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Association of Umbilical Cord Management Strategies With Outcomes of Preterm Infants
A Systematic Review and Network Meta-analysis

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IMPORTANCE It is unclear which umbilical cord management strategy is the best for preventing mortality and morbidities in preterm infants.

OBJECTIVE To systematically review and conduct a network meta-analysis comparing 4 umbilical cord management strategies for preterm infants: immediate umbilical cord clamping (ICC), delayed umbilical cord clamping (DCC), umbilical cord milking (UCM), and UCM and DCC.

DATA SOURCES PubMed, Embase, CINAHL, and Cochrane CENTRAL databases were searched from inception until September 11, 2020.

STUDY SELECTION Randomized clinical trials comparing different umbilical cord management strategies for preterm infants were included.

DATA EXTRACTION AND SYNTHESIS Data were extracted for bayesian random-effects meta-analysis to estimate the relative treatment effects (odds ratios [OR] and 95% credible intervals [CrI]) and surface under the cumulative ranking curve values.

MAIN OUTCOMES AND MEASURES The primary outcome was predischarge mortality. The secondary outcomes were intraventricular hemorrhage, severe intraventricular hemorrhage, need for packed red blood cell transfusion, and other neonatal morbidities. Confidence in network meta-analysis software was used to assess the quality of evidence and grade outcomes.

RESULTS Fifty-six studies enrolled 6852 preterm infants. Compared with ICC, DCC was associated with lower odds of mortality (22 trials, 3083 participants; 7.6% vs 5.0%; OR, 0.64; 95% CrI, 0.39-0.99), intraventricular hemorrhage (25 trials, 3316 participants; 17.8% vs 15.4%; OR, 0.73; 95% CrI, 0.54-0.97), and need for packed red blood cell transfusion (18 trials, 2904 participants; 46.9% vs 38.3%; OR, 0.48; 95% CrI, 0.32-0.66). Compared with ICC, UCM was associated with lower odds of intraventricular hemorrhage (10 trials, 645 participants; 22.5% vs 16.2%; OR, 0.58; 95% CrI, 0.38-0.84) and need for packed red blood cell transfusion (9 trials, 688 participants; 47.3% vs 32.3%; OR, 0.36; 95% CrI, 0.23-0.53), with no significant differences for other secondary outcomes. There was no significant difference between UCM and DCC for any outcome.

CONCLUSIONS AND RELEVANCE Compared with ICC, DCC was associated with the lower odds of mortality in preterm infants. Compared with ICC, DCC and UCM were associated with reductions in intraventricular hemorrhage and need for packed red cell transfusion. There was no significant difference between UCM and DCC for any outcome. Further studies directly comparing DCC and UCM are needed.

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Supplemental content

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Umbilical cord/placental transfusion refers to the transfer of blood to a baby from the time of birth to the time of umbilical cord clamping. The additional blood volume may be relevant for preterm infants because a larger amount of blood is sequestered in the placenta compared with term infants.[1] Delayed umbilical cord clamping (DCC; ≥30 seconds) is endorsed for practice by several bodies for term and preterm infants.[2,3] The exceptions for DCC in preterm infants include those who need immediate resuscitation after birth. For such circumstances, an alternative technique has been in practice, umbilical cord milking (UCM), which consists of gently grasping the umbilical cord and squeezing the cord from the placenta toward the infant 2 to 4 times. Three or 4 repetitions of milking the intact cord deliver approximately 14 mL/kg of blood,[4] a volume similar to that delivered in a 2-minute DCC in term infants.[5] However, data from preterm lambs identified fluctuations in carotid artery pressure and flow with UCM, which may place extremely preterm infants at risk of intraventricular hemorrhage.[6] Conversely, none of the preterm lambs received antenatal steroids, and all were anesthetized and instrumented prior to delivery, which makes extrapolation to preterm human infants challenging. A few trials[7-9] have evaluated the combination of UCM and DCC (UCM+DCC) in comparison with DCC or immediate umbilical cord clamping (ICC) and reported varying results. Therefore, the objective of our systematic review and network meta-analysis (NMA) was to evaluate the effectiveness and safety of various umbilical cord management strategies in preterm infants: DCC, UCM, UCM+DCC, and ICC.

Key Points

Question Which umbilical cord management strategy is associated with reducing mortality and morbidities in preterm infants?

Findings In this network meta-analysis of 56 trials including 6852 preterm infants, compared with immediate umbilical cord clamping, delayed umbilical cord clamping was associated with lower odds of mortality and intraventricular hemorrhage, and umbilical cord milking was associated with lower odds of intraventricular hemorrhage. There was no significant difference between delayed umbilical cord clamping and umbilical cord milking for any outcome.

Meaning Delayed umbilical cord clamping should be the preferred strategy for preterm infants; however, larger trials directly comparing delayed umbilical cord clamping and umbilical cord milking are needed.

Methods

This study complied with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis extension statement for reporting NMA of health care interventions.[10] The protocol was registered in PROSPERO (CRD42019118241).[11]

Inclusion Criteria

Randomized clinical trials of preterm infants born at younger than 37 weeks' gestation or low-birth-weight infants (<2500 g) who received DCC, UCM (intact or cut cord), UCM+DCC, or ICC (<30 seconds) were included. Quasirandomized trials were excluded. Only fully published articles (from 1988-2020) were included. Abstracts presented at conferences were read but not included unless full studies were published. Observational studies, narrative reviews, systematic reviews, case reports, letters, editorials, and commentaries were excluded but were read to identify potential studies.

Interventions

Immediate CC was defined as clamping the umbilical cord immediately (<30 seconds) after birth of the infant. Delayed CC was defined as clamping the umbilical cord at least 30 seconds after birth. Umbilical cord milking consisted of grasping the intact or cut umbilical cord and squeezing the cord from the placenta 2 to 4 times toward the infant. Finally, UCM+DCC was defined as squeezing the intact cord from the placenta toward the infant immediately after birth and then clamping the cord at least 30 seconds after birth.

Outcomes

The primary outcome was predischarge mortality. Secondary outcomes were intraventricular hemorrhage, severe intraventricular hemorrhage (grade 3 or 4),[12] receipt of packed red blood cell transfusion, late-onset sepsis, bronchopulmonary dysplasia defined as oxygen use at 36 weeks' postmenstrual age,[13] necrotizing enterocolitis (≥stage II per modified Bell staging),[14] retinopathy of prematurity requiring treatment, and neurodevelopmental impairment at approximately 2 years of corrected age.

Information Sources and Search Methods

The electronic databases PubMed, Embase, CINAHL, and Cochrane CENTRAL, and the Chinese Academic Journal database were searched from inception until September 11, 2020, without language restrictions. Trials were searched using the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov. Unpublished and gray literature were searched through ProQuest, OpenGrey, and Google Scholar. Searches were conducted by an information specialist, and supplemental hand searches were conducted by the reviewers. The reference lists of eligible studies and review articles were searched. Attempts were made to contact the authors of published studies, abstracts, and ongoing trials for additional data on methods and results from any of the studies, but we received no responses. Only published data were used for those studies, where available. A detailed search strategy is provided in eTable 1 in the Supplement.

Study Selection and Data Extraction

Three authors (B.J., R.T., and S.S.) independently reviewed abstracts, selected trials, and extracted data. Disagreements were resolved through discussion or by involving a third reviewer (P.S.). Multiple publications of the same study were identified, and duplication of the data was avoided. Variables such as population, inclusion and exclusion criteria, intervention,

control, and primary and secondary outcomes were recorded from each included study.

Risk-of-Bias Assessment

Three authors (B.J., R.T., and S.S.) independently used the Cochrane risk of bias tool[15] to evaluate the quality of included trials across 7 domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias). The possible judgments for these domains were "high risk," "low risk," or "unclear risk" of bias. Considering that blinding of participants and personnel is not feasible with these interventions, we excluded that domain before making a final judgment for each study as follows: "low risk," if all domains were judged to be of low risk or when a maximum of 1 domain was judged "unclear risk"; "moderate risk," if at least 2 domains were judged to be of unclear risk and no domains were judged "high risk"; and "high risk" if any domain was judged to be of high risk.

Quality-of-Evidence Assessment

Two review authors (B.J. and R.T.) used the Confidence in Network Meta-analysis (CINeMA) Web application (University of Bern) to judge the confidence in the NMA results considering 6 domains: within-study bias (judged according to majority risk of bias in included trials), indirectness (judged as low/moderate or high based on relevance of study to the research question), imprecision (by assessing credible interval), heterogeneity, and incoherence. Each domain was judged as having no concerns, some concerns, or major concerns. The latter would downgrade the level of evidence by 1 level. An overall confidence rating of either high, moderate, low, or very low confidence was given to each outcome comparison.[16]

Data Synthesis and Analyses

The available direct comparisons between the umbilical cord management strategies were presented using a network diagram. The node size represented number of patients and the line thickness represented number of trials for the respective comparison. For each outcome, NMA were conducted using a random-effects model with bayesian approach[17] for the direct and indirect cord management strategies comparisons under the transitivity assumption. Transitivity was subjectively evaluated by comparing study population; assessing variability in intervention; and evaluating distribution of effect modifiers (gestational age at birth, timing of delayed cord clamping, mode of delivery, and location of trial) in included studies (eTable 2 in the Supplement). Because inclusion criteria for gestational age differed between included studies, we preplanned subgroup analyses for infants of fewer than 33 weeks' gestation and fewer than 29 weeks' gestation. Apart from gestational age, other modifiers were similarly distributed and did not violate the assumption of transitivity. Post hoc sensitivity analyses were conducted including only studies with low risk of bias. For comparisons of outcomes between strategies, group-based analyses were applied to estimate the management strategies' effects, the odds ratios (ORs) of the outcomes, and the 95% credible intervals (95% CrIs). We also estimated the relative rankings of the umbilical cord management strategies for each outcome using the distribution of the ranking probabilities and used the surface under the cumulative ranking curve (SUCRA)[18] to assess the overall rankings of the management strategies for each outcome. Heterogeneity was assessed using the I^2 values for direct comparisons. Between-studies heterogeneity was evaluated using tau^2 values for NMA. Incoherence was assessed by comparing direct and indirect estimates using the node-splitting method. When incoherence was identified, sensitivity analyses were conducted excluding the strategy for which incoherence was identified.

Meta-regression

Network meta-regression was conducted to examine the possible effect of the birth mode on the associations between the strategies and predischarge mortality and intraventricular hemorrhage. Publication bias was assessed by the comparison adjusted funnel plot using the Egger test.[19] All analyses were performed in a bayesian framework using the GeMTC package in R, version 4.0.0 (The R Foundation).[20]

Results

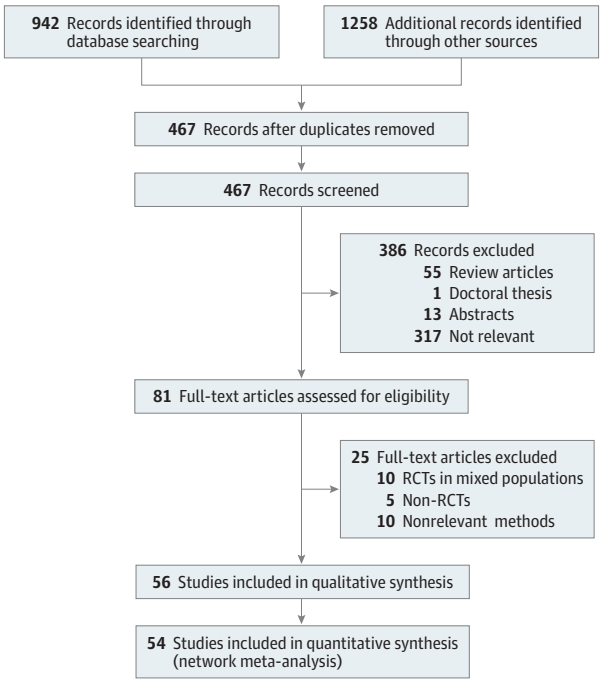
Study Selection and Study Characteristics

The process of identification and selection of studies is summarized in **Figure 1**. Fifty-six randomized clinical trials enrolling 6852 infants were included. The characteristics of the included studies are summarized in the **Table**.[7-9,21-76] Eight studies were published in the Chinese language.[28,47,50-52,74-76] Twenty-five studies were excluded after full review. Of these excluded studies, 10 studies were of mixed populations (term and preterm infants), 5 studies were nonrandomized clinical trials, and 10 studies had methods (inclusion criteria and population) not relevant to this review (eTable 3 in the Supplement).

Summary of Included Studies

Thirty-one studies[21-52] compared DCC with ICC, of which 1 study reported neurodevelopmental outcomes.[30] Among these studies, the duration of DCC ranged from at least 30 seconds to more than 180 seconds. Thirteen studies compared UCM with ICC,[53-65] including 2 studies[58,62] in which the umbilical cord was cut and 11 studies in which the cord was intact during UCM. The milking was done at or below the level of the placenta, depending on the mode of delivery. The distance of milking varied from 20 to 30 cm, and the umbilical cords were milked 2 to 4 times at rates of 5 to 10 cm/s in included studies. Five studies compared UCM with DCC,[66-72] of which 2 studies reported long-term neurodevelopmental outcomes.[68,71] Two studies compared UCM+DCC vs ICC,[7,8] of which 1 study reported neurodevelopmental outcomes,[8] and 1 study compared UCM+DCC vs DCC.[9] Four studies were multiple-arm studies.[73-76]

Figure 1. Summary of Study Selection Process



RCT indicates randomized clinical trial.

Risk of Bias Assessment

The risk of bias assessment of included studies is shown in eFigure 1 in the Supplement. All included studies had high risk of bias in the domain of blinding of participants and personnel owing to the nature of the intervention (conducted on preterm infants). Twenty-two studies (39%) had overall low risk of bias.

Network Plots

The network plots for head-to-head comparisons between the different cord management strategies for primary and secondary outcomes are presented in **Figure 2**. The network plots for gestational age subgroups are presented in eFigures 2 and 3 in the Supplement.

Primary Outcome

A total of 42 trials including 5851 infants reported the primary outcome of predischarge mortality. The overall mortality was 6.2% (364 of 5851). Compared with ICC, DCC was associated with lower odds of mortality (22 trials, 3083 participants; 7.6% vs 5.0%; OR, 0.64; 95% CrI, 0.39-0.99; I^2 = 0%; confidence rating: moderate) (**Figure 3**; eTable 4 in the Supplement). None of the other comparisons were associated with significant differences in mortality, including the comparison between UCM and DCC (Figure 3).

Secondary Outcomes

A total of 41 trials, including 5519 infants reported intraventricular hemorrhage, 29 trials including 4388 infants reported severe intraventricular hemorrhage, and 30 trials including 4319 infants reported need for packed red blood cell transfusion. Compared with ICC, DCC was associated with significantly lower odds of intraventricular hemorrhage (25 trials; 3316 participants; 17.8% vs 15.4%; OR, 0.73; 95% CrI, 0.54-0.97; I^2 = 13%; confidence rating: high) and need for packed red blood cell transfusion (18 trials, 2904 participants; 37% vs 46%; OR, 0.48; 95% CrI, 0.32-0.66; I^2 = 45%; confidence rating: high) (Figure 3 and **Figure 4**; eTable 4 and eFigure 4 in the Supplement). Compared with ICC, UCM was associated with significantly lower odds of intraventricular hemorrhage (10 trials, 645 participants; 22.5% vs 16.2%; OR, 0.58; 95% CrI, 0.38-0.84; I^2 = 0%; confidence rating: high) and need for packed red blood cell transfusion (9 trials, 688 participants; 47.3% vs 32.3%; OR, 0.36; 95% CrI, 0.23-0.53; I^2 = 0%; confidence rating: high) (Figures 3 and 4; eTable 4 and eFigure 4 in the Supplement). There were no significant differences among the different cord management strategies with regards to other prespecified secondary outcomes. There were no significant differences between UCM and DCC for any prespecified secondary outcomes (Figures 3 and 4; eTable 4 and eFigure 4 in the Supplement). Sensitivity analyses of only low risk of bias studies revealed that results of all outcomes did not differ (wider confidence interval) between strategies; however, the directions of effects were similar to those in the overall comparison (eTable 5 in the Supplement).

Subgroup Analyses

For preterm infants of less than 33 weeks' gestation, compared with ICC, DCC was associated with significantly lower odds of mortality (12 trials, 2291 participants; 9.4% vs 5.8%; OR, 0.58; 95% CrI, 0.30-0.96; I^2 = 22%; confidence rating: moderate) and need for packed red blood cell transfusion (10 trials, 2234 participants; 56.7% vs 45.9%; OR, 0.42; 95% CrI, 0.23-0.66; I^2 = 74%; confidence rating: moderate). Similarly, compared with ICC, UCM was associated with significantly lower odds of intraventricular hemorrhage (7 trials, 433 participants; 24.5% vs 18.4%; OR, 0.64; 95% CrI, 0.38-0.96; confidence rating: moderate) and need for packed red blood cell transfusion (5 trials, 243 participants; 82.5% vs 61.7%; OR, 0.34; 95% CrI, 0.17-0.64; confidence rating: high) (eTables 4 and 6 in the Supplement).

For preterm infants of less than 29 weeks' gestation, compared with ICC, DCC was associated with significantly lower odds of severe intraventricular hemorrhage (1 trial, 37 participants; 20% vs 5.9%; OR, 0.18; 95% CrI, 0.03-0.99; confidence rating: moderate), and UCM was associated with significantly lower odds of need for packed red blood cell transfusion (2 trials, 115 participants; 88% vs 66%; OR, 0.17; 95% CrI, 0.03-0.91) (eTables 4 and 7 in the Supplement).

Ranking Probability

For the outcome of mortality, UCM+DCC had the highest probability of being the best umbilical cord management strategy in preterm infants, with a SUCRA value of 0.84; however, there was incoherence between direct and indirect comparison and imprecision in estimates (eTable 8 and eFigure 5 in the Supplement). The second-best strategy for

Table. Characteristics of Included Studies

Source	Population, No.	Inclusion criteria, wk	Exclusion criteria	Intervention	Control
Comparison: DCC vs ICC (n = 31)					
Tarnow-Mordi et al,[21] 2017	Total: 1566	GA <30	Fetal hemolytic disease, hydrops fetalis, TTTS, genetic syndromes, and potentially lethal malformations	DCC: ≥60 s	ICC: <10 s
	DCC: 784				
	ICC: 782				
Armanian et al,[22] 2017	Total: 63	GA ≤34	Admission to NICU, twin pregnancy, parent refusal to participate, major congenital anomalies, asphyxia	DCC: 30-45 s	ICC: <10 s
	DCC: 32				
	ICC: 31				
Backes et al,[23] 2016	Total: 40	GA 22 (+ 5 d) to 27+ 6 d)	Placental abruption, placental previa, multiple gestations, chromosomal abnormalities, major congenital malformation, intent to withhold care	DCC: 30 to 45 s	ICC: <10 s
	DCC: 18			VD: 10 to 15 in below the mother's introitus	
	ICC: 22			CD: below the level of the incision	
Baezinger et al,[24] 2007	Total: 39	GA 24-32	Multiple deliveries, perinatal asphyxia, major fetal malformations, refusal of consent	DCC: 15 cm below the placenta in CD and as low as possible for VD	ICC: <20 s
	DCC: 15			Time: 60-90 s	
	ICC: 24				
Chu et al,[25] 2019	Total: 38	GA 24-32	Major life-threatening fetal anomalies, multiple gestations, intrauterine fetal demise, or plan for stem cell collection and cord blood banking	DCC: 10-15 cm below the introitus (VD) or at the incision level (CS)	ICC: <10 s
	DCC: 19			Time: 30-45 s	
	ICC: 19				
Datta et al,[26] 2017	Total: 117	GA 34-36 (+ 6 d)	Congenital anomaly, hydrops and Rh-negative pregnancy	DCC: >30 to 60 s	ICC: <20 s
	DCC: 58				
	ICC: 59				
Dipak et al,[27] 2017	Total: 78	GA 27-31 (+ 6 d)	Multiple gestation, Rh-negative mother, placenta previa, abruption-placenta, major congenital anomalies, hydrops, FGR with abnormal Doppler waveforms, fetal distress	DCC: 10-15 in below the introitus/incision	ICC: <10 s
	DCC: 26			Time: 60 s	
	DCC with ergometrine: 25				
	ICC: 27				
Dong et al,[28] 2016	Total: 90	GA 25 (+ 4 d) to 31 (+ 6 d)	Requiring immediate resuscitation, placenta previa, placental abruption	DCC: 45 s	ICC: <10 s
	DCC: 46				
	ICC: 44				
Duley et al,[29,30] 2017	Total: 254	GA <32	Monochorionic twins or clinical evidence of TTTS, triplet or higher-order multiple pregnancy, and known major congenital malformation	DCC: ≥2 min	ICC: <20 s
	DCC: 134				
	ICC: 120				
Gokmen et al,[31] 2011	Total: 42	GA 24-31 (+ 6 d)	Vaginal bleeding, major fetal anomalies, IUGR, TTTS or discordant twin growth, maternal drug abuse	DCC: 30-45 s	ICC: <10 s
	DCC: 21				
	ICC: 21				
Hofmeyr et al,[32] 1988	Total: 38	GA <35	Multiple pregnancies	DCC: >60 s	ICC: Immediate
	DCC: 24				
	ICC: 14				
Hofmeyr et al,[33] 1993	Total: 86	Expected BW <2000 g	None reported	DCC: 60-120 s	ICC: Immediate
	DCC: 40				
	ICC: 46				
Kinmond et al,[34] 1992	Total: 36	GA 27-33	Hemolytic disease or major congenital malformations	DCC: >30 s	ICC: <20 s
	DCC: 19				
	ICC: 17				

(continued)

Table. Characteristics of Included Studies (continued)

Source	Population, No.	Inclusion criteria, wk	Exclusion criteria	Intervention	Control
Varij Kazemi et al,[35] 2017	Total: 70 DCC: 35 ICC: 35	GA <32 and BW <1500 g delivered via cesarean birth	Maternal use of anticoagulant drugs; birth asphyxia; need for resuscitation, birth trauma; need for advanced resuscitation; infants from multiple gestation or breech presentation; and maternal conditions such as preeclampsia, hypertension, and uncontrolled diabetes	DCC: 30-45 s	ICC: <10 s
Kugelman et al,[36] 2007	Total: 65 DCC: 30 ICC: 35	GA 24-34 (+ 6 d)	Vaginal bleeding, major anomaly, severe IUGR, GD treated with insulin, TTTS or discordant twins, maternal drug abuse	DCC: 30-45 s	ICC: 5-10 s
Malik et al,[37] 2013	Total: 80 DCC: 40 ICC: 40	GA 30-36 (+ 6 d)	Congenital anomalies, Rh-negative mothers	DCC: 120 s	ICC: <30 s
McDonnell and Henderson-Smart et al,[38] 1997	Total: 46 DCC: 23 ICC: 23	GA 26-33	Severe fetal distress, IUGR with abnormal umbilical arterial Doppler velocity waveforms, hemolytic disease, or major malformations	DCC: 30 s	ICC: Immediate
Mercer et al,[39] 2003	Total: 32 DCC: 16 ICC: 16	GA 24-31 (+ 6 d)	Intent to withhold or withdraw care, placenta previa or abruption, bleeding, major anomaly	DCC: 30-45 s, 10-15 in below introitus/incision	ICC: 5-10 s
Mercer et al,[40] 2006	Total: 72 DCC: 36 ICC: 36	GA 24-31 (+ 6 d)	Major congenital anomalies, multiple gestations, intent to withhold care, severe maternal illness, placenta abruption, or previa	DCC: 30-45 s, 10-15 in below introitus/incision	ICC: <10 s
Oh et al,[41] 2011	Total: 33 DCC: 16 ICC: 17	GA 24-27 (+ 6 d)	None reported	DCC: 30-45 s, 10 cm below introitus/incision	ICC: <10 s
Rabe et al,[42] 2000	Total: 40 DCC: 19 ICC: 20	GA <33	Rh incompatibility, fetal hydrops, congenital abnormalities, Apgar <3 at 0 min, multiple pregnancy	DCC: 45 s, 20 cm below introitus/incision	ICC: <20 s
Rana et al,[43] 2018	Total: 100 DCC: 50 ICC: 50	GA <34	Known congenital anomalies, severe preeclampsia or eclampsia, uncompensated heart disease, any abnormal bleeding before cord clamping, twins or triplets, babies requiring immediate resus at birth	DCC: 120 s	ICC: <30 s
Ranjit et al,[44] 2015	Total: 82 DCC: 41 ICC: 41	GA 30-36 (+ 6 d)	Rh negative status, monoamniotic-monochorionic twins, need for resuscitation	DCC: 120 s, mother's abdomen (VD) or thighs (CS)	ICC: Immediate
Ruangkit et al,[45] 2018	Total: 101 DCC: 51 ICC: 50	GA 28-36	Prenatally diagnosed major congenital anomaly in any infants, TTTS or TAPS, discordant twins, any intrauterine fetal death, hydrops, antepartum or intrapartum hemorrhage, or when the medical care clinician declined performing DCC	DCC: 30-60 s, mother's perineum (VD) or thighs (CS)	ICC: <5 s
Salae et al,[46] 2016	Total: 86 DCC: 42 ICC: 44	GA 34-36 (+ 6 d)	Thalassemia, preeclampsia, GD, renal impairment, placental abnormality, major congenital anomaly, multiple gestation, instrumental delivery, abnormal fetal tracing	DCC: 120 s	ICC: Immediate
Shi et al,[47] 2017	Total: 60 DCC: 30 ICC: 30	GA <37	Sick mother (high blood pressure), anemia, blood group incompatibility, TTTS	DCC: Wait until cord pulsation ceased	ICC: 5-10 s

(continued)

Table. Characteristics of Included Studies (continued)

Source	Population, No.	Inclusion criteria, wk	Exclusion criteria	Intervention	Control
Strauss et al,[48] 2008	Total: 105 DCC: 45 ICC: 60	GA 30-36	Unable to perform studies; nonsurvivors	DCC: 60 s, 10-15 in below introitus (VD), beside mother's thigh (CS)	ICC: <15 s
Ultee et al,[49] 2008	Total: 37 DCC: 18 ICC: 19	GA 34-36 (+ 6 d) born by vaginal route	Diabetes, GD, PIH, congenital abnormality, twins, Apgar scores <5 at 1 min, <7 at 5 min	DCC: 180 s	ICC: <30 s
Zhang et al,[50] 2018	Total: 116 I: 55 C: 61	GA: 32-36 (+ 6 d)	Congenital abnormalities, hemolysis, maternal anemia, TTTS, APH, early discharge	DCC: 60 s	ICC: <30 s
Zheng et al,[51] 2019	Total: 96 I: 72 C: 24	GA 28-34; VD	Maternal anemia, hemolytic disease, CNS abnormalities, coagulopathy	DCC: 30-120 s DCC(A): 30 s DCC(B): 60 s DCC (C): 120 s	ICC: <10 s
Zhu et al,[52] 2020	Total: 115 I: 75 C: 40	GA 28-36 (+ 6 d)	PIH, APH, maternal anemia, maternal thrombocytopenia, cardiac complications, PPH, asphyxia, or transferred to another hospital	DCC: 30-120 s DCC(A): 30-60 s DCC(B): 60-120 s	ICC: immediate
Comparison: UCM vs ICC (n = 13)					
Alan et al,[53] 2014	Total: 44 UCM: 22 ICC: 22	GA ≤32 and BW ≤1500 g	Suspected TTTS or discordant twins, major congenital anomalies or chromosomal anomalies, vaginal bleeding owing to placenta previa or abruption or placental tear, hemolytic disease of the fetus and newborn, IUGR, maternal GD treated with insulin, hydrops fetalis, and refused parental consent	iUCM Level: At the level of placenta in C/S, below in VD Distance: 25-30 cm No. of times: 3 Speed: 5 cm/s	ICC: <10 s
El-Naggar et al,[54] 2019	Total: 73 UCM: 37 ICC: 36	GA 24-30 (+ 6 d)	Monochorionic twins, major congenital anomalies, placental abruption, fetal anemia and intention to withhold resuscitation	iUCM Level: At or below the level of placenta Distance: 20 cm No. of times: 3 Speed: 10 cm/s	ICC: <10 s
Hosono et al,[55] 2008	Total: 40 UCM: 20 ICC: 20	GA 24-28	Multiple births, major congenital anomalies or chromosomal anomalies, and hydrops fetalis	iUCM Level: At or below the level of the placenta Distance: 20 cm No. of times: 2-3 Speed: 10 cm/s	ICC: Immediate
Katheria et al,[56] 2014	Total: 60 UCM: 30 ICC: 30	GA 23-31 (+ 6 d)	Imminent delivery, monochorionic multiples, incarcerated mothers, placenta previa, concern for abruptions, or refusal to perform the intervention by the obstetrician	iUCM Level: Below mother's introitus at VD or below the level of the incision at CS Distance: 20 cm No. of times: 2 Speed: 10 cm/s	ICC: Immediate
Kilicdag et al,[57] 2016	Total: 54 UCM: 29 ICC: 25	GA ≤32	Congenital anomalies, placenta abruption, IUGR, TTTS, discordant twin growth, VD, and Rh hemolytic disease	iUCM Level: At the level of the placenta Distance: 20 cm No. of times: 4 Speed: 10 cm/s	ICC: Immediate

(continued)

Table. Characteristics of Included Studies (continued)

Source	Population, No.	Inclusion criteria, wk	Exclusion criteria	Intervention	Control
Kumar et al,[58] 2015	Total: 200 UCM: 100 ICC: 100	GA 32-36 (+ 6 d)	Umbilical cord length less than 25 cm, nonvigorous at birth, Rh-negative or retrovirus-positive mothers, hydrops fetalis, major congenital anomalies, cord prolapse or cord anomalies, placental abruption, placenta previa, or accreta or chorioamnionitis excluded only if infants were born limp	cUCM Level: Clamped and cut within 30 s at placental end Distance: 25 cm No. of times: 3 Speed: 10 cm/s	ICC: Immediate
Lago-Leal et al,[59] 2019	Total: 138 UCM: 69 ICC: 69	GA 24-36 (+ 6 d)	Umbilical cord abnormalities (true and false knots, short cord, nuchal cords), major congenital anomalies or chromosomal anomalies, hydrops fetalis, TTTS, or placental abruption	iUCM Level: Unspecified Distance: 20 cm No. of times: 4 Speed: Unspecified	ICC: <20 s
Li et al,[60] 2018	Total: 102 UCM: 48 ICC: 54	GA 28-37 and complicate by PPROM before birth	Congenital anomalies, Rh hemolytic disease, IUGR, multiple births; placental abruption; or other pregnancy complications	iUCM Level: at the level of or below the placenta Distance: 20 cm No. of times: 4 Speed: 10 cm/s	ICC: immediate
March et al,[61] 2013	Total: 75 UCM: 36 ICC: 39	GA 24-28	Antenatally diagnosed major fetal congenital anomaly, known Rh sensitization, hydrops fetalis, known recent maternal exposure to parvovirus, elevated peak systolic velocity of the fetal middle cerebral artery or suspicion of placental abruption owing to excessive maternal bleeding or uterine hypertonicity	iUCM Level: At or below the level of the placenta (VD), same level as the placenta (CS) Delivery: 20 cm No. of times: 3 Speed: Unspecified	ICC: Immediate
Ram Mohan et al,[62] 2018	Total: 60 UCM: 30 ICC: 30	GA <37	Neonates born to Rh-negative mothers, antenatally diagnosed major congenital anomalies, multiple gestations, hydrops, and cord prolapse	cUCM Level: umbilical cord clamped and cut Distance: 25 cm No. of times: 3 Speed: 10 cm/s	ICC: Immediate
Silahli et al,[63] 2018	Total: 75 UCM: 38 ICC: 37	GA <32	TTTS, fetal and maternal bleeding, dysmorphic features, and conotruncal heart disease	iUCM Level: At or below the level of the placenta (VD) or at the same level (CS) Distance: 20 cm No. of times: 3 times Speed: Unspecified	ICC: <10 s
Song et al,[64] 2017	Total: 66 UCM: 34 ICC: 32	GA 24-32 (+ 6 d)	Multiple gestations, Rh sensitization, fetal hydrops, or major fetal anomalies	iUCM Level: 20 cm below the level of the placenta No. of times: 4 Speed: 20 cm/2 s	ICC: Immediate
Xie et al,[65] 2020	Total: 256 UCM: 122 ICC: 134	GA <34	PPH, major congenital anomalies, hydrops fetalis, hemolysis disease, multiple births, or SGA infants	iUCM Distance: 20 cm No. of times: 4	ICC: Immediate
Comparison: UCM+DCC vs ICC (n = 2)					
Elimian et al,[7] 2014	Total: 200 UCM+DCC: 99 ICC: 101	GA 24-34	Known major fetal structural or chromosomal abnormalities, multiple gestations, diabetes, IUGR, or non-reassuring fetal heart tracings	UCM+DCC: 3-4 passes of UCM+DCC >30 s after birth	ICC: <5 s

(continued)

Table. Characteristics of Included Studies (continued)

Source	Population, No.	Inclusion criteria, wk	Exclusion criteria	Intervention	Control
Mercer et al,[8] 2016	Total: 208 UCM+DCC: 103 ICC: 105	GA 24-31 (+ 6 d)	Multiple gestation, prenatally diagnosed major congenital anomalies, severe or multiple maternal illnesses, and mothers who were at risk for loss to follow-up	UCM+DCC: 30-45 s, 10-15 in below introitus (VD)/placenta (CS) + milking once	ICC: <10 s
Comparison: UCM vs DCC (n = 5)					
Bichkar et al,[66] 2019	Total: 49 UCM: 25 DCC: 24	GA 26-31 (+ 6 d) delivered via CS	Infants requiring resuscitation, monochorionic multiples, placenta previa, abruptions, Rh sensitization, hydrops, life-threatening congenital anomalies, HIV, and hepatitis B surface antigen-positive mothers	iUCM Level: 20 cm below the level of the placenta No. of times: 4 Speed: 20 cm/2 s	DCC: ≥45 s
Katheria et al,[67,68] 2015	Total: 197 UCM: 75 DCC: 79	GA <32	Monochorionic multiples, incarcerated mothers, placenta previa, concern for abruptions, Rh sensitization, hydrops, congenital anomalies, or the obstetrician declining intervention	iUCM Level: Holding the infant at or approximately 20 cm below placenta Length: Unspecified No. of times: 4 Speed: Unspecified	DCC: ≥45 s
Katheria et al,[69] 2019	Total: 474 UCM: 236 DCC: 238	GA 23-31	Major congenital anomalies, severe placental abruption, transplacental incision, cord prolapse, hydrops, accreta, monochorionic multiple births, fetal or maternal risk for severe compromise at delivery, and family unlikely to follow up	iUCM Level: Below the level of incision (CS) or below the level of introitus (VD) Length: 20 cm No. of times: 3 Speed: 10 cm/s	DCC: ≥60 s
Rabe et al,[70,71] 2011	Total: 58 UCM: 27 DCC: 31	GA 24-32 (+ 6 d)	Multiple pregnancies, fetal hydrops, Rh sensitization, or known major congenital abnormalities	iUCM Level: 20 cm below the level of the placenta (VD) or to the mother's side (CS) No. of times: 4 Speed: 10 cm/s	DCC: >30 s
Shirk et al,[72] 2019	Total: 204 UCM: 100 DCC: 104	GA 23-34 (+ 6 d)	Congenital anomalies, precipitous delivery, placental abruption, uterine rupture, infants at risk of anemia (ie, parvovirus B19 infection and allo/isoimmunization) or patient delivered at outside institution after random assignment; category 3 fetal heart rate tracing or prolonged fetal bradycardia	iUCM Level: Level of the maternal abdomen (CS); level of the perineum (VD) Length of milking: 20 cm No. of times: 4 Speed: Unspecified	DCC: >60 s
Comparison: UCM+DCC vs DCC (n = 1)					
Krueger et al,[9] 2015	Total: 67 UCM+DCC: 35 DCC: 32	GA 22-31 (+ 6 d)	Known anomalies or suspected placental abruption	UCM+DCC: 4 Times stripping of the cord 30 s, below the level of the placenta	DCC: 30 s; Below the level of the placenta
Comparison: 3 arm trials viz UCM, DCC and ICC (n = 4)					
Finn et al,[73] 2019	Total: 44 UCM: 18 ICC: 12 DCC: 14	GA <32	Major congenital anomaly, bleeding from placenta previa, placental abruption or accreta, TTTS, hydrops, and cord prolapse	iUCM Level: At or below the level of the placenta Distance: 20 cm No. of times: 3 Speed: 10 cm/s DCC: 60 s after delivery	ICC: <20 s

(continued)

Table. Characteristics of Included Studies (continued)

Source	Population, No.	Inclusion criteria, wk	Exclusion criteria	Intervention	Control
Li et al,[74] 2020	Total: 45	GA <37; singleton	APH, maternal anemia, IUGR, congenital abnormalities, cord abnormalities, cardiac abnormalities, hemolysis, and polycythemia	iUCM	ICC: Immediate
	UCM: 15			Distance: 25 cm	
	ICC: 15			No. of times: 2-5	
	DCC: 15			Speed: 10 cm/s	
				DCC: 30-120 s	
Niu et al,[75] 2016	Total: 120	GA 34-35	Congenital abnormalities, asphyxia, need of respiratory support, and/or no evidence of PPROM or APH	iUCM	ICC: <30 s
	UCM: 40			Distance: 30 cm	
	ICC: 40			No. of times: 4	
	DCC: 40			DCC: 60-120 s	
Zhou et al,[76] 2018	Total: 120	GA <32	Incomplete patient record, too sick, premature discharge, umbilical cord <25 cm length, umbilical knots, and/or asphyxia	iUCM	ICC: Immediate
	UCM: 40			Distance: 10 cm below the level of the placenta	
	ICC: 38			No. of times: 3	
	DCC: 42			Speed: 10 cm/s	
				DCC: Clamped 45 s after delivery	

Abbreviations: APH, antepartum hemorrhage; BW, birthweight; CNS, central nervous system; CS, cesarean section; cUCM, cut umbilical cord milking; DCC, delayed umbilical cord clamping; FGR, fetal growth restriction; GA, gestational age; GD, gestational diabetes; ICC, immediate umbilical cord clamping; iUCM, intact umbilical cord milking; IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit; PIH, pregnancy-induced hypertension; PPH, postpartum hemorrhage; PPROM, preterm premature rupture of membranes; Rh, rhesus; SGA, small for gestational age; TAPS, transfusion-associated polycythemia sequence; TTTS, twin-to-twin transfusion syndrome; VD, vaginal delivery.

mortality was DCC (SCRA, 0.62); this result was statistically significant, coherent, and precise. For prespecified secondary outcomes, DCC was the best strategy for severe intraventricular hemorrhage (SUCRA, 0.64) and late-onset sepsis (SUCRA, 0.72), whereas UCM was the best strategy for intraventricular hemorrhage (SUCRA, 0.93), bronchopulmonary dysplasia (SUCRA, 0.71), retinopathy of prematurity requiring treatment (SUCRA, 0.93), and need for packed red blood cell transfusion (SUCRA 0.96) (eTable 8 and eFigure 5 in the Supplement). For primary outcome and prespecified secondary outcomes in subgroups, SUCRA values are shown in eTable 8 in the Supplement.

Statistical Heterogeneity and Meta-regression

Statistical heterogeneity in direct comparison was identified to be none or minimal (I^2 values <50%), except for the outcomes of intraventricular hemorrhage (UCM+DCC vs ICC for <37 weeks' gestation and DCC vs UCM for <33 weeks' gestation): sepsis (DCC vs ICC for <37 weeks' gestation and <33 weeks' gestation), packed red blood cell transfusion (DCC vs ICC for <33 weeks' gestation), necrotizing enterocolitis (DCC vs UCM for <33 weeks' gestation), and bronchopulmonary dysplasia (DCC vs UCM for <29 weeks' gestation). Network meta-regression analysis using the mode of birth as an independent variable revealed no significant effect of mode of birth on any outcome. However, compared with ICC, the point estimates for OR for mortality and intraventricular hemorrhage increased with increasing proportions of cesarean births. This implies potential differential effects of interventions based on mode of birth (eTable 9 in the Supplement), and further studies are warranted. Incoherence was infrequent when it was feasible to address. We identified incoherence in the domains of mortality and bronchopulmonary dysplasia for the comparisons between UCM+DCC vs ICC and UCM+DCC vs DCC. This was likely owing to small study effect, especially for the UCM+DCC group. Post hoc subgroup analyses excluding the UCM+DCC arm (owing to incoherence) revealed similar findings (eTable 10 in the Supplement). Between-studies heterogeneity assessment revealed no significant P values for tau^2, except for the outcome of bronchopulmonary dysplasia (eTable 11 in the Supplement). There was no evidence of publication bias for the outcome of mortality (P = .77 via the Egger test; eFigure 6 in the Supplement).

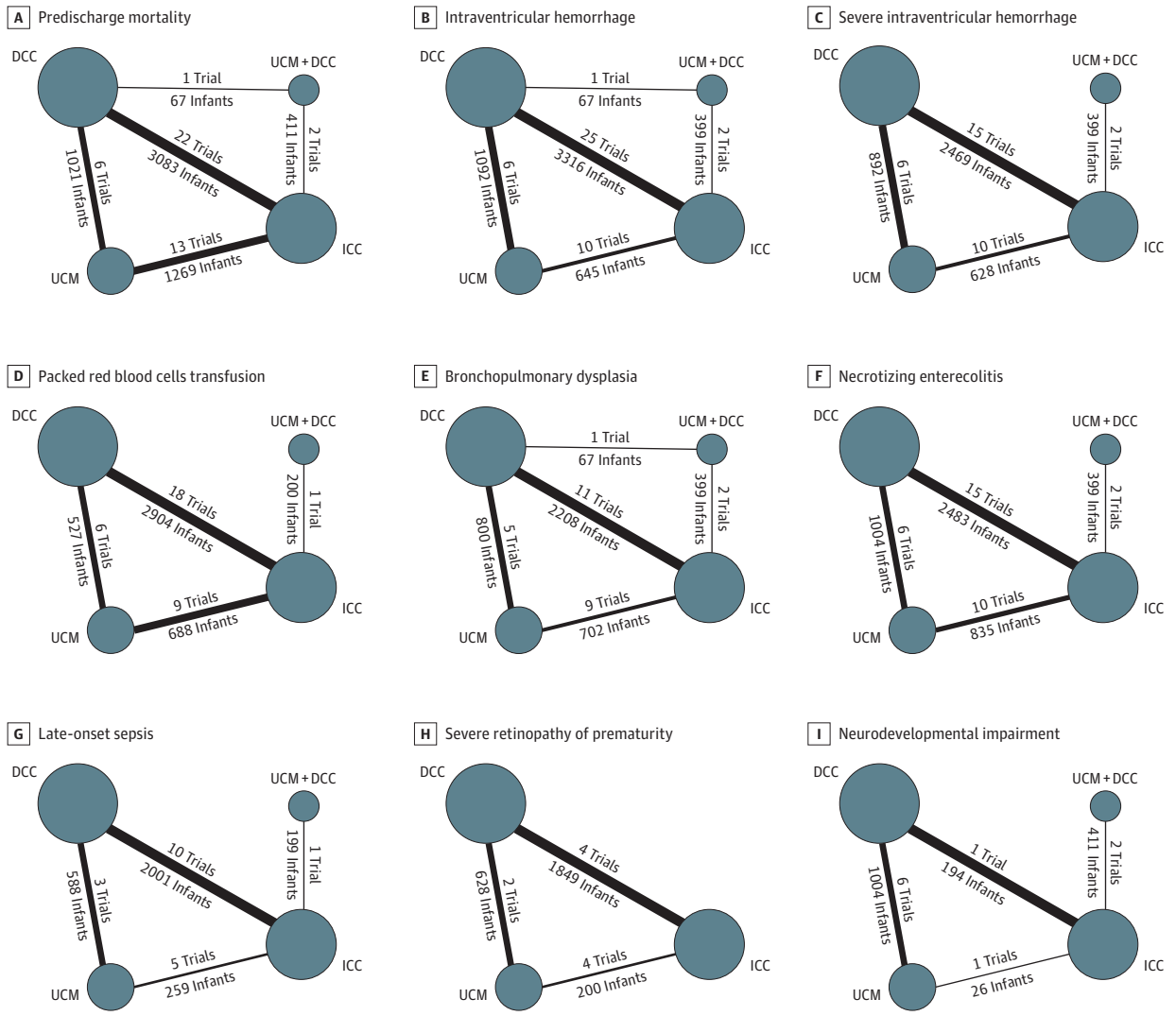
Quality-of-Evidence Assessment

The quality-of-evidence assessments for primary and secondary outcomes are shown in eTable 4 in the Supplement. The confidence ratings assessed by CINeMA ranged from low to high confidence in the results of the NMA. The most common reasons for downgrading the evidence quality were within-study bias, heterogeneity, and imprecision of results.

Discussion

In this systematic review and NMA of 56 randomized clinical trials of umbilical cord management strategies for preterm infants, compared with ICC, DCC had lower odds of mortality. In addition, DCC+UCM had lower odds of intraventricular hemorrhage and need for packed red blood cell transfusion compared with ICC. There were no significant differences between any of the strategies for any other prespecified outcomes.

Figure 2. Network Plots for Mortality and Severe Intraventricular Hemorrhage Across Study Population and Subgroups



Each node indicates an umbilical cord management modality and is sized proportionally to the number of infants who received the modality. Each line connecting 2 nodes indicates a direct comparison between 2 modalities, and the thickness of each is proportional to the number of trials directly comparing the 2 modalities.

DCC indicates delayed umbilical cord clamping; ICC, immediate umbilical cord clamping; UCM, umbilical cord milking; UCM+DCC, combination of umbilical cord milking followed by delayed cord clamping.

Previous Systematic Reviews and Important Differences From Our Study

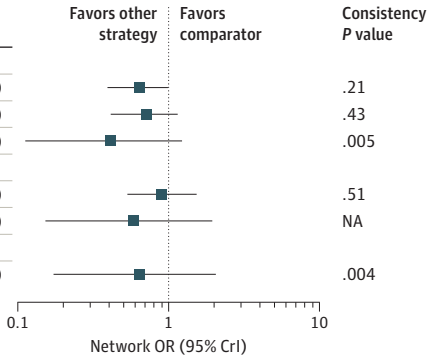
Fogarty et al[77] compared DCC with ICC in 2834 preterm infants enrolled in 18 randomized controlled trials.[77] The infants allocated to DCC had significantly lower risk of all-cause mortality prior to discharge in the whole group and among infants of 28 weeks' gestation or less (3 randomized controlled trials; 996 infants), with a reported high quality of evidence. The 2019 Cochrane review[78] compared DCC with ICC in 3100 preterm infants enrolled in 25 randomized controlled trials and showed that infants in the DCC group had significant reductions in all-cause mortality and any grade intraventricular hemorrhage, with no reductions in any other neonatal morbidities.[78] Both these reviews suggested DCC as the standard-of-care umbilical cord management strategy in vigorous preterm infants. Our NMA results are also suggestive of similar findings.

Controversy exists regarding the applicability of DCC in nonvigorous preterm infants and those delivered via cesarean section, where it might be ineffective owing to the lack of tonic uterine contractions.[21,67] Umbilical cord management has been suggested as an alternative to DCC. In a systematic review comparing UCM with DCC or ICC, Balasubramanian et al[79] reported that, compared with DCC, UCM significantly increased the risk of severe intraventricular hemorrhage in preterm infants (4 randomized controlled trials; 718 infants; number needed to harm: 29; grade: low); but compared with ICC,

Figure 3. Treatment Effects on Outcomes of Predischarge Mortality, Intraventricular Hemorrhage, and Severe Intraventricular Hemorrhage (Preterm Infants <37 Weeks' Gestation)

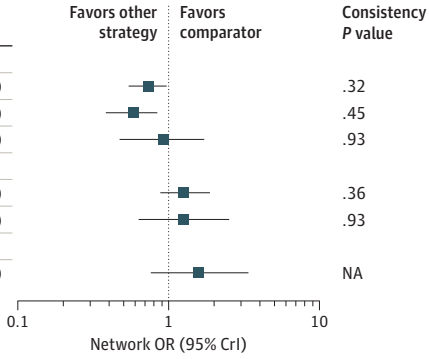
A Mortality prior to discharge

Comparison	Quality	No. of trials (No. of participants)	Direct OR (95% CrI)	Indirect OR (95% CrI)	Network OR (95% CrI)	Consistency *P* value
ICC (comparator)						
DCC	Moderate	22 (3083)	0.54 (0.26-0.92)	1.09 (0.40-3.28)	0.64 (0.39-0.99)	.21
UCM	Moderate	13 (1269)	0.80 (0.40-1.49)	0.51 (0.15-1.39)	0.71 (0.41-1.15)	.43
UCM + DCC	Moderate	2 (411)	0.62 (0.18-2.09)	0 (0-0.07)[a]	0.41 (0.11-1.23)	.005
UCM (comparator)						
DCC	Moderate	6 (1021)	1.04 (0.48-2.36)	0.71 (0.27-1.78)	0.89 (0.53-1.54)	.51
UCM + DCC	Moderate	0	NA	0.58 (0.15-1.96)	0.58 (0.15-1.96)	NA
DCC (comparator)						
UCM + DCC	Moderate	1 (67)	0 (0-0.11)[b]	1.03 (0.28-3.99)	0.64 (0.17-2.07)	.004



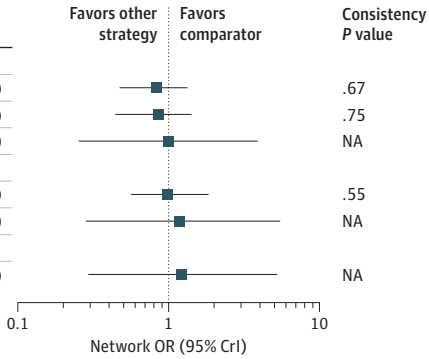
B Intraventricular hemorrhage

Comparison	Quality	No. of trials (No. of participants)	Direct OR (95% CrI)	Indirect OR (95% CrI)	Network OR (95% CrI)	Consistency *P* value
ICC (comparator)						
DCC	High	25 (3316)	0.68 (0.46-0.93)	0.99 (0.51-2.05)	0.73 (0.54-0.97)	.32
UCM	High	10 (645)	0.64 (0.38-1.07)	0.48 (0.23-0.87)	0.58 (0.38-0.84)	.45
UCM + DCC	Moderate	2 (399)	0.93 (0.44-1.89)	0.85 (0.16-4.69)	0.92 (0.47-1.73)	.93
UCM (comparator)						
DCC	Moderate	7 (1092)	1.47 (0.90-2.68)	1.01 (0.53-1.86)	1.27 (0.88-1.89)	.36
UCM + DCC	Moderate	1 (67)	1.18 (0.23-6.49)	1.27 (0.58-2.85)	1.25 (0.63-2.54)	.93
DCC (comparator)						
UCM + DCC	Moderate	0	NA	1.59 (0.76-3.42)	1.59 (0.76-3.42)	NA



C Severe intraventricular hemorrhage

Comparison	Quality	No. of trials (No. of participants)	Direct OR (95% CrI)	Indirect OR (95% CrI)	Network OR (95% CrI)	Consistency *P* value
ICC (comparator)						
DCC	Moderate	15 (2469)	0.89 (0.42-1.54)	0.58 (0.18-2.36)	0.83 (0.47-1.34)	.67
UCM	Moderate	10 (628)	0.72 (0.36-1.34)	1.32 (0.30-3.71)	0.85 (0.44-1.42)	.75
UCM + DCC	Moderate	2 (399)	1.00 (0.25-3.94)	NA	1.00 (0.25-3.94)	NA
UCM (comparator)						
DCC	Moderate	6 (892)	0.79 (0.38-1.96)	1.32 (0.48-3.44)	0.98 (0.56-1.85)	.55
UCM + DCC	Moderate	0	NA	1.19 (0.28-5.58)	1.19 (0.28-5.58)	NA
DCC (comparator)						
UCM + DCC	Moderate	0	NA	1.22 (0.29-5.34)	1.22 (0.29-5.34)	NA



CrI indicates credible interval; DCC, delayed umbilical cord clamping; ICC, immediate umbilical cord clamping; NA, not available; OR, odds ratio; UCM, umbilical cord milking.

[a] Actual values are 1.01×10^{-9} (1.21×10^{-29}; 0.07).

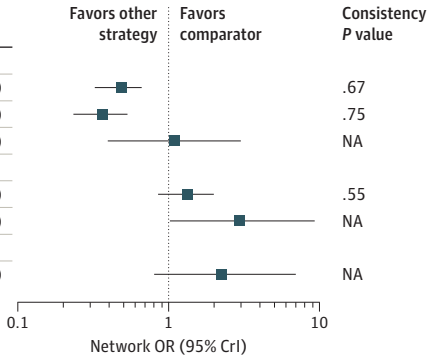
[b] Actual values are 3.6×10^{-11} (2.0×10^{-36}; 0.11).

UCM significantly reduced the need for packed red blood cell transfusion. The increase in rates of severe intraventricular hemorrhage stemmed from the results of the "premature infants receiving cord milking or DCC trial."[69] This multicenter noninferiority trial of UCM or DCC (474 neonates of <32 weeks' gestation) was prematurely terminated because the first interim analysis revealed a significantly increased risk of severe intraventricular hemorrhage with UCM (22% vs 6%; $P = .002$) among infants born at 23 to 27 (+6 days) weeks' gestation (182 neonates). This risk was not evident in the 27 to 31 (+6 days) weeks' gestation subgroup or in the overall analysis of the 23 to 31 (+6 days) weeks' gestation group, and there were no differences in mortality between the UCM and DCC groups. In our NMA, UCM was not associated with reduction in mortality; however, it was associated with reduction in intraventricular hemorrhage.

Figure 4. Treatment Effects on Outcomes of Need for Packed Red Cell Transfusion, Late-Onset Sepsis, and Bronchopulmonary Dysplasia (Preterm Infants <37 Weeks' Gestation)

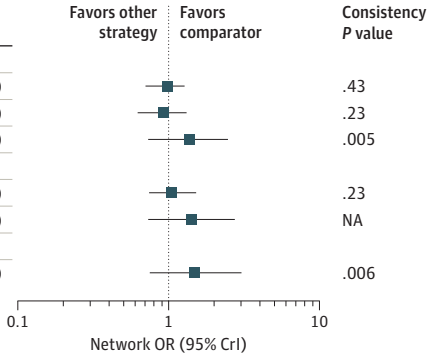
A Packed red blood cell transfution

Comparison	Quality	No. of trials (No. of participants)	Direct OR (95% CrI)	Indirect OR (95% CrI)	Network OR (95% CrI)	Consistency *P* value
ICC (comparator)						
DCC	High	18 (2904)	0.50 (0.32-0.69)	0.41 (0.17-0.91)	0.48 (0.32-0.66)	.67
UCM	High	9 (688)	0.34 (0.20-0.56)	0.39 (0.18-0.78)	0.36 (0.23-0.53)	.75
UCM + DCC	Moderate	1 (200)	1.09 (0.39-3.05)	NA	1.09 (0.39-3.05)	NA
UCM (comparator)						
DCC	Moderate	6 (527)	1.21 (0.66-2.12)	1.56 (0.79-2.88)	1.33 (0.85-2.01)	.55
UCM + DCC	Moderate	0 (0)	NA	3.00 (1.02-9.54)	3.00 (1.02-9.54)	NA
DCC (comparator)						
UCM + DCC	Moderate	0 (0)	NA	2.25 (0.80-7.14)	2.25 (0.80-7.14)	NA



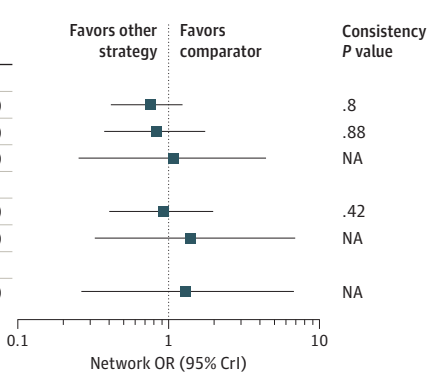
B Bronchopulmonary dysplasia

Comparison	Quality	No. of trials (No. of participants)	Direct OR (95% CrI)	Indirect OR (95% CrI)	Network OR (95% CrI)	Consistency *P* value
ICC (comparator)						
DCC	Moderate	11 (2208)	1.02 (0.69-1.37)	0.74 (0.36-1.58)	0.99 (0.70-1.28)	.43
UCM	Moderate	9 (702)	0.77 (0.47-1.23)	1.22 (0.64-2.24)	0.93 (0.62-1.32)	.23
UCM + DCC	Moderate	2 (399)	1.56 (0.84-2.88)	0 (0-0.10)[a]	1.39 (0.73-2.50)	.005
UCM (comparator)						
DCC	Moderate	5 (800)	0.90 (0.56-1.44)	1.44 (0.77, 2.66)	1.05 (0.74-1.53)	.23
UCM + DCC	Moderate	0 (0)	NA	1.50 (0.74, 3.08)	1.50 (0.74-3.08)	NA
DCC (comparator)						
UCM + DCC	Moderate	1 (67)	0 (0, 0.22)[b]	1.63 (0.85, 3.32)	1.42 (0.73-2.78)	.006



C Late onset sepsis

Comparison	Quality	No. of trials (No. of participants)	Direct OR (95% CrI)	Indirect OR (95% CrI)	Network OR (95% CrI)	Consistency *P* value
ICC (comparator)						
DCC	Moderate	10 (2001)	0.75 (0.39-1.25)	0.93 (0.15-6.10)	0.76 (0.41-1.24)	.8
UCM	Moderate	5 (259)	0.91 (0.31-2.91)	0.79 (0.09-4.81)	0.83 (0.37-1.76)	.88
UCM + DCC	Moderate	1 (199)	1.07 (0.25-4.50)	NA	1.07 (0.25-4.50)	NA
UCM (comparator)						
DCC	Moderate	3 (588)	1.19 (0.44-3.98)	0.61 (0.14-2.36)	0.92 (0.40-1.99)	.42
UCM + DCC	Moderate	0 (0)	NA	1.41 (0.32-7.06)	1.41 (0.32-7.06)	NA
DCC (comparator)						
UCM + DCC	Moderate		NA	1.29 (0.26-6.92)	1.29 (0.26-6.92)	NA



CrI indicates credible interval; DCC, delayed umbilical cord clamping; ICC, immediate umbilical cord clamping; NA, not available; OR, odds ratio; UCM, umbilical cord milking.

[a] Actual values are 2.4×10^{-9} (2.8×10^{-32}; 0.10).

[b] Actual values are 3.6×10^{-10} (7.1×10^{-28}; 0.22).

None of the previous reviews cited here have compared the various umbilical cord management strategies simultaneously. There were no significant differences among all strategies with regards to severe intraventricular hemorrhage. This is in contrast to previous traditional meta-analyses. The reasons for this could include higher sample size in our NMA, the use of a random-effects rather than a fixed-effects model for the meta-analysis, and the exclusion of randomized infants delivered by vaginal delivery from the trial by Katheria et al[67] in a previous meta-analysis.[79] In subgroup analyses, infants who received DCC had significant reductions in mortality (<33 weeks' gestation subgroup) or severe intraventricular hemorrhage (<29 weeks' gestation subgroup). These findings may be supportive of DCC as a preferred strategy vs UCM; however, we did not identify any specific outcome differences between DCC and UCM in network comparison.

This review has several strengths. In particular, the use of bayesian NMA enabled comparisons among currently used umbilical cord management strategies in preterm infants while increasing statistical power by taking advantage of indirect network pathways. This systematic review used robust methods guided by the Cochrane handbook[15] and the CiNEMA approach for appraising quality of evidence.[16] The bayesian statistical methods provided ranking probabilities and allowed comparison of all strategies simultaneously. The subgroup analysis assessed the robustness of the findings.

Limitations

Out study has a number of limitations. First, although this systematic review is, to our knowledge, the largest yet performed, the overall small sample sizes for most included studies (except 2 trials[21,69]), especially in infants of less than 29 weeks' gestation, limit the generalizability of our findings to this fragile and high-risk population. Second, the direct comparisons between UCM and DCC had smaller sample sizes than the optimal information sizes. Third, there were some differences in the baseline characteristics of included trials: mainly in the domains of gestational age; birth weight; variation in the technique for UCM (location, distance, number, speed, and allowance of refill); and variation in the timing of DCC. This prompted us to use a random-effects instead of a fixed-effects model for the meta-analysis as well as to conduct prespecified subgroup analyses. Fourth, only 4 studies across 4 interventions out of a total 56 trials reported long-term neurodevelopmental outcomes, providing very limited evidence.

Implications for Clinicians and Researchers

Based on the best available evidence, this systematic review and NMA identified the cord management strategies of DCC and UCM are significantly better than ICC for preventing certain morbidities. Delayed umbilical cord clamping is associated with significantly reduced mortality. We have categorically identified the utility of these strategies (DCC and UCM) for reducing the need for packed red cell transfusion in preterm infants. We identified no differences in any of the outcomes between DCC and UCM; however, considering concerns over the safety of UCM for extremely preterm infants in one study,[69] further well-designed, multicenter trials with adequate power comparing UCM and DCC are warranted. Until more evidence is available, DCC should be performed when it is feasible, and when it is not feasible owing to an immediate need for resuscitation, UCM may be considered as an alternative. The mortality advantage identified in this study for DCC could have significant implications worldwide, considering the simplicity of the intervention.

Conclusions

Compared with ICC, DCC was associated with the lower odds of mortality in preterm infants. Compared with ICC, DCC and UCM were associated with reductions in intraventricular hemorrhage and need for packed red cell transfusion. There was no significant difference between UCM and DCC for any outcome. Further studies directly comparing DCC and UCM are needed.

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Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: Jasani, Torgalkar, Ye, Shah.
Statistical analysis: Jasani, Torgalkar, Ye, Shah.
Administrative, technical, or material support: Shah.
Supervision: Jasani, Shah.

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