OBSTETRICS

Delayed clamping vs milking of umbilical cord in preterm infants: a randomized controlled trial

Samantha K. Shirk, DO; Stephanie A. Manolis, DO, MBA; Donna S. Lambers, MD; Kathleen L. Smith, MD, PhD

BACKGROUND: It has been established that delayed umbilical cord clamping in preterm infants results in improvement in neonatal anemia, need for transfusion, incidence of necrotizing enterocolitis, and intraventricular hemorrhage by increasing neonatal circulating blood volume. However, the effects of umbilical cord milking as an alternative to delayed clamping in preterm infants are unclear.

OBJECTIVE: The primary objective of this study was to compare the effect of delayed clamping vs milking of the umbilical cord on the initial hematocrit concentration in preterm births (23–34 weeks gestation). In addition, we sought to compare the effects of delayed clamping vs milking on the incidences of intraventricular hemorrhage, necrotizing enterocolitis, and need for transfusion (secondary objectives).

STUDY DESIGN: The study was an unblinded randomized controlled trial of singleton preterm infants who were born 23 weeks 0 days to 34 weeks 6 days gestation and were assigned to 1 of 2 controlled study groups: delayed cord clamping for 60 seconds or milking of the cord towards the infant 4 times before clamping. Randomization occurred via block randomization with an allocation ratio of 1 to 1. The patients' third stage of delivery was standardized for route of delivery and randomization arm. All comparisons were preformed with an intent-to-treat analysis approach. The study was powered at 80% with a probability value of .05 for the primary outcome measure of a hematocrit difference of 3% between the 2 groups.

RESULTS: Of the 204 randomized patients, 104 were assigned to the delayed subgroup, and 100 were assigned to the milking subgroup. There were no significant differences in baseline maternal characteristics noted between groups. Though there was not any statistically significant difference in neonatal outcomes between the cord clamping and milking groups, the occurrences of transfusion (15.5% vs 9.1%; $P=.24$), necrotizing enterocolitis (5.8% vs 3.0%; $P=.49$), and intraventricular hemorrhage (15.5% vs 10.1%; $P=.35$) were all lower in the milking group. The milking group had higher initial hematocrit concentration compared with the delayed clamping group, although this was not significant (51.8 [6.2%] vs 49.9 [7.7%]; $P=.07$]. Peak bilirubin levels and need for phototherapy were similar between groups.

CONCLUSION: This study demonstrates that milking the umbilical cord may be an acceptable alternative to delayed cord clamping because there were similar effects on neonatal hematocrit concentrations and the need for neonatal transfusions and no increased risk for complications or neonatal morbidity. The present data support the concept that milking of the umbilical cord may offer an efficient and timely method of providing increased blood volume to the infant.

Key words: bilirubin, cord clamping, cord milking, hematocrit, hemoglobin, intraventricular hemorrhage, necrotizing enterocolitis, neonatal anemia, phototherapy, transfusion

In 2012, the American College of Obstetricians and Gynecologists recommended a delay of 30–60 seconds in umbilical cord clamping for all preterm deliveries.[1] The Royal College of Obstetricians and Gynaecologists also recommends deferring umbilical cord clamping for healthy term and preterm infants for 2–5 minutes after birth.[2] The World Health Organization recommends delayed cord clamping, defined as cessation of pulsations or 120–180 seconds, as the standard of care for infants who do not require resuscitation.[1] Systematic reviews completed by Rabe et al[3,4] and McDonald et Al,[5] who investigated the effects of delayed umbilical cord clamping, have shown that delayed clamping increases the transfer of blood to the infant from the placenta, thereby increasing newborn infant circulating blood volume, improving blood pressure, and reducing the incidences of blood transfusion, intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC). Other investigators have shown that delayed clamping has the ability to decrease the need for preterm neonatal transfusions for anemia, to increase iron stores, and to decrease the number of infants with IVH and NEC.[3,6,7–9] Fogarty et al[10] performed a metaanalysis of 18 randomized controlled trials that included 2834 preterm neonates <37 weeks gestation. In their systematic review, they found that delayed umbilical cord clamping reduced hospital deaths, reduced the incidence of IVH and NEC, and increased peak hematocrit concentration, when compared with early cord clamping.

An alternative to delayed clamping is to milk, or strip, the umbilical cord towards the newborn infant, thereby decreasing the time from birth to clamping of the cord. A randomized controlled trial by Upadhyay et al,[8] who investigated cord milking vs early cord clamping in neonates at >35 weeks gestation, concluded that umbilical cord milking improved hemoglobin concentration and iron status at 6 weeks of life, which suggests the safety profile of umbilical cord milking in neonates. Furthermore, a systematic review of 12 randomized controlled trials that involved 531 preterm infants, defined as <32 weeks gestation, concluded that enhanced placental transfusion through delayed clamping, cord milking, or a combination of both resulted in lower mortality rates and lower incidences of

Cite this article as: Shirk SK, Manolis SA, Lambers DS, et al. Delayed clamping vs milking of umbilical cord in preterm infants: a randomized controlled trial. Am J Obstet Gynecol 2019;220:482.e1-8.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2019.01.234

AJOG at a Glance

Why was this study conducted?

This study was conducted in an effort to further compare cord milking vs delayed clamping in preterm infants and to determine whether umbilical cord milking is an acceptable alternative to delayed cord clamping.

Key findings

The key findings of the study include no statistically significant differences in neonatal outcomes (hematocrit concentration, need for transfusions, intraventricular hemorrhage, and necrotizing enterocolitis) that were investigated between delayed clamping of 30–60 seconds and milking of umbilical cord 4 times.

What does this add to what is known?

This study further supports previously published data that umbilical cord milking may be equivalent to delayed clamping for increasing circulating neonatal blood volume, thereby preventing neonatal anemia and decreasing the need for transfusions.

NEC and infection than immediate clamping.[11] Katheria et al[12] compared umbilical cord milking and delayed cord clamping in preterm cesarean deliveries and found that milking improved circulating blood volume in this setting. A study by Kumar et al[7] investigated the hematologic effects of umbilical cord milking compared with early cord clamping in preterm neonates, defined as 32–36 weeks gestation. Results from this study noted a higher hemoglobin concentration but also saw increased rates of jaundice that required phototherapy. In another randomized controlled trial, Rabe et al[13] investigated the placentofetal blood transfusion in 58 preterm neonates, defined as gestational age <33 weeks, with delayed clamping of 30 seconds vs milking of umbilical cord 4 times. They concluded that milking the cord achieved a similar amount of placentofetal blood transfusion compared with delayed clamping by evaluating hemoglobin concentrations and the need for transfusions. These findings suggest that milking of cord may be equivalent to delayed clamping in the prevention of neonatal anemia and need for transfusions; however, the sample size of 58 neonates in the study is a limitation in its applicability.

Despite several studies that investigated umbilical cord milking or delayed clamping in preterm infants with strong evidence of lower incidences of NEC and enhanced neonatal outcomes, a study by Tarnow-Mordi et al[14] that investigated delayed clamping vs immediate clamping showed no statistically significant difference in primary outcomes of death or major morbidity. In fact, results of the study state that the preferred care of infants judged to need immediate resuscitation remains unknown and that more evidence for timing of cord clamping is needed. Furthermore, despite calls by Fogarty et al[10] for further research that specifically would compared delayed clamping to cord milking, there are limited studies. Further clinical trials are needed to investigate the potential benefits of delayed clamping vs milking in preterm infants.

The primary objective of this study was to compare the effect of delayed clamping vs milking of the umbilical cord on the hematocrit concentration in preterm births defined as 23–34 weeks gestation. Secondary objectives were to evaluate neonatal composite outcomes of IVH and NEC and the need for transfusion between the 2 groups and to determine whether umbilical cord milking is an acceptable alternative to delayed cord clamping.

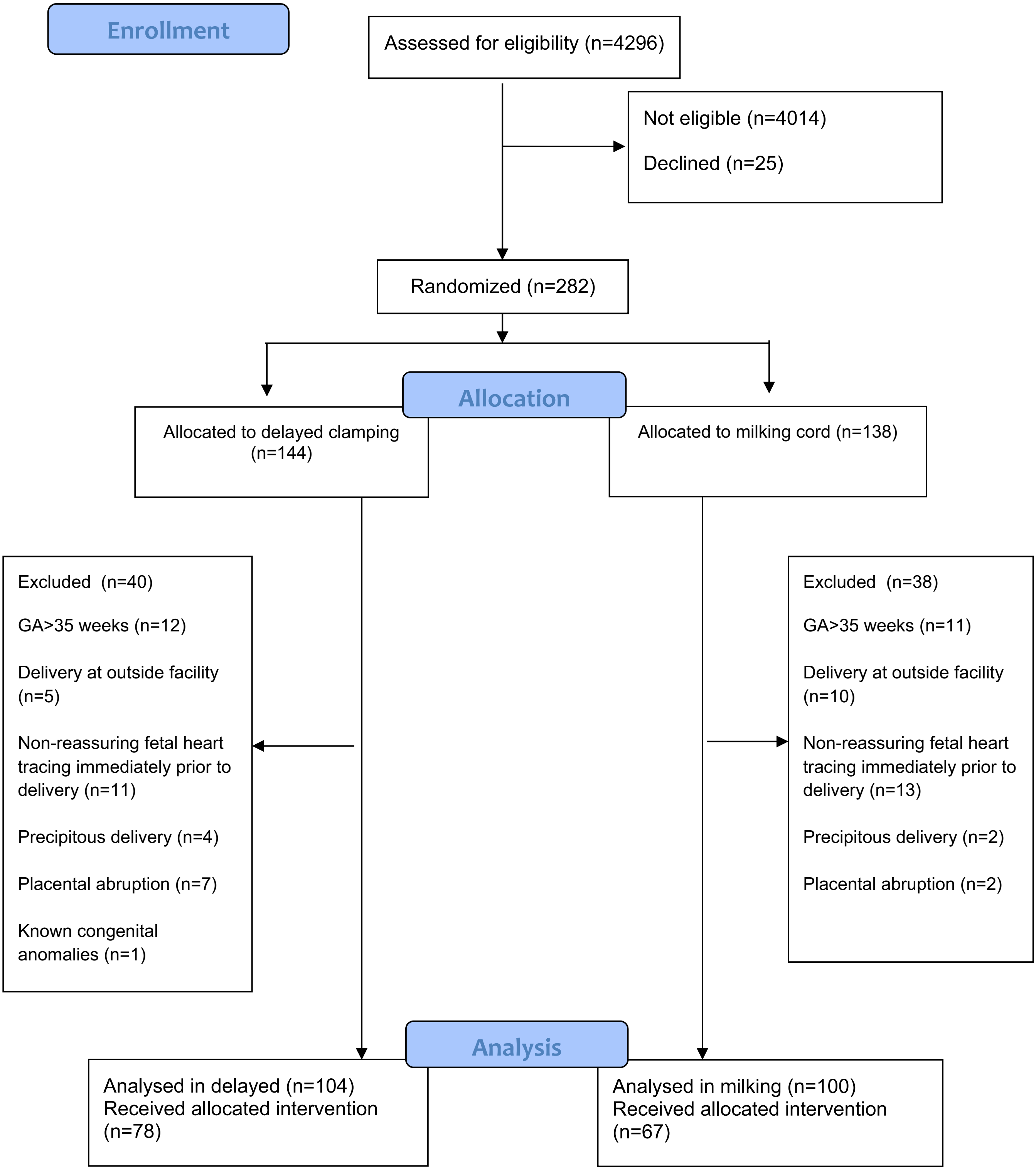
Materials and Methods

This study was an unblinded randomized controlled trial that compared neonatal composite outcomes between delayed cord clamping and milking of the cord in preterm infants born from 23 weeks 0 days gestation to 34 weeks 6 days gestation. Institutional Review Board approval was obtained from the Tri-Health Institutional Review Board. The study was registered at clinicaltrials.gov (NCI:NCT02092103), and the CONSORT guidelines were followed.[15] Informed consent was obtained from each patient who was enrolled.

Patient participation

The study setting was Good Samaritan Hospital in Cincinnati, OH; the patient population was selected from the resident obstetrics and maternal fetal medicine services from April 18, 2014, through June 5, 2018. Patients were recruited and consented by trained research nursing staff. Recruitment was ceased after completion of the full sample size. The inclusion criteria were patients with singleton pregnancies who had been admitted to the hospital with expected preterm delivery based on pregnancy or medical diagnoses between 23 weeks 0 days to 34 weeks 6 days gestation. Exclusion criteria were known major and minor congenital anomalies that had been identified on prenatal sonography (not including trisomy markers), those with precipitous delivery that prevented completion of the protocol, placental abruption at the time of/or as the indication for delivery, uterine rupture, infants known to be at risk of anemia (ie, Parvovirus B19 infection and allo/isoimmunization), or patient delivered at outside institution after random assignment. Once enrolled, if a patient had a category 3 fetal heart rate tracing or prolonged fetal bradycardia that led to emergent delivery, she was then excluded from the analysis because of anticipated difficulty with compliance to the protocol.[16] The patients were assigned randomly via block randomization with an allocation ratio of 1 to 1 to either delayed umbilical cord clamping for 60 seconds or milking of umbilical cord 4 times before clamping.[12,13] Allocation sequence was unknown until random assignment via sealed opaque envelopes. Electronic medical record documentation of study participation and group assignment was

FIGURE
CONSORT flow diagram



Flow of patients from assessment of eligibility through intervention and on to analysis.

GA, gestational age.

Shirk et al. RCT of delayed clamping vs milking of the umbilical cord. Am J Obstet Gynecol 2019.

TABLE 1
Maternal and obstetric factors

Demographic	Total (N=204)	Delayed (n=104)	Milking (n=100)	*P* value
Maternal age, y[a]	28 (23–32)	28 (22–32)	28 (23–33)	.335
Maternal race[b]				.353
Black	77 (37.7)	35 (33.6)	43 (43.0)	
Asian	1 (0.5)	1 (1.0)	0	
White	116 (56.9)	62 (59.6)	54 (46.6)	
Hispanic	3 (1.5)	2 (1.9)	1 (1.0)	
Other/unknown	6 (3.0)	4 (3.8)	2 (2.0)	
No or insufficient prenatal care[b]	6 (2.9)			
Advanced maternal age[b,c]	34 (16.7)	14 (13.6)	20 (20.0)	.301
Diabetes mellitus[b,c]	21 (10.4)	7 (6.8)	14 (14.1)	.139
Chronic hypertension[b,c]	27 (13.3)	10 (9.7)	17 (17.0)	.186
Preeclampsia[b,c]	66 (32.5)	29 (28.2)	37 (37.0)	.232
Fetal growth restriction[b,c]	30 (14.8)	12 (11.7)	18 (18.0)	.282
Preterm labor[b,c]	38 (18.7)	21 (20.4)	17 (17.0)	.661
Preterm premature rupture of membranes[b,c]	106 (52.2)	55 (53.4)	51 (51.0)	.840
Cerclage[b,c]	13 (6.4)	7 (6.8)	6 (6.0)	>.999
Preterm labor/preterm premature rupture of membranes[b,c]	122 (60.1)	63 (61.2)	59 (59.0)	.864
Placental abnormality[b,c]	5 (2.5)	3 (2.9)	2 (2.0)	>.999

[a] Data are given as median (interquartile range); [b] Data are given as n (%); [c] Missing data.

Shirk et al. RCT of delayed clamping vs milking of the umbilical cord. Am J Obstet Gynecol 2019.

used to promote compliance to the randomization arm of the study.

This study was controlled by standardization of the patients' third stage of delivery for route of delivery and for randomization arm. During a cesarean delivery, the infant was held at the level of the maternal abdomen; with a vaginal delivery, the infant was held at the level of the perineum. The delayed clamping protocol consisted of palpation of neonatal heart rate at umbilical cord insertion for 60 seconds, with timing determined by infant warmer that was initiated at delivery of infant. The milking protocol consisted of manual milking or stripping of approximately 20 cm of umbilical cord from the placental end to the infant's umbilicus 4 times, with time allowed for cord refill between each milking maneuver. The milking protocol was adapted from previous studies that investigated cord milking.[7,12,13]

Data were collected on both the mother and the infant; maternal and neonatal diagnoses were determined with standard definitions of the respective colleges. Data regarding cord care compliance with randomization and indication for noncompliance were collected where available. All data were collected with completion of a chart review by the principal investigator and entered into an electronic data base.

Sample size calculation

Sample size calculation was performed a priori and powered at 80% with an alpha level of .05 for the primary outcome measure of a hematocrit difference of 3% between the delayed clamping and milking groups with the use of a 2-tail analysis.[17] A 3% difference was selected with the anticipation that there would be a lower difference between milking and delayed clamping than the 7% hematocrit difference that has been seen between delayed and immediate clamping.[1] With these calculations, the sample size was determined to be 200. To account for an estimated 15% drop out, we projected enrolling 232 patients. A higher than anticipated number of patients were excluded after random assignment, and enrollment was continued to reach the appropriate sample size.

Statistical analysis

Continuous variables were examined with the use of histograms, normal Q-Q plots, and box plots. The Kolmogorov-Smirnov and Shapiro-Wilk tests of normality were applied to determine which variables were distributed normally. The Student *t* test was used to compare continuous variables that were distributed normally; the Mann Whitney *U* test was used to analyze those continuous variables not normally distributed. The chi-square test with continuity correction, or Fisher's exact test where appropriate, was used to compare frequencies of dichotomous variables between the groups. Prespecified subgroup analyses were performed for infants at <28 weeks gestation and only for infants who survived to discharge. To account for possible confounding effects, prespecified logistic regression analyses were performed to determine the adjusted effects of delayed cord clamping vs milking on transfusion risk, NEC, IVH, survival, and composite morbidity variables (NEC, IVH, death, and the need for transfusion). A prespecified intent-to-treat analysis strategy was used. After the assessment of compliance with assigned protocols, a post-hoc analysis that separated subjects by actual intervention received was also performed. Statistical analyses were performed using the IBM SPSS statistical software package (version 22.0; IBM, Armonk, NY).

Results

A total of 282 patients were consented and assigned randomly, with a total of 204 women who completed the protocol and whose data were analyzed. The Figure illustrates the patient flowsheet

TABLE 2
Obstetric outcomes

Demographic	Total (N=204)	Delayed (n=104)	Milking (n=100)	*P* value
Gestational age, wk[a]	32.0 (29.3—34.0)	32.0 (29.2—34.0)	32.1 (29.5—34.0)	.462
28.0-34.9[b]	175 (85.8)	87 (83.7)	88 (88.0)	.491
23.0-27.9[b]	29 (14.2)	17 (16.3)	12 (12.0)	
Birthweight, g[c]	1599±581	1579±576	1620±587	.617
Blood gas pH[b,d]				
Arterial pH <7.1	11 (6.5)	5 (6.2)	6 (6.7)	>.999
Arterial pH	7.19 (0.56)	7.23 (0.09)	7.14 (0.77)	.327
Venous pH <7.1	5 (2.7)	4 (4.4)	1 (1.1)	.206
Venous pH	7.26 (0.54)	7.31 (0.09)	7.21 (0.76)	.238
Apgar score[a]				
At 1 min	6 (5—8)	7 (5—8)	7 (5—8)	.829
At 5 min	8 (7—9)	9 (7—9)	8 (7—9)	.278
Apgar score <7[b,d]				
At 1 min	89 (44.1)	44 (42.7)	45 (45.5)	.803
At 5 min	33 (16.3)	15 (14.6)	18 (18.0)	.636
Mode of delivery[b,d]				
Spontaneous vaginal	96 (47.1)	53 (26.0)	43 (21.1)	.1
Operative vaginal	3 (1.5)	0 (0)	3 (1.5)	.09
Cesarean	105 (51.5)	51 (49.0)	54 (54.0)	.49
Indication for delivery[b,d]				
Spontaneous	130 (64.7)	70 (68.6)	60 (60.6)	
Iatrogenic	71 (35.3)	32 (31.4)	39 (39.4)	.297

[a] Data are given as median (interquartile range); [b] Data are given as n (%); [c] Data are given as mean (standard deviation); [d] Missing data.

Shirk et al. RCT of delayed clamping vs milking of the umbilical cord. Am J Obstet Gynecol 2019.

from screening to delivery. Seventy-eight women were excluded because of previously the described exclusion criteria. Each milking maneuver took 1—2 seconds, for a total of 6 seconds on average; the average time for delayed clamping was 30—60 seconds, as documented in the electronic medical record.

Data for maternal demographics and complications are given in Table 1. The maternal age ranged from 16—47 years, with the median being 28 years old. There were no differences in maternal baseline characteristics between groups.

Obstetric outcomes were then analyzed for each study group as shown in Table 2. The median gestational age for delivery was 32 weeks. A total of 85.8% of patients (175/204) were in the 28—34 week subgroup, and 14.2% of patients (29/204) were in the 23—27 week subgroup. Of the extremely preterm subgroup, 58.6% of patients (17/29) were assigned randomly to the delayed subgroup, and 41.4% of patients (12/29) were assigned randomly to the milking subgroup. There were no significant differences between the delayed clamping and milking groups with respect to the mode of delivery, birthweight, cord blood arterial and venous pH, Apgar scores, and the number of infants with arterial or venous pH <7.1.

Our primary objectives of comparison of neonatal outcomes are shown in Table 3. No statistical differences between the 2 groups were noted. However, there was a trend toward higher hemoglobin concentration, fewer neonates with low hemoglobin concentration <15g/dL, and fewer transfusions in the milking group, although no variable reached statistical significance. There were also no statistical differences between peak bilirubin concentration, need for phototherapy, or temperature on admission to the neonatal intensive care unit.

Compliance to the assigned protocol was assessed; 25% of the delayed group (26/104) and 33% of the milking group (33/100) did not receive the intervention to which they were assigned randomly. Some of the explanations that wee documented and collected from chart review include practitioner discomfort with clinical situation because of poor neonatal effort or tone, practitioner unaware of the assigned protocol, or the

TABLE 3
Neonatal outcomes in delayed clamping and milking groups

Demographic	Delayed (n=104)	Milking (n=100)	*P* value
Hemoglobin concentration (first draw), g/dL[a]	16.8±2.5	17.2±2.1	.20
Hematocrit concentration (first draw), %[a]	49.9±7.7	51.8±6.2	.07
Low hemoglobin concentration, <15.6 g/dL[b]	29 (29.6)	18 (19.6)	.15
High hemoglobin concentration, >18.6 g/dL[b]	20 (20.4)	24 (26.1)	.45
Time of hemoglobin/hematocrit, min[c]	77 (50–127)	70 (47–134)	.40
Peak bilirubin concentration, mg/dL[a]	8.8±2.5	8.8±2.2	.93
Received phototherapy[b]	88 (88)	85 (85.9)	.65
Temperature[b]			
>37.5°C	12 (11.7)	10 (10.1)	.89
<36.5°C	13 (12.6)	11 (11.1)	.91
Transfusion[b]	16 (15.5)	9 (9.1)	.24
Necrotizing enterocolitis[b]	6 (5.8)	3 (3.0)	.49
Intraventricular hemorrhage[b]	16 (15.5)	10 (10.1)	.35
Neonatal intensive care unit length of stay, d[c]	25 (16–43)	24.5 (14–44)	.79
Death before discharge[b]	4 (3.8)	5 (5.0)	.74
Composite morbidity[b]	28 (26.9)	23 (23.0)	.63

[a] Data are given as mean±standard deviation; [b] Data are given as n (%); [c] Data are given as median (interquartile range).

Shirk et al. RCT of delayed clamping vs milking of the umbilical cord. Am J Obstet Gynecol 2019.

cord was clamped and cut without delay or milking. Additional analyses were performed post hoc on the actual intervention that the pregnancy received. As shown in Table 4, there were still no statistically significant differences in neonatal outcomes between the 2 groups when the actual intervention that was received was evaluated (data regarding those who received immediate clamping not shown; n=19).

Neonatal mortality rate between the milking and delayed groups was not statistically significant, with a probability value of .74. Neonatal variables were combined for a composite of morbidity and mortality rate calculations. Composite morbidity occurred in 23.0% of the milking group (23/100) and in 26.9% of the delayed clamping group (28/104), again with a nonsignificant probability value of .63. Multivariate logistic regression analysis that accounted for possible confounding by maternal comorbidities or obstetric complications did not demonstrate a significant association between delayed clamping vs milking groups and transfusion rate, NEC, IVH, survival, or composite morbidity variables (data not shown).

Multiple a priori analyses of subgroups were completed (data not displayed within tables). Analyses that were performed for the subgroups of only survivors, only infants delivered from 23 weeks 0 day to 27 weeks 6 days gestation, and only survivors born at 23 weeks 0 days to 27 weeks 6 days gestation revealed results similar to analyses of the whole study group. In addition, multivariate logistic regression analyses failed to demonstrate statistically significant differences in transfusion rates, NEC, IVH, or composite morbidity variables when we accounted for maternal age, gestational age, maternal comorbidities, and indication for or mode of delivery.

Comment

Principal findings

The current standard of care for delivery of preterm infants is to delay clamping for 30–60 seconds after delivery.[1] Unfortunately, in specific cases, these 30–60 seconds may delay necessary resuscitation by the neonatal teams. In this randomized controlled trial, it is demonstrated that milking the umbilical cord may be an acceptable alternative to delayed cord clamping because there were similar effects on newborn infant hematocrit concentrations, rates of NEC and IVH, need for neonatal transfusions, and no increased risk for complications.

Results in context

When the major outcomes that are outlined in Table 3 were evaluated, similar outcomes were achieved with milking as compared with delayed umbilical cord clamping. Even though the data are not considered significant, fewer transfusions were required in the milking group compared with the delayed clamping group. This finding may be significant in delivery situations that require efficient and immediate neonatal resuscitation. With our study protocol, cord milking 4 times took approximately 6 seconds, allowing timely and efficient resuscitation of the infant by the neonatal intensive care unit staff. Studies have shown that low birthweight infants who undergo delayed cord clamping are warmer that those who undergo immediate cord clamping, possibly because of the warm placental blood transfusion to the newborn infant.[18] Umbilical cord milking allows rapid placement of the newborn infant under the radiant warmer in addition to rapid transfer of warm placental blood.

Despite concerns that cord milking may provide a rapid bolus of blood that results in increased systolic blood pressures and hyperbilirubinemia, our data are consistent with other studies that found that cord milking does not result in higher bilirubin levels nor increased need for phototherapy.[3,9,12] Concerns about rapid changes in venous pressure during cord milking were addressed in a trial that demonstrated no greater increase in venous pressures with cord milking compared with uterine contractions or a newborn infant cry during intact placental circulation.[19] Placental blood during cord milking is directed towards

TABLE 4
Neonatal outcomes between delayed and milking groups with actual intervention received

Demographic	Delayed (n=112)	Milking (n=73)	*P* value
Hemoglobin concentration (first draw), g/dL[a]	17.1±2.5	17.1±2.3	.98
Hematocrit concentration (first draw), %[a]	50.7±7.4	51.6±6.8	.44
Low hemoglobin concentration, <15.6 g/dL[b]	29 (29.6)	13 (19.7)	.36
High hemoglobin concentration, >18.6 g/dL[b]	25 (22.9)	16 (24.2)	.86
Time of hemoglobin/hematocrit, min[c]	77 (50–120)	69 (49–152)	.98
Peak bilirubin concentration, mg/dL[a]	9.1±2.5	8.5±2.3	.09
Received phototherapy[b]	96 (88.1)	61 (84.7)	.51
Temperature[b]			
>37.5°C	14 (12.6)	8 (11.3)	>.99
<36.5°C	10 (9.0)	11 (15.5)	.24
Transfusion[b]	12 (10.8)	10 (14.1)	.64
Necrotizing enterocolitis[b]	4 (3.6)	4 (5.6)	.71
Intraventricular hemorrhage[b]	16 (14.4)	8 (11.3)	.66
Neonatal intensive care unit length of stay, d[c]	23 (14–38)	27 (16–50)	.79
Death before discharge[b]	5 (4.5)	3 (4.2)	>.99
Composite morbidity[b]	26 (23.2)	19 (26.4)	.73

[a] Data are given as mean±standard deviation; [b] Data are given as n (%); [c] Data are given as median (interquartile range).
Shirk et al. RCT of delayed clamping vs milking of the umbilical cord. Am J Obstet Gynecol 2019.

the lungs during a time when there is a rapid fall in pulmonary resistance, unlike any other time when increased blood volume is provided to the infant.[12]

In regards to concerns about group compliance, similar outcomes were noted when data were evaluated by actual intervention received rather than by intent to treat. There were again no statistical differences between variables that were studied when we evaluated those actually received milking of umbilical cord vs delayed clamping.

Research implications

Because this was a negative study that compared milking vs delayed clamping, future research studies should be considered with a noninferiority design. In addition, our study was powered adequately to evaluate a difference in hematocrit concentration, a surrogate measure for need for transfusion for the whole study population. However, further studies that will evaluate effects in extremely preterm infants who are born at <28 weeks gestation are needed, because these infants are at highest risk for NEC, IVH, and other adverse neonatal outcomes.

Strengths and limitations

The main strength of our study is its design as a randomized controlled trial with completed sample size across all modes of delivery. In addition, the study included only preterm infants, which is a subgroup of patients who have not been included in large numbers in past studies that have evaluated the effects of cord milking vs delayed clamping. Finally, the study was designed with standardized delivery protocols for both arms and routes of delivery. The main limitation of the study was the low number of participants in the extremely preterm group, which is defined as <28 weeks gestation. Only 14.2% of participants were within this group. However, it can be postulated that similar effects would be noted in this subpopulation based on previously published literature. March et al[20] demonstrated a 50% reduction in total IVH in the milking group in a randomized controlled trial of 75 extremely premature neonates, born <29 weeks gestation. In addition, in a retrospective study of umbilical cord milking in 318 infants born at <30 weeks gestation that was performed by Patel et al,[21] cord milking was associated with reductions in IVH, NEC, and death before hospital discharge. As suggested by these authors, it is possible that cord milking may have greater benefits in smaller, more immature neonates. Another limitation of the study may be that the sample size calculation was powered for the primary outcome of hematocrit difference of 3% between the delayed clamping and milking groups. Although this outcome serves as a surrogate for the risk of transfusion and other neonatal complications, the study was underpowered for the more rare secondary outcomes such as NEC, IVH, and neonatal death. The possibility of a type 2 error with respect to these secondary outcomes cannot be eliminated.

Conclusion

There is a considerable body of evidence to support the practice of providing additional blood volume to term and preterm neonates. Given the findings of this study, we propose that milking of the umbilical cord before clamping is an acceptable alternative to delayed clamping of the umbilical cord, especially in those situations where delayed clamping may delay necessary resuscitation by the neonatal teams or be contraindicated for obstetric indications. ■

Acknowledgment

Special thanks to Peggy Walsh, RN, and Rita Doerger, RN, for patient recruitment, TriHealth, Cincinnati, OH.

References

1. Committee on Obstetric Practice ACoO, Gynecologists. Committee Opinion No. 543: timing of umbilical cord clamping after birth. Obstet Gynecol 2012;120:1522–6.
2. American College of Nurse Midwives. Delayed Umbilical Cord Clamping: Position Statement. Available at: http://www.midwife.org/ACNM/files/ACNMLibraryData/UPLOADFILENAME/000000000290/Delayed-Umbilical-Cord-Clamping-May-2014.pdf. Published May 2014. Approved May 2014. Accessed August 1, 2018.

3. Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database Syst Rev 2012;8:CD003248.

4. Rabe H, Reynolds G, Diaz-Rossello J. A systematic review and meta-analysis of a brief delay in clamping the umbilical cord of preterm infants. Neonatology 2008;93:138–44.

5. McDonald SJ, Middleton P, Dowswell T, Morris PS. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane Database Syst Rev 2013;7:CD004074.

6. Pisacane A. Neonatal prevention of iron deficiency. BMJ 1996;312:136–7.

7. Kumar B, Upadhyay A, Gothwal S, Jaiswal V, Joshi P, Dubey K. Umbilical cord milking and hematological parameters in moderate to late preterm neonates: a randomized controlled trial. Indian Pediatr 2015;52:753–7.

8. Upadhyay A, Gothwal S, Parihar R, et al. Effect of umbilical cord milking in term and near term infants: randomized control trial. Am J Obstet Gynecol 2013;208:120.e1–6.

9. Al-Wassia H, Shah PS. Efficacy and safety of umbilical cord milking at birth: a systematic review and meta-analysis. JAMA Pediatr 2015;169:18–25.

10. Fogarty M, Osborn DA, Askie L, et al. Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. Am J Obstet Gynecol 2018;218:1–18.

11. Backes CH, Rivera BK, Haque U, et al. Placental transfusion strategies in very preterm neonates: a systematic review and meta-analysis. Obstet Gynecol 2014;124:47–56.

12. Katheria AC, Truong G, Cousins L, Oshiro B, Finer NN. Umbilical cord milking versus delayed cord clamping in preterm infants. Pediatrics 2015;136:61–9.

13. Rabe H, Jewison A, Alvarez RF, et al. Milking compared with delayed cord clamping to increase placental transfusion in preterm neonates: a randomized controlled trial. Obstet Gynecol 2011;117:205–11.

14. Tarnow-Mordi W, Morris J, Kirby A, et al. Delayed versus immediate cord clamping in preterm infants. N Engl J Med 2017;377:2445–55.

15. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.

16. Macones GA, Hankins GD, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines. Obstet Gynecol 2008;112:661–6.

17. Hosono S, Mugishima H, Fujita H, et al. Umbilical cord milking reduces the need for red cell transfusions and improves neonatal adaptation in infants born at less than 29 weeks' gestation: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2008;93:F14–9.

18. Kaempf JW, Tomlinson MW, Kaempf AJ, et al. Delayed umbilical cord clamping in premature neonates. Obstet Gynecol 2012;120: 325–30.

19. McCausland AM, Holmes F, Schumann WR. Management of cord and placental blood and its effect upon the newborn. Calif Med 1949;71: 190-19.

20. March MI, Hacker MR, Parson AW, Modest AM, de Veciana M. The effects of umbilical cord milking in extremely preterm infants: a randomized controlled trial. J Perinatol 2013;33: 763–7.

21. Patel S, Clark EA, Rodriguez CE, Metz TD, Abbaszadeh M, Yoder BA. Effect of umbilical cord milking on morbidity and survival in extremely low gestational age neonates. Am J Obstet Gynecol 2014;211:519. e1–7.

Author and article information

From the Department of Obstetrics and Gynecology, TriHealth, Cincinnati, OH.

Received Nov. 9, 2018; revised Jan. 26, 2019; accepted Jan. 28, 2019.

The authors report no conflict of interest.

Presented at the 39th SMFM Annual Conference in Oral Concurrent Session 8, Las Vegas, NV, February 16, 2019.

Corresponding author: Samantha Shirk, DO. skshirk24@gmail.com