.0)	2.5 (1.5–3.5)

[a] No statistically significant difference was observed among the 3 groups for any of the outcomes.
[b] Tachypnea (RR: >60/minute), transient respiratory distress, grunting.
[c] Protracted jaundice, urinary tract infection, respiratory tract infection, fever.

could be implemented easily. The advantages of umbilical cord clamping at least at 1 minute after birth could decrease the prevalence of iron-deficiency anemia in the first year of life, especially in populations with limited access to health care. This trial was focused mainly on cord-clamping timing and its effect on the newborn, particularly in the first hours and days of life. We have shown our hypothesis to be true and additionally proved the protective effect of late cord clamping on neonatal anemia at birth. However, bearing in mind the significance of the consequences of this intervention on iron stores during the first months of life, we followed up the infants until 6 months of age. Follow-up controlled studies should focus on the relationship between delayed cord clamping and the presence of anemia and iron status in infants.

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