Efficacy and Safety of Umbilical Cord Milking at Birth
A Systematic Review and Meta-analysis

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**IMPORTANCE** Umbilical cord milking (UCM) is suggested to improve neonatal outcomes.

**OBJECTIVES** To perform a systematic review and meta-analysis of the efficacy and safety of UCM in full-term and preterm neonates.

**DATA SOURCES** A systematic search of MEDLINE, EMBASE, CINAHL, the Cochrane Database of Clinical Trials, the clinicaltrials.gov database, and the reference list of retrieved articles from 1940 to 2014.

**STUDY SELECTION** Randomized clinical trials comparing UCM with other strategies of handling the umbilical cord at birth in full-term and preterm infants. Seven of the 18 initially identified studies were selected.

**DATA EXTRACTION AND SYNTHESIS** Two reviewers independently extracted data and assessed the risk for bias in included trials using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

**MAIN OUTCOMES AND MEASURES** Neonatal mortality before discharge from the hospital.

**RESULTS** We included 7 randomized clinical trials involving 501 infants. Infants with a gestational age of less than 33 weeks allocated to UCM compared with control conditions showed no difference in the risk for mortality (risk ratio [RR], 0.75 [95% CI, 0.35 to 1.64]; risk difference [RD], −0.02 [95% CI, −0.09 to 0.04]), hypotension requiring volume expanders (RR, 0.71 [95% CI, 0.41 to 1.25]; RD, −0.09 [95% CI, −0.22 to 0.05]), or inotrope support (RR, 0.77 [95% CI, 0.51 to 1.17]; RD, −0.10 [95% CI, −0.25 to 0.05]). Higher initial levels of hemoglobin (mean difference, 2.0 [95% CI, 1.3-2.7] g/dL) and hematocrit (mean difference, 4.5% [95% CI, 1.5%-7.4%]) were identified in the UCM groups. We found a reduced risk for oxygen requirement at 36 weeks (RR, 0.42 [95% CI, 0.21 to 0.83]; RD, −0.14 [95% CI, −0.25 to −0.04]) and for intraventricular hemorrhage of all grades (RR, 0.62 [95% CI, 0.41 to 0.93]; RD, −0.12 [95% CI, −0.22 to −0.02]) in infants assigned to UCM. Among infants with a gestational age of at least 33 weeks, UCM was associated with higher hemoglobin levels in the first 48 hours in 224 infants (mean difference, 1.2 [95% CI, 0.8-1.5] g/dL) and at 6 weeks of life in 170 infants (mean difference, 1.1 [95% CI, 0.7-1.5] g/dL).

**CONCLUSIONS AND RELEVANCE** Umbilical cord milking was associated with some benefits and no adverse effects in the immediate postnatal period in preterm infants (gestational age, <33 weeks), however, further studies are warranted to assess the effect of UCM on neonatal and long-term outcomes.
n 1949, McCausland et al1 surveyed members of the American Board of Obstetrics and Gynecology and reported no uniformity of practice in their management of umbilical cord and placental blood. The benefits of delayed cord clamping (DCC) and other strategies to influence placental transfusion at birth have been under investigation for decades.2,3 Recently, interest in the evidently old procedure of transferring residual blood from the placenta to the infant by means of DCC or umbilical cord milking (UCM) has shown a resurgence. However, practice among obstetricians varies 7 decades later.

A recent Cochrane review reported that DCC in preterm infants was associated with fewer transfusions of packed red blood cells and a lower risk for intraventricular hemorrhage (IVH) and necrotizing enterocolitis compared with immediate cord clamping (ICC).4 Concerns about polycythemia, hyperbilirubinemia, and delay in transition were not sustained in the review. Because of the level of heterogeneity between trials included in that review, no clear effect on other outcomes could be concluded. For full-term infants, DCC is suggested; however, to our knowledge, long-term outcomes of DCC have not been investigated in detail.5 Furthermore, the optimal timing for DCC has yet to be determined because studies varied in the duration, from less than 30 seconds to 180 seconds in preterm infants6 and as long as 300 seconds in full-term infants.5

The stripping of blood from the umbilical cord, or UCM, was pondered for years and suspected to be beneficial,1,6-10 Nevertheless, methodologic limitations of older studies hindered the adoption of UCM as a standard of care. A more recent series of studies assessed the safety and efficacy of UCM.11-17 The key difference between DCC and UCM is the mechanism of cord blood transfer to the infant. In DCC, a passive transfer of additional blood volume occurs at a slow rate, mostly by uterine contractions, whereas in UCM an active transfer of additional blood volume occurs at a rapid rate and within a short time, which may or may not be beneficial to neonates, especially preterm neonates. Our objective was to perform a systematic review and meta-analysis of the efficacy and safety of UCM in full-term and preterm infants.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines18 for the conduct and reporting of this review. Both of us independently assessed and identified articles for eligibility and collected data for this study. All discrepancies encountered in the review process were resolved by consensus.

Criteria for Considering Studies for Review

Study Population

We included studies of full-term and preterm infants. We made an a priori decision to compare the 2 populations (gestational age [GA], <33 and ≥33 weeks) separately because effects and outcomes of interest would be distinct for these two groups.

Type of Studies

We included randomized clinical trials (RCTs) published in the form of original research articles in peer-reviewed journals. Quasi-RCTs, observational studies, narrative reviews, letters, editorials, abstracts, and commentaries were excluded, as were duplicate reports that lacked additional information. Case reports and series, qualitative studies, review articles, and studies that did not report UCM methods were read to identify other potential studies but excluded from the meta-analysis.

Type of Intervention

We included studies that investigated UCM vs a control intervention (other strategies of handling the umbilical cord at birth, including ICC, DCC, or no intervention) and reported any outcomes of interest. The investigators must have reported the UCM procedure in detail so that it is replicable.

Outcomes

Studies were included if they reported a primary outcome of neonatal mortality before discharge from the hospital or any 1 of the following secondary outcomes:

1. Condition at birth (ie, cord arterial pH, Apgar scores at 1 and 5 minutes);
2. Hematological variables, including the first hematocrit and hemoglobin levels measured within 48 hours of birth, the need for transfusion of packed red blood cells before discharge, peak serum bilirubin level before discharge, hyperbilirubinemia requiring phototherapy, polycythemia (venous hematocrit level, >65% [to convert to a proportion of 1.0, multiply by 0.01]) at any time during admission, and levels of hemoglobin and ferritin at 3 to 6 months of age;
3. Short-term morbidities, including respiratory distress syndrome, hypotension in the first 24 hours of birth requiring volume or inotrope support, IVH of all grades,19 severe IVH (grade III or IV), oxygen dependency at 28 days and 36 weeks of corrected GA,20 stage II or III necrotizing enterocolitis,21 late-onset sepsis, retinopathy of prematurity, patent ductus arteriosus, and duration of hospital stay; and
4. Neurodevelopmental outcomes at 18 and 24 months.

Review Methods

Search Strategy

Published RCTs were identified using manual and electronic search strategies. This search was applied to MEDLINE (1946 to April 2014), EMBASE (1980 to April 2017), CINAHL (1982 to April 2014), and the Cochrane Central Register of Controlled Trials (April 2014) (eMethods in the Supplement). We also searched the online meta-register of Current Controlled Trials for relevant ongoing clinical trials (April 2014). Additional citations were sought by hand searching the reference list of the retrieved articles.

Data Extraction

Data extraction was performed using a standardized data collection form. Any discrepancies in extracted data were resolved by consensus. We contacted authors to obtain additional or missing data.
Table 1. Characteristics of the Included Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Population</th>
<th>UCM Characteristic</th>
<th>Control Condition</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alan et al,16 2014</td>
<td>44 Preterm infants (GA, ≥32 wk) with birth weight ≥1500 g</td>
<td>3</td>
<td>5 cm/s</td>
<td>ICC</td>
</tr>
<tr>
<td>Erickson-Owens et al,17 2012</td>
<td>24 Full-term infants delivered by elective CD</td>
<td>5</td>
<td>Not reported</td>
<td>ICC</td>
</tr>
<tr>
<td>Hosono et al,11 2008</td>
<td>40 Preterm infants (GA, 24-28 wk)</td>
<td>2-3</td>
<td>20 cm within 2 s</td>
<td>ICC</td>
</tr>
<tr>
<td>Katheria et al,15 2014</td>
<td>60 Preterm infants (GA, 23 wk to 31 wk 6 d)</td>
<td>3</td>
<td>20 cm in 2 s</td>
<td>ICC</td>
</tr>
<tr>
<td>March et al,12 2013</td>
<td>75 Preterm infants (GA, 24-28 wk)</td>
<td>3</td>
<td>Not reported</td>
<td>ICC</td>
</tr>
<tr>
<td>Rabe et al,14 2011</td>
<td>58 Preterm infants (GA, 24 wk to 32 wk 6 d)</td>
<td>4</td>
<td>20 cm in 2 s</td>
<td>DCC at 30 s</td>
</tr>
<tr>
<td>Upadhyay et al,13 2013</td>
<td>200 Infants (GA, &gt;34 wk 6 d)</td>
<td>3</td>
<td>10 cm/s</td>
<td>DCC within 30 s</td>
</tr>
</tbody>
</table>

Abbreviations: CD, cesarean delivery; DCC, delayed cord clamping; DM, diabetes mellitus; GA, gestational age; HDNB, hemolytic disease of newborn; ICC, immediate cord clamping; IUGR, intrauterine growth restriction; TTTS, twin-to-twin transfusion syndrome; UCM, umbilical cord milking.

Assessment of Risk for Bias

Both reviewers independently assessed the risk for bias in each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.22 Any disagreements were resolved by discussion and consensus. The risk for bias was assessed using the following key criteria: sequence generation, allocation concealment, blinding of assessors, and attrition bias. We assessed each criterion as having a low, high, or unclear risk for bias. An overall risk for bias was determined for each study according to the criteria suggested by Higgins and Green.22

Data Synthesis and Statistical Analysis

Similar to other meta-analyses, we made no adjustment for multiple analyses. For categorical outcomes, we calculated the pooled risk ratio (RR) and the related 95% CI. For continuous outcomes, we calculated the pooled mean difference (MD) and the corresponding 95% CI. When heterogeneity was not observed, the fixed-effect modeling approach was applied using the Mantel-Haenszel method23 for categorical variables and the inverse variance method for continuous variables. When heterogeneity was detected, a random-effects model was applied using the DerSimonian and Laird method.23 Heterogeneity across studies was assessed by calculating the I² values and Q statistics.24 P < .10 was defined to note statistical significance in the analysis of heterogeneity.

When results in studies were presented in different forms, we attempted to contact authors to obtain original data so that means and SDs could be computed. When that attempt was unsuccessful, we assumed normal distribution of the data, substituted the median for the mean, and calculated the SD from the upper and lower interquartile range (IQR) using the following formula: 75th percentile − 25th percentile = 1.35 SD. When ranges were given, we used the formula suggested by Hozo et al.25

Subgroup Analyses

We planned to perform a subgroup analysis by control intervention (none or ICC and DCC); however, the limited number of studies precluded such subgroup analyses. We assessed whether the control intervention explained some of the heterogeneous results. Clinical heterogeneity in the included studies was assessed and is reported in Table 1 by describing the populations included, treatment groups compared, and variations in procedures of UCM. We planned to assess publication bias using a funnel plot if 10 studies were included in a meta-analysis.

Results

Study Identification

The first screen of titles and abstracts identified 18 potential citations for secondary review. A detailed evaluation of the retrieved citations identified 7 studies11-17 for inclusion in this review (Figure 1). In addition, we found 3 ongoing studies in the Current Controlled Trials meta-register.26-28

Description of Studies

The number of infants in each study, description of the UCM method, how the cord was handled in the control group, and inclusion and exclusion criteria are depicted in Table 1. The de-
cription of the UCM technique varied among studies, including the number of times the cord was stripped toward the infant, the milking speed, and whether the cord was cut before or after milking. Upadhyay et al\textsuperscript{13} cut the cord at 25 cm of length from the umbilical stump and then milked the cord. None of the other included trials milked the cord this way, which might have affected the volume of blood transfused. Milking of the umbilical cord was compared with ICC in 5 trials\textsuperscript{11,12,14-17} and with DCC in 2 trials.\textsuperscript{13,14} Delayed cord clamping in the control group was defined as DCC at 30 seconds\textsuperscript{14} or within 30 seconds.\textsuperscript{13} The GA groups of the samples were heterogeneous across trials. Erickson-Owens et al\textsuperscript{17} included infants delivered by cesarean delivery only. All trials but Katheria et al\textsuperscript{15} excluded infants with major congenital anomalies, and all but Katheria et al\textsuperscript{14} and Erickson-Owens et al\textsuperscript{17} noted the exclusion of infants with hydrops fetalis. Multiple pregnancies were excluded by Hosono et al,\textsuperscript{11} Upadhyay et al,\textsuperscript{13} and Rabe et al,\textsuperscript{14} and Alan et al\textsuperscript{16} and Erickson-Owens et al\textsuperscript{17} excluded fetuses with suspected intrauterine growth restriction. Reporting of outcomes varied across studies. Only Upadhyay et al\textsuperscript{13} collected and reported data on maternal hemoglobin levels and antenatal iron supplementation. Hosono et al,\textsuperscript{11} Rabe et al,\textsuperscript{14} and Alan et al\textsuperscript{16} reported no significant difference in intra- genic blood loss between the 2 groups, and only Alan et al\textsuperscript{16} presented the guideline they followed for transfusion of packed red blood cells in preterm infants.

**Risk for Bias Among Included Studies**
Most studies had a low risk for bias. All studies reported that blinding of the clinicians involved was not possible because of the nature of the intervention (eTable in the Supplement).

**Comparison of Preterm Infants**

**Primary Outcome**
Five studies\textsuperscript{11,12,14-16} of 277 infants reported outcomes of UCM vs a control condition in preterm infants (GA, <33 weeks). We found no statistically significant difference in the risk for death between infants assigned to UCM and the control group (RR, 0.75 [95% CI, 0.35-1.64]; \(P = .48\)) (Figure 2A).

**Secondary Outcomes**
The results of reported secondary outcomes in the trials are detailed in Table 2. We found a reduced risk for oxygen requirement at 36 weeks (RR, 0.42 [95% CI, 0.21-0.83]) (Figure 2B) and IVH of all grades (RR, 0.62 [95% CI, 0.41-0.93]) (Figure 2C) in infants assigned to UCM. Hemoglobin and ferritin levels at 3 to 6 months of age and neurodevelopmental outcomes were not reported in any of the included studies. Some of the outcomes, which were reported in nonparametric measures, are described below.

**Cord Arterial pH**
Rabe et al\textsuperscript{14} reported no difference in cord arterial pH between groups (UCM group median, 7.3 [range, 6.8-7.4]; control group median, 7.3 [range, 6.9-7.3]; \(P = .31\)). March et al\textsuperscript{16} reported no difference in cord pH but did not specify whether the blood was venous or arterial (UCM group median, 7.3 [IQR, 7.3-7.3]; control group median, 7.3 [IQR, 7.3-7.4]; \(P = .44\)).

DCC indicates delayed cord clamping; UCM, umbilical cord milking.

**Appgar Scores**
Hosono et al\textsuperscript{11} reported higher 1-minute Apgar scores in infants who underwent UCM (MD, 1.2 [95% CI, 0.02-2.4]), whereas no difference in Apgar scores at 1 minute was reported by March et al\textsuperscript{16} (UCM group median, 4 [IQR, 1-5.5]; control group median, 4 [IQR, 2-5]; \(P = .75\)). Alan et al\textsuperscript{16} (UCM group median, 7 [range, 3-8]; control group median, 7 [range, 2-8]; \(P = .77\)), and Katheria et al (data unavailable).\textsuperscript{15} We found no statistically significant difference in Apgar scores at 5 minutes in the 5 studies that reported this outcome.\textsuperscript{11,12,14-16}

**Duration of Hospital Stay**
No difference in median days of hospital stay between comparison groups was reported by Rabe et al\textsuperscript{14} (UCM group median, 46 [IQR, 13-315] days; control group median, 50 [IQR, 1-189] days; \(P = .58\)). Alan et al\textsuperscript{16} reported similar results (UCM group median, 47 [range, 17-72] days; control group median, 53 [range, 17-83] days; \(P = .33\)).

**Comparison of Full-term Infants**
Upadhyay et al\textsuperscript{13} and Erickson-Owens et al\textsuperscript{17} reported outcomes of UCM vs a control condition in 224 infants with a GA of at least 33 weeks. Neither study reported outcomes on mortality, cord arterial pH or cord blood gas levels, hypotension requiring intervention, the need for transfusion of packed red blood cells, or neurodevelopmental outcomes. Erickson-Owens et al\textsuperscript{17} reported no statistically significant difference in Apgar scores at 1 and 5 minutes between the 2 groups but statistically significantly higher hematocrit values in the UCM group (MD, 7.5% [95% CI, 0.7%-1.5%]). Umbilical cord milking resulted in significantly higher hemoglobin values in the first 48 hours after birth (for the 224 participants in both stud-
ies, MD, 1.2 [95% CI, 0.8-1.5] g/dL [to convert to grams per liter, multiply by 10.0]; P = .34]. We found no significant difference between the 2 groups in peak bilirubin level in 24 participants in the study by Erickson-Owens et al17 (MD, 0.6 [95% CI, −1.9 to 3.0] mg/dL [to convert to micromoles per liter, multiply by 17.104]) and in the need for phototherapy for the 224 participants in both studies13,17 (RR, 5.0 [95% CI, 0.3-247)] at 6 weeks of age with controls (P < .05).

#### Discussion

In what is, to our knowledge, the first systematic review of UCM, we identified 7 eligible studies of 501 full-term and preterm infants. Most of the included studies were of high quality and had a low risk for bias. We found heterogeneity in the method of actual implementation of UCM between studies. In infants with a GA of less than 33 weeks, UCM was not associated with a difference in the primary outcome of the risk for mortality before discharge; however, UCM was associated with higher initial hemoglobin values, a lower risk for oxygen requirement at a postmenstrual age of 36 weeks, and a lower risk for IVH of all grades. These improvements did not translate into a reduction in the need for blood transfusion or in the risk for severe IVH or periventricular leukomalacia. Although hemat-
ocrit levels were significantly higher in the UCM group, no study reported an increased risk for polycythemia or hyperbilirubinemia requiring treatment. In infants with a GA of at least 33 weeks, UCM was associated with a higher hematocrit level, no increase in the risk for hyperbilirubinemia. None of the studies evaluated long-term neurodevelopmental outcomes.

We could not make relevant comparisons because of the absence of previous reviews of UCM. However, we believe that this review provides a fair comparison between our analysis and those of DCC. Both procedures lead to placental transfusion in active or passive forms. DeMarsh et al reported that the blood volume of the newborn infant varies according to the amount of placental transfusion after birth. Depriving infants of placental blood predisposes them to anemia early in life, which of interest compared with meta-analyses of DCC in preterm infants, which found no clear difference between different and of interest compared with meta-analyses of DCC.

Table 2. Comparison of Umbilical Cord Milking vs Control Intervention in Preterm Infants

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>RR or MD (95% CI)</th>
<th>RD (95% CI)</th>
<th>NNT</th>
<th>I² Value, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality before discharge</td>
<td>5</td>
<td>277</td>
<td>0.75 (0.35 to 1.64)</td>
<td>-0.02 (-0.09 to 0.04)</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension requiring volume expanders</td>
<td>3</td>
<td>138</td>
<td>0.71 (0.41 to 1.25)</td>
<td>-0.09 (-0.22 to 0.05)</td>
<td>NA</td>
<td>64</td>
</tr>
<tr>
<td>Hypotension requiring inotrope support</td>
<td>3</td>
<td>138</td>
<td>0.77 (0.51 to 1.17)</td>
<td>-0.10 (-0.25 to 0.05)</td>
<td>NA</td>
<td>84</td>
</tr>
<tr>
<td>Initial hematocrit level, g/dL</td>
<td>3</td>
<td>159</td>
<td>2.0 (1.3 to 2.7)</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Initial hematocrit level, %</td>
<td>5</td>
<td>277</td>
<td>4.5 (1.5 to 7.4)</td>
<td>NA</td>
<td>NA</td>
<td>63</td>
</tr>
<tr>
<td>Maximal serum bilirubin level, mg/dL</td>
<td>5</td>
<td>277</td>
<td>0.1 (-0.4 to 0.6)</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Need for phototheraphy</td>
<td>2</td>
<td>135</td>
<td>0.95 (0.88 to 1.03)</td>
<td>-0.05 (-0.12 to 0.01)</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Need for PRBC transfusion</td>
<td>5</td>
<td>271</td>
<td>0.81 (0.62 to 1.05)</td>
<td>-0.16 (-0.32 to 0.00)</td>
<td>NA</td>
<td>62</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>3</td>
<td>138</td>
<td>1.03 (0.78 to 1.35)</td>
<td>0.01 (-0.14 to 0.17)</td>
<td>NA</td>
<td>52</td>
</tr>
<tr>
<td>Oxygen requirement at postmenstrual age of 36 wk</td>
<td>4</td>
<td>191</td>
<td>0.42 (0.21 to 0.83)</td>
<td>-0.14 (-0.25 to -0.04)</td>
<td>8 (5-28)</td>
<td>38</td>
</tr>
<tr>
<td>Oxygen requirement at 28 d</td>
<td>4</td>
<td>194</td>
<td>0.93 (0.53 to 1.64)</td>
<td>-0.01 (-0.13 to 0.10)</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Intraventricular hemorrhage grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>5</td>
<td>277</td>
<td>0.62 (0.41 to 0.93)</td>
<td>-0.12 (-0.22 to -0.02)</td>
<td>9 (5-50)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;III</td>
<td>4</td>
<td>196</td>
<td>0.83 (0.36 to 1.90)</td>
<td>-0.02 (-0.10 to 0.06)</td>
<td>NA</td>
<td>35</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical management</td>
<td>5</td>
<td>271</td>
<td>1.85 (0.33 to 10.53)</td>
<td>0.02 (-0.04 to 0.08)</td>
<td>NA</td>
<td>60</td>
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<tr>
<td>Perforation</td>
<td>3</td>
<td>156</td>
<td>0.87 (0.25 to 3.01)</td>
<td>-0.01 (-0.08 to 0.07)</td>
<td>NA</td>
<td>15</td>
</tr>
<tr>
<td>Periventricular leukomalacia</td>
<td>3</td>
<td>170</td>
<td>0.67 (0.12 to 3.75)</td>
<td>-0.01 (-0.07 to 0.04)</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>3</td>
<td>168</td>
<td>0.91 (0.73 to 1.13)</td>
<td>-0.05 (-0.16 to 0.06)</td>
<td>NA</td>
<td>23</td>
</tr>
<tr>
<td>Requiring treatment</td>
<td>2</td>
<td>98</td>
<td>1.00 (0.18 to 5.51)</td>
<td>0.00 (-0.09 to 0.09)</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Late-onset sepsis</td>
<td>4</td>
<td>213</td>
<td>0.84 (0.58 to 1.21)</td>
<td>-0.06 (-0.17 to 0.06)</td>
<td>NA</td>
<td>12</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>3</td>
<td>138</td>
<td>0.91 (0.56 to 1.48)</td>
<td>-0.03 (-0.18 to 0.12)</td>
<td>NA</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: MD, mean difference; NA, not applicable; NNT, number needed to treat; PRBC, packed red blood cells; RD, risk difference; RR, risk ratio.

SI conversion factors: To convert bilirubin to micromoles per liter, multiply by 17.104; hematocrit to a proportion of 1.0, multiply by 0.01; and hemoglobin to grams per liter, multiply by 10.0.

*Indicates statistically significant results.

Furthermore, Katheria et al demonstrated a greater superior vena caval flow in preterm infants (GA, <32 weeks) allocated to UCM compared with ICC. Anemia and low systemic blood flow (as measured by superior vena cava flow) are known risk factors for neurologic insults in the first week after birth. Placental transfusion resulting from DCC or UCM might improve systemic perfusion and mitigate fluctuation in cerebral perfusion pressure, leading to a reduction in neurologic injury. However, superior vena cava flow can be considered a surrogate marker of perfusion in neonates, and further studies are needed to confirm or refute this finding.

The finding of a significantly lower risk for oxygen requirement at a postmenstrual age of 36 weeks in the UCM group is different and of interest compared with meta-analyses of DCC in preterm infants, which found no clear difference between groups. Recently, interest in the potential for progenitor or stem cell therapies to prevent or treat bronchopulmonary dysplasia in preterm infants has grown. In animal models, treatment with cord blood–derived mesenchymal stromal cells showed promising results in the prevention of adverse effects of hyperoxia-induced lung injury. The possibility of transfer of some progenitor cells during UCM has been speculated.

We planned to perform subgroup analysis by controlled intervention (DCC or ICC). However, the small number of trials in the present review precluded this analysis. A fundamental
physiological distinction between these two methods warrants careful examination of such comparison when further information is available. A large body of evidence suggests that additional flow of blood from the placenta to the infant through DCC has several advantages to the newborn and does not result in harm. However, controversies exist over what constitutes the optimal time of DCC and the safety of this method when active resuscitation of the newborn is anticipated. Moreover, the delay in severing the umbilical cord might interfere with controlling maternal bleeding and suturing the uterine incision in cesarean delivery or the episiotomy or perineal tear in vaginal delivery. On the other hand, UCM is believed to be a simple intervention that can be performed in seconds rather than minutes. This method may be appealing in cases of anticipated birth asphyxia, given the importance of time in such situations. We can also speculate that pushing certain progenitor cells in some situations, such as autologous blood transfusion, is a subject of human trials in birth asphyxia. Given the suggestions by professional organizations to use DCC as a method of choice, conceiving any new studies of UCM without considering DCC as the control intervention will be very difficult, and further research comparing these two methods is warranted.

This review is, to our knowledge, the first to assess UCM and its effect on neonatal outcomes. A comprehensive literature search, standard methodologic approach, and contact of original authors to obtain missing information are some of the strengths of this review. However, we acknowledge the limitations of this review. First, the inclusion and exclusion criteria and measured outcomes varied widely across studies. Second, although the method of UCM was described in detail in all trials, the way it was attained varied widely among these trials. Third, methodologic limitations of earlier evidence and the small number of participants, the heterogeneity of the eligible population, and the varied study outcomes in the current evidence reduce the power of the meta-analysis to detect statistically significant differences in the health outcome of interest and to draw meaningful conclusions. Fourth, the measures used to describe the central tendency for many outcomes varied between studies and included parametric and nonparametric measures for the same outcome. We assumed normal distribution in some cases; however, concern always remains when such assumptions are made.

Based on the findings of this review of 7 studies, UCM may have beneficial effects; however, further studies are needed before widespread use can be recommended, and its use at present should be restricted to RCTs. Because DCC is recommended for widespread adoption, future studies of UCM should, in most instances, consider DCC as the control intervention. Use of a more consistent study population, uniform inclusion and exclusion criteria, and well-defined outcome measures, including delineation of physiological status after clamping, can help mitigate heterogeneity across studies to better support data synthesis and understand the effects of UCM on important neonatal and childhood outcomes.

Conclusions

Umbilical cord milking was associated with some benefits and no adverse effects in the immediate postnatal period in preterm infants (GA, <33 weeks). However, further studies are warranted to assess the effect of UCM on neonatal and long-term outcomes.

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