Pediatric RESEARCH

SYSTEMATIC REVIEW

Short-term efficacy of umbilical cord milking in preterm infants: systematic review and meta-analysis

Joshuan J. Barboza[1,2], Leonardo Albitres-Flores[2,3], Marco Rivera-Meza[2], Jaime Rodriguez-Huapaya[2], José Caballero-Alvarado[2,4], Vinay Pasupuleti[5] and Adrian V. Hernandez[6]

BACKGROUND: To systematically evaluate short-term efficacy of UCM versus other interventions in preterm infants.
METHODS: Six engines were searched until February 2020 for randomized controlled trials (RCTs) assessing UCM versus immediate cord clamping (ICC), delayed cord clamping (DCC), or no intervention. Primary outcomes were overall mortality, intraventricular hemorrhage (IVH), and patent ductus arteriosus (PDA); secondary outcomes were need for blood transfusion, mean blood pressure (MBP), serum hemoglobin (Hb), and ferritin levels. Random-effects meta-analyses were used.
RESULTS: Fourteen RCTs ($n = 1708$) were included. In comparison to ICC, UCM did not decrease mortality (RR 0.5, 95% CI 0.2–1.1), IVH (RR 0.7, 95% CI 0.5–1.0), or PDA (RR 1.0, 95% CI 0.7–1.5). However, UCM reduced need of blood transfusion (RR 0.5, 95% CI 0.3–0.9) and increased MBP (MD 2.5 mm Hg, 95% CI 0.5–4.5), Hb (MD 1.2 g/dL, 95% CI 0.8–1.6), and ferritin (MD 151.4 ng/dL, 95% CI 59.5–243.3). In comparison to DCC, UCM did not reduce mortality, IVH, PDA, or need of blood transfusion but increased MBP (MD 3.7, 95% CI 0.6–6.9) and Hb (MD 0.3, 95% CI −0.2–0.8). Only two RCTs had high risk of bias.
CONCLUSIONS: UCM did not decrease short-term clinical outcomes in comparison to ICC or DCC in preterm infants. Intermediate outcomes improved significantly with UCM.

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IMPACT:

- In 14 randomized controlled trials (RCTs), umbilical cord milking (UCM) did not reduce mortality, intraventricular hemorrhage, or patent ductus arteriosus compared to immediate (ICC) or delayed cord clamping (DCC).
- UCM improved mean blood pressure and hemoglobin levels compared to ICC or DCC. In comparison to ICC, UCM reduced the need for blood transfusion.
- We updated searches until February 2020, stratified by type of control, and performed subgroup analyses.
- There was low quality of evidence about clinical efficacy of UCM. Most of RCTs had low risk of bias.
- UCM cannot be recommended as standard of care for preterm infants.

INTRODUCTION

Umbilical cord milking (UCM) is a procedure involving a quick "stripping" of blood from the umbilical cord of a newborn, usually within 20 s.[1] In preterm infants, the recommended approach is to perform delayed cord clamping (DCC) instead of immediate cord clamping (ICC), to avoid delaying any procedure.[2] After birth, blood flow in the umbilical cord usually continues for a few minutes. Additional blood is transferred from mother to baby during this time, known as placental transfusion.[3] UCM could be a suitable alternative to placental blood transfusion without delaying the procedures in the delivery room. The main benefit of UCM is gain of hemoglobin (Hb), which avoids the appearance of anemia in premature babies[4]: 39% fewer transfusions have been shown for anemia, 41% fewer patients with intraventricular hemorrhage (IVH), and 38% fewer patients with necrotizing enterocolitis.[5]

A few systematic reviews have assessed the efficacy of UCM. The study by Nagano et al.[6] in 2018 assessed the benefits of UCM compared to DCC in 255 preterm infants. They found that UCM decreased IVH cases compared to DCC. These authors found no significant effects of UCM on mortality hematocrit level, need of transfusion, Hb level at birth, and other secondary outcomes; however, the study only included two randomized controlled trials (RCTs). Al-Wassia and Shah[7] in 2014 assessed efficacy and safety of UCM at birth in 217 preterm infants from seven RCTs; they concluded that there no statistically significant difference in mortality with UCM compared with DCC or ICC in preterm infants. Authors found that Hb and hematocrit increased in UCM compared to DCC or ICC in preterm infants. Dang et al.[8] in 2015 found that necrotizing enterocolitis, IVH, mortality, and need of transfusion were less with UCM than with ICC in 292 preterm infants from six RCTs.

[1]Unidad de Revisiones Sistemáticas y Meta-análisis (URSIGET), Vicerrectorado de Investigacion, Universidad San Ignacio de Loyola (USIL), Lima, Peru; [2]TAU-RELAPED Group, Trujillo, Peru; [3]Facultad de Medicina, Universidad Nacional de Trujillo, Trujillo, Peru; [4]Escuela de Postgrado, Universidad Privada Antenor Orrego, Trujillo, Peru; [5]ProEd Communications, Inc, Cleveland, OH, USA and [6]Health Outcomes, Policy, and Evidence Synthesis (HOPES) Group, University of Connecticut School of Pharmacy, Storrs, CT, USA
Correspondence: Joshuan J. Barboza (jbarbozameca@relaped.com)

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These authors also found that initial Hb was increased with UCM than with ICC.

We systematically assessed the efficacy of UCM compared with ICC, DCC, or no intervention in preterm infants. Our study aimed to evaluate the efficacy of UCM compared to each clamping technique and not overall as existing systematic reviews. Also, we evaluated subgroup analyses for key baseline patient and study characteristics.

METHODS

Our systematic review was reported in accordance to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[9]

Data sources

We performed searches in Pubmed, Scopus, Web of Science, Ovid-Medline, Cochrane Central, and EMBASE from inception to February 10, 2020. We selected abstracts of RCTs evaluating preterm infants and where the primary intervention was UCM compared to ICC, DCC, or no intervention. There was no limit by year of publication. Case reports, editorials, narrative reviews, and meta-analyses were excluded.

Study selection

Two authors (J.J.B., J.C.-A.) independently reviewed titles and abstract content according to inclusion and exclusion criteria. Relevant studies were selected and full texts were searched for further evaluation. Discrepancies in selections were consulted with a third author (A.V.H.), and consensus was reached. Selected articles were stored in the Endnote X9 software.

Outcomes

Primary outcomes were overall mortality, patent ductus arteriosus (PDA), and IVH. Secondary outcomes were need for blood transfusion, mean blood pressure (MBP), Hb and ferritin levels, need of inotropes, peak bilirubin, and duration of phototherapy. We used definitions given by the authors of original RCTs.

Data extraction

Two authors (J.J.B., J.C.-A.) independently extracted data using predefined forms. Disagreements were resolved by consensus, and a third author (A.V.H.) was consulted if needed. Extracted data were: first author, year, study design, country(ies), number of participants, type of intervention, type of control, birth weight, gestational age, APGAR at 1 and 5 min, mortality, PDA, IVH, Hb, serum ferritin, MBP, need for inotropes, peak bilirubin and duration of phototherapy, and need for blood transfusion.

Assessment of risk of bias

RCTs were assessed using the Cochrane risk of bias tool.[10] This tool evaluates seven items: generation of random sequence (selection bias), allocation concealment (selection bias), blinding of participants and researchers (performance bias), blinding of outcome assessment (detection bias), blinding and incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. Two reviewers (J.J.M., J.C.-A.) independently assessed the risk of bias by classifying each item separately as low, uncertain, or at high risk of bias. An RCT with high risk of bias in any of the items of randomization or blinding was considered as high risk of bias.

Statistical analyses

Random-effects models and the inverse variance method were used for all meta-analyses. Effects of UCM were described with relative risks (RRs) and mean differences (MDs) with their 95% confidence intervals (95% CIs) for dichotomous and continuous outcomes, respectively. Heterogeneity among studies was investigated using the I^2 statistic: 0–30% meant low, 30–60% moderate, and >60% high heterogeneity. We performed subgroup analyses by birth weight (<1500 g versus ≥1500 g), follow-up time (<12 h versus ≥12 h), and gestational age (<32 versus ≥32 weeks) for both primary and secondary outcomes. We also performed sensitivity analyses for the primary outcomes using fixed-effects models and the Mantel–Haenzel method due to the expected paucity of events per arm (i.e., <10% incidence of dichotomous outcomes). The *metabin* and *metacont* functions of the meta library of R 3.5.1 were used (www.r-project.org).

Ethical considerations

This is a systematic review of published and open information where no human subjects participated. Approval from an IRB/ethics committee was not necessary.

RESULTS

Study selection

A total of 3885 abstracts of RCTs were identified in databases; 1762 duplicate abstracts were removed. Of the 2123 screened abstracts, 2087 were excluded. Thus 36 full-text studies were assessed for eligibility. Twenty-two studies were excluded owing to the following reasons: outcomes different from outcomes of interest in 2 studies, different populations in 4 studies, non-RCTs in 2, conference abstracts in 13 studies, and Chinese language in 1 study (Fig. 1). We therefore included 14 RCTs.[11–24]

Characteristics of the included RCTs

Main characteristics of included RCTs are summarized in Table 1. A total of 1708 premature infants were evaluated. Patients included in these trials were vigorous preterm infants. All trials were conducted between 2008 and 2019 and compared UCM and ICC or DCC. With respect to the UCM process across all trials, preterm infants were placed at or below the level of the placenta, and about 20 cm of the cord was milked toward the umbilicus three times before clamping. Speed of milking was approximately 10 cm/s. Ten RCTs assessed the UCM compared to ICC,[11,13–15,17–21,23] four RCTs assessed the UCM compared to DCC in preterm infants,[12,16,22,24] and one study assessed both ICC and DCC.[21] Mean age was 29.6 gestational weeks, and mean birth weight was 1286 g. Follow-up ranged from 12 h since birth to 6 weeks since birth. Seven trials measured outcomes before 12 h from birth,[11,13,15–17,20,24] while 7 other studies measured outcomes ≥12 h.[12,14,18,19,21–23] Eleven studies reported weights <1500 g,[11,13–16,18–22] and 3 studies reported weights ≥1500 g.[17,23,24] Ten studies reported gestational age <32 weeks,[11–16,18,20–22] and four studies reported gestational age ≥32 weeks.[17,19,23,24]

Risk of bias assessment

Overall, two trials had high risk of bias[12,16]: one trial showed high risk of selection bias (random sequence generation),[16] another trial showed high risk of performance bias (blinding of participants and staff).[12] Four trials showed high risk for attrition bias.[13,17,23,24] Regarding selection, detection, reporting, and other biases, all other trials showed either low or unclear risk of bias (Supplementary Fig. S1).

Effect of UCM on primary outcomes

UCM did not reduce overall mortality in comparison to ICC (RR 0.5, 95% CI 0.2–1.1, $p = 0.07$, $I^2 = 0\%$) or DCC (RR 1.0, 95% CI 0.6–1.6, $p = 0.9$, $I^2 = 0\%$). UCM compared ICC or DCC did not reduce overall mortality (RR 0.8, 95% CI 0.5–1.2, $p = 0.2$, $I^2 = 0\%$; Fig. 2a). UCM did not reduce IVH in comparison to ICC (RR 0.7, 95% CI 0.5–1.0, $p = 0.05$, $I^2 = 0\%$) or DCC (RR 0.9, 95% CI 0.6–1.3, $p = 0.6$, $I^2 = 0\%$). UCM compared to ICC or DCC did not reduce IVH (RR 0.8, 95% CI 0.7–1.1, $p = 0.1$, $I^2 = 0\%$; Fig. 2b). UCM did not reduce PDA in comparison to ICC (RR 1.0, 95% CI 0.7–1.5, $p = 1.0$, $I^2 = 23\%$) or DCC (RR 0.7, 95% CI 0.4–1.2, $p = 0.2$, $I^2 = 0\%$). UCM compared ICC

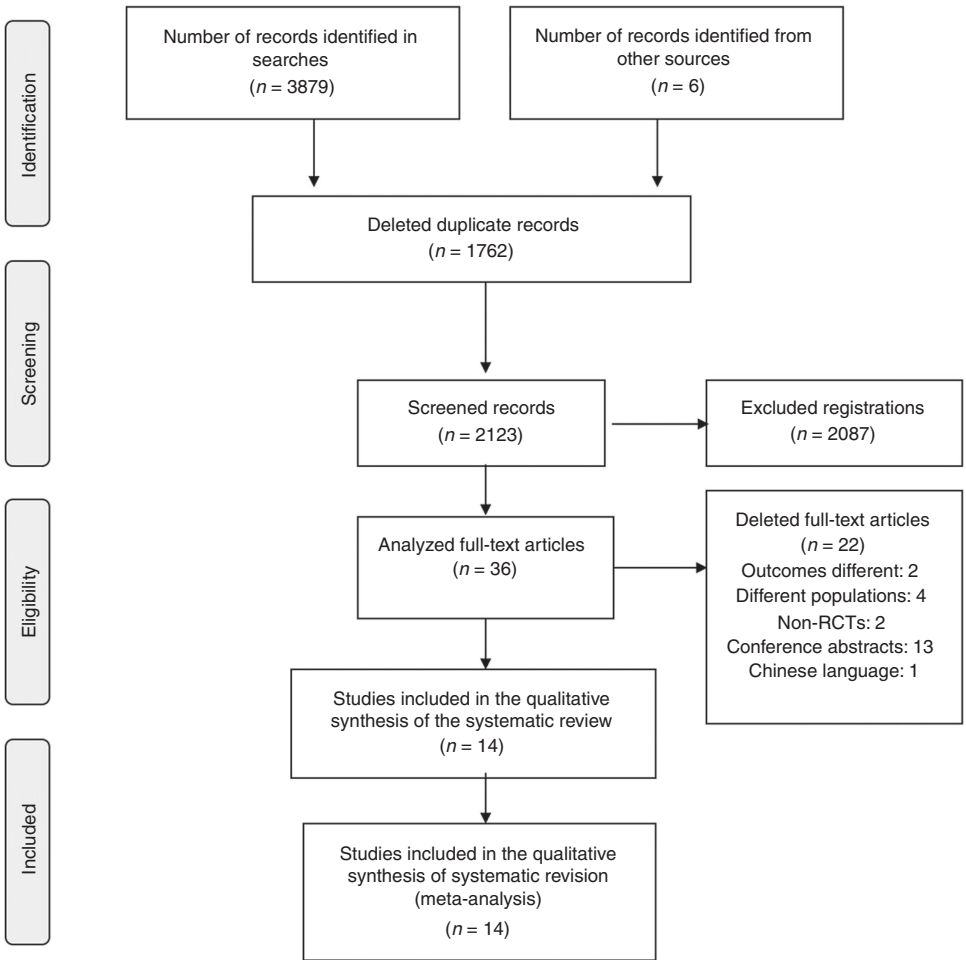

Fig. 1 Flow chart of the study selection process. PRISMA flow diagram with process of identification, screening, eligibility and included studies in systematic review *n* number of studies.

or DCC did not reduce PDA (RR 0.9, 95% CI 0.7–1.2, $p = 0.5$, $I^2 = 5.1\%$; Fig. 2c).

Effects of UCM on secondary outcomes

In comparison to ICC, UCM significantly reduced the need of blood transfusion (RR 0.5, 95% CI 0.3–0.9, $p = 0.01$, $I^2 = 0\%$). However, UCM did not reduce the need of blood transfusion in comparison to DCC (RR 1.0, 95% CI 0.6–1.6, $p = 1.0$, $I^2 = 64\%$). UCM compared ICC or DCC did not reduce the need of blood transfusion (RR 0.8, 95% CI 0.6–1.2, $p = 0.3$, $I^2 = 46\%$; Fig. 3a). UCM significantly increased MBP in comparison to ICC (MD 2.5, 95% CI 0.5–4.5, $p = 0.03$, $I^2 = 60\%$) or DCC (MD 3.7, 95% CI 0.6–6.9, $p = 0.02$, $I^2 = 0\%$). UCM compared ICC or DCC significantly increased MBP (MD 2.6, 95% CI 1.0–4.2, $p = 0.00$, $I^2 = 43.1\%$; Fig. 3b). UCM significantly increased Hb in comparison to ICC (MD 1.2 g/dL, 95% CI 0.8–1.6, $p < 0.0001$, $I^2 = 42.5\%$) or DCC (MD 0.3 g/dL, 95% CI −0.2 to 0.8, $p = 0.2$, $I^2 = 23\%$). UCM compared ICC or DCC significantly increased Hb (MD 0.9 g/dL, 95% CI 0.5–1.3, $p < 0.0001$, $I^2 = 62.9\%$; Fig. 3c). Finally, in comparison to ICC, UCM significantly increased serum ferritin (MD 151.4 ng/dL, 95% CI 59.5–243.3, $p = 0.001$, $I^2 = 71\%$). There were no ferritin data available for the comparison of UCM versus DCC (Fig. 3d).

Other secondary outcomes such as need for inotropes, peak bilirubin, and duration of phototherapy were not affected by UCM (Supplementary Fig. 2a–c).

Subgroup analyses

Subgroup analyses by birth weight, follow-up time, and gestational age for both primary and secondary outcomes did not show differences with the overall analyses for primary and secondary outcomes (Supplementary Figs. S3–S42).

Sensitivity analyses

Effects of the primary outcomes were similar to main analyses when using fixed-effects models with Mantel–Haenzel method (Supplementary Figs. S43–S45).

DISCUSSION

Main findings

In this systematic review, we did not find a reduction of overall mortality, IVH, or PDA with UCM when compared with ICC or DCC in premature infants. However, UCM reduced the need of blood transfusion and increased MBP and Hb levels when compared with ICC or DCC. In comparison to ICC, UCM increased ferritin levels. Heterogeneity of effects was low for clinical outcomes and moderate to high for secondary outcomes. Subgroup and sensitivity analyses provided similar results to main analyses.

What is known in the literature about the research question?

Hb values may increase in the UCM group, as UCM provides blood volume to a 2-min delay in cord clamping in newborns as measured by residual placental blood volume.[25] In uterus, one-third of the fetus's blood volume is in the placenta at any one time. At birth, a major shift occurs in the cardiac output to the lungs—changing from 8% to 10% in fetal life to 50% in neonatal life. This shift requires a rapid increase of blood volume to fill the

Table 1. Baseline characteristics of included randomized controlled trials.

Author (reference)	Country	Length of follow-up	Sample size	Gestational age, in weeks (SD)	Birth weight, in g (SD)	UCM details	Control details	Evaluated outcomes
Finn et al.[21]	Ireland	12 h since birth	30	28.4 (5.4)	930 (1180)	Cord milking at or below the level of the placenta and an assistant stripped the cord, 20 cm over 2 s, 3 times in the direction of the infant	ICC: immediate cord clamping was defined as clamping the umbilicus within 20 s of delivery DCC: cord was clamped at 60 s after delivery	EEG and cerebral NIRS
Katheria et al.[22]	United States of America	12 h since birth	474	28.4 (2.4)	—	Umbilical cord was milked during approximately 2 s allowing refill and then repeating 3 more times	Hold the infant below the level of the incision for at least 60 s in warm, sterile towels	Death or severe intraventricular hemorrhage
Shirk et al.[24]	United States of America	24 h since birth	204	32.1 (1.5)	1579 (576)	Manual milking or stripping of approximately 20 cm of umbilical cord from the placental end to the infant's umbilicus 4 times	DCC: umbilical cord was clamped <60 s after delivery	Transfusion risk, NEC, IVH, survival, and composite morbidity variables
Lago Leal et al.[23]	Spain	6 months since birth	138	33.4 (3.1)	1816 (637)	Nearly 20 cm of the umbilical cord were vigorously milked toward the umbilicus four times before clamping the cord	ICC: umbilical cord was clamped <20 s after delivery	Requirement of PRBC or phototherapy
El-Naggar[20]	Canada	12 h since birth	73	27.2 (2)	1061 (383)	Manual milking or stripping of approximately 20 cm of umbilical cord from the placental end to the infant's umbilicus 4 times	ICC: umbilical cord clamped within 10 s of birth as per standard practice at that time	Systemic blood flow as represented by echo-derived superior venacava (SVC) flow at 4–6 h after birth
Mohan et al.[19]	Canada	72 h since birth	60	33 (2.2)	1400 (876.6)	Milked from the cut end toward the baby 3 times with a speed of 10 cm/s and clamped at 2–3 cm by the end of initial steps	ICC: umbilical cord clamped within 10 s of birth as per standard practice at that time	Hemoglobin and serum ferritin at 6 weeks of life
Song[18]	Korea	28 days since birth	66	30.1 (2.5)	1256 (270.8)	Milked the umbilical cord from the placenta toward the neonate 4 times at a speed of 20 cm/2 s before clamping the cord	ICC: the cord was immediately clamped after the baby was delivered	Hematological parameters and mortality
Kumar et al.[17]	India	6 weeks since birth	200	34.5 (1.5)	2397 (268)	Cord was held upright and milked thrice toward baby at a speed of 10 cm/s, and then clamped at 2–3 cm from umbilicus	ICC: cord was clamped and cut immediately at 2–3 cm from umbilicus	Hemoglobin and serum ferritin at 6 weeks of age
Katheria et al.[16]	United States of America	24 h since birth	154	28 (2)	1255 (413)	The cord was pinched as close to the placenta as possible and milked toward the infant over a 2-s duration	DCC: waiting at least 45 s before clamping the cord	Mortality, hemodynamics values, and morbidity
Katheria[15]	United States of America	42 days since birth	60	28 (3)	1170 (356)	Having the assistant milk about 20 cm of umbilical cord over 2 s (counting aloud), repeating 2 additional times	ICC: cord was clamped and cut immediately at birth	Mortality, hemodynamics values, and morbidity
Alan[14]	Turkey	28 days since birth	44	22.4 (1.8)	1103 (236)	Milked vigorously toward the umbilicus for 3 times at a speed of approximately 5 cm/s	ICC: immediate cord clamping	Number and volume of PRBC transfusions received by the infant during the first 35 days of life
March et al.[13]	Spain	28 days since birth	75	26.3 (0.6)	755 (91.4)	Nearly 20 cm of the umbilical cord was actively milked toward the umbilicus three times before clamping the cord	ICC: cord clamped and cut immediately after delivery	Need for red blood cell transfusion in the first 28 days of life

Table 1. continued

Author (reference)	Country	Length of follow-up	Sample size	Gestational age, in weeks (SD)	Birth weight, in g (SD)	UCM details	Control details	Evaluated outcomes
Rabe et al.[12]	UK	42 days since birth	58	29.5 (2.7)	1235 (468)	Cord being milked toward the neonate four times at a speed of 20 cm/2 s	DCC: the umbilical cord then was clamped at 30 s	Neonatal blood hematocrit and hemoglobin at 1 h after birth
Hosono[11]	Japan	36 h since birth	40	26.6 (1.2)	836 (223)	Cord was vigorously milked toward the umbilicus two to three times before clamping the cord. Milking speed was about 20 cm per 2 s	ICC: cord was clamped and cut immediately at birth	Measure was the probability of not needing transfusion

UCM umbilical cord milking, *ICC* immediate cord clamping, *DCC* delayed cord clamping, *PDA* patent ductus arteriosus, *IVH* intraventricular hemorrhage, *NEC* necrotizing enterocolitis, *PRBC* packed red blood cells, *SD* standard deviation, *EEG* electroencephalogram *NIRS* cerebral near infrared spectroscopy.

capillary beds surrounding each alveolus to assist with lung tissue recruitment and expansion.[26] The placenta serves as the blood reservoir designed to meet this immediate demand for increased blood volume. UCM supports placental transfusion and results in a 20–30% increase in whole blood and a 50–60% increase in red blood cell volume.[27] If the umbilical cord is clamped before an adequate placental transfusion has been achieved, a significant blood volume might be withheld causing hypoperfusion. UCM increases systemic blood volume, stabilize cerebral oxygenation and perfusion, and consequently decrease the incidence of IVH.[28]

There have been three previous systematic reviews with meta-analyses evaluating the effect of UCM in comparison to ICC or DCC in preterm infants.[6–8] The systematic review by Al-Wassia and Shah in 2014 in 7 trials ($n = 217$ preterm infants) assessed the efficacy and safety of UCM in comparison to ICC, DCC, or no intervention.[7] These authors evaluated the effects of UCM on several clinical and intermediate outcomes (Supplementary Table S1). They found that preterm infants with a gestational age < 33 weeks allocated to UCM compared with control showed no difference in the risk of overall mortality. These authors also found decreased oxygen requirements at 36 weeks and IVH risk and higher levels of Hb and hematocrit in the UCM groups.

A second systematic review by Dang et al. in 2015 in 6 trials ($n = 292$ preterm infants) evaluated our same question.[8] Their primary outcome was need of blood transfusion, and several other outcomes were evaluated (Supplementary Table S1). They found that there was a decrease in the incidence of transfusion in the UCM group compared to the ICC group. These investigators also found that necrotizing enterocolitis, IVH, and overall mortality were less likely to occur in the UCM group compared to the ICC group; also, that Hb was higher in the UCM group compared to the ICC group.

Finally, the study performed by Nagano et al. in 2018 assessed the benefits of UCM versus DCC in 2 trials ($n = 255$ preterm infants) (Supplementary Table S1). These investigators found that UCM decreased IVH compared to DCC.[6] They found no difference in overall mortality risk, hematocrit level, Hb at birth, serum bilirubin, polycythemia, duration of phototherapy, necrotizing enterocolitis, oxygen dependence, sepsis, and length of hospital stay in the UCM groups in comparison to DCC.

What our study adds to the literature

In comparison to the three previous systematic reviews[6–8] (Supplementary Table S1), we searched six engines, and previous studies did not search Ovid-Medline and Web of Science. All studies used Cochrane Central database, Medline, and EMBASE. The number of databases is essential, because it involves a more significant discovery of information, abstracts, and texts for the systematic review process. Although there is no standard number for the databases to use, the Cochrane Collaboration recommends using at least three essential databases (Scopus, EMBASE, and Medline); however, the databases also depend on the type of study to be carried out and the topic or scenario in which it is going to developed.

Our study assessed the efficacy of UCM compared with ICC or DCC in preterm infants. In contrast to other studies, our study approached each control separately and also reported results for ICC and DCC together. This separate analysis of each control is important, since differences in the effects have been found for each control in each of the outcomes. It is essential to know which cord intervention techniques may have significant influence on evaluated outcomes. Although some studies report that UCM is the most effective alternative to DCC in the hemodynamic state of prematurity[16,22,24] and that it is an alternative procedure to avoid perinatal complications, only one study reported that DCC has similar effects on mortality [RR 2.14, 95% CI 0.93–4.93], IVH [RR 1.32, 95% CI 0.55–3.17], and Hb within first 24 h of birth [MD −0.20 mg/dL, 95% CI 1.57–1.17], than to applying UCM in

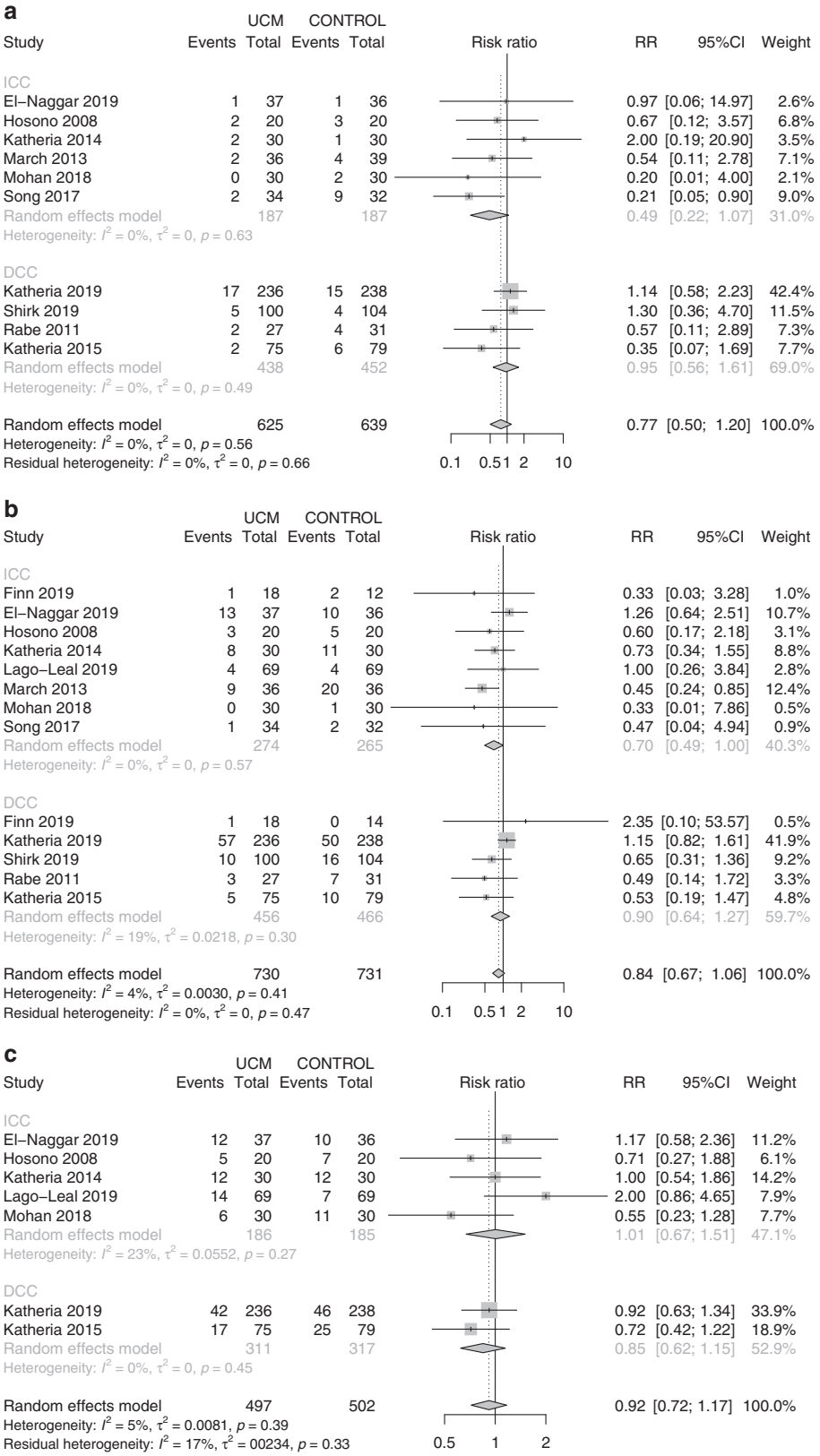

Fig. 2 Forest plot by control (ICC and DCC) for primary outcomes. Effect of UCM on primary outcomes by type of controls: **a** overall mortality, **b** IVH, and **c** PDA. ICC Inmediate cord clamping; DCC Delayed cord clamping; RR Relative risk.

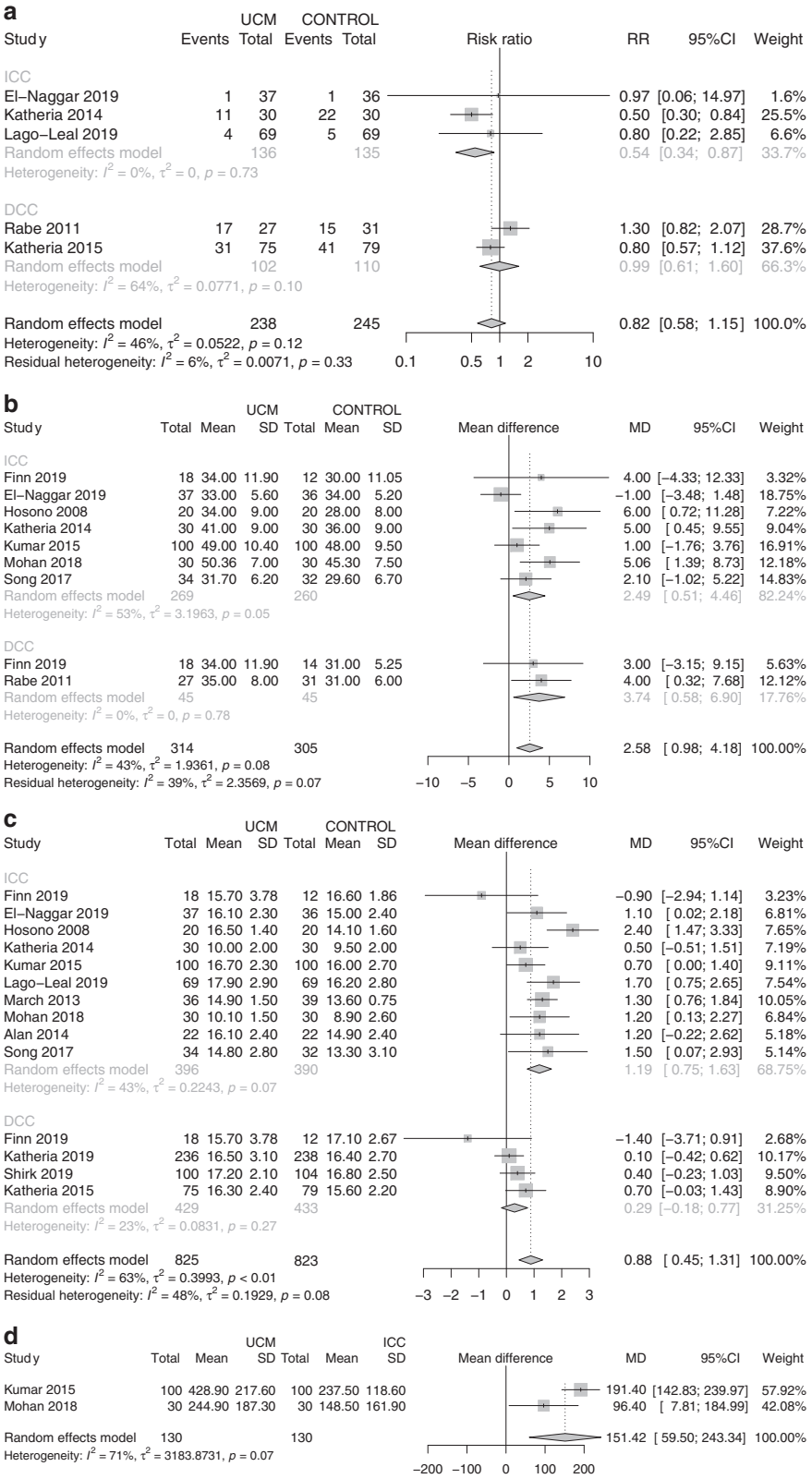

Fig. 3 Forest plot by control (ICC and DCC) for secondary outcomes. Effects of UCM on secondary outcomes by type of controls: **a** need for transfusion, **b** MBP in mm Hg, **c** Hb in g/dL, and **d** Ferritin in ng/mL. ICC Inmediate cord clamping; DCC Delayed cord clamping; RR Relative risk.

premature infants.[12] In a systematic review conducted by Fogarty et al.[29] in 2018 analyzing 18 RCTs of preterm infants, mortality was lower in the DCC group compared to ICC [RR, 0.68, 95% CI, 0.52–0.90]. The mechanism of reduced mortality with DCC is not known, but its positive effects on blood transfusions and blood pressure stability seem to suggest that the benefits are hemodynamic. Also, Fogarty et al. found that DCC had larger effect on the number of infants receiving a later blood transfusion

[RR 0.81, 95% CI 0.74–0.87] and peak hematocrit [MD 2.73%, 95% CI 1.94–3.52] in comparison to ICC.

There were worse outcomes for the extremely preterm population in Katheria et al.[13] The test for interaction between gestational age strata and treatment group was significant for severe IVH only ($p = 0.003$); among infants born at 23–27 weeks' gestation, severe IVH was statistically significantly higher with UCM than with delayed umbilical cord clamping (22% [20/93] versus 6% [5/89], respectively; risk difference, 16% [95% CI 6–26%]; $p = 0.002$).

Physiological effects of UCM with and without placental refill in comparison to ICC and physiological-based cord clamping (PBCC) were evaluated by Blank et al.[30] in preterm lambs. Authors found that UCM in preterm lambs caused considerable hemodynamic disturbances in carotid artery blood flow and systemic blood pressure without increasing pulmonary blood flow. Neither UCM without placental refill nor PBCC resulted in a placental transfusion, whereas UCM with placental refill did. Finally, cerebral oxygenation decreased the least in PBCC lambs in comparison to other interventions. In line with our conclusions, authors suggested that further review of UCM is warranted before adoption into routine clinical practice.

Our study performed meta-analyses with random-effects meta-analyses using the inverse variance method. Al-Wassia et al.[7] performed meta-analyses with fixed-effects models and Mantel–Haenzel method. Dang et al.[8] performed meta-analyses with random-effects models and Mantel–Haenzel method. Nagano et al.[6] performed meta-analyses with fixed-effects models and Mantel–Haenzel method. All studies analyzed a small number of RCTs, so the random-effects model was suitable for analysis. The generalized use of DerSimonian–Laird heterogeneity variance estimator in random-effects meta-analysis is not recommended because it produces estimates with a more negative bias than most other methods in odds ratio meta-analyses with small studies or rare events and, to a lesser extent, in standardized mean difference meta-analyses with small studies.[31] However, all studies applied DerSimonian–Laird variance methods in their analyses. Our study applied inverse variance method with random effects, with the Paule–Mandel variance method. This method is often approximately impartial when DerSimonian–Laird is negatively biased.[32] However, the results also showed that Paule–Mandel has a high positive bias when there are large differences in study size, which was not found in our study.

The prevalence of mortality reported was lowest in Al-Wassia et al. study in the ICC groups than in the other systematic reviews performed, including our study (8% in Al-Wassia et al. versus 17% in our study). Our study reported lower mortality prevalence for the DCC group compared to the study by Nagano et al. (10% in Nagano et al. versus 5% in our study). Mean Hb values found in this study were higher compared to our findings; however, our study included fewer UCM versus DCC trials. This study is different than ours because they evaluated the risk for oxygen requirement at 36 weeks in patients with UCM compared to DCC. However, our study added PDA assessment and analyzed two different comparison groups, such as UCM versus ICC and versus DCC. Dang et al. found significant effects on more outcomes, including mortality and IVH, compared to our study. This study reported a considerably lower effect on the need for transfusion compared to our study. Also, this study reported higher Hb value compared to our study. In comparison to Nagano et al., our study approached more controls and studies. Compared to our study, this review found significant effects on the reduction of IVH in UCM versus DCC, whereas our study had a non-significant effect.

We performed subgroup analyses by birth weight, follow-up time, and gestational age for both primary and secondary outcomes. Only the Dang et al.[8] study performed subgroup analyses by clinical characteristics identified in the studies but did not report their results as subgroups. We also performed sensitivity analyses for the primary outcomes using fixed-effects models and Mantel–Haenzel method. No other study performed sensitivity analyses.

Limitations

Our study had some limitations. First, there was substantial methodological heterogeneity across trials, associated with different sample sizes, types of evaluated outcomes, and methods of analyses. Second, there was high heterogeneity in the effects of our secondary outcomes. However, subgroup analyses of secondary outcomes by birth weight, gestational age, and follow-up time gave similar effects to main analyses. Third, it was not possible to evaluate outcomes at longer follow-up. Fourth, risk of bias was high in two trials, particularly due to lack of correct randomization and blinding methods. Finally, the total sample of preterm infants was relatively small.

CONCLUSIONS

UCM did not affect overall mortality, IVH, or PDA in preterm infants in comparison to ICC or DCC. UCM increased MBP and Hb and decreased the need of blood transfusions in preterm neonates in comparison to ICC or DCC. Additional RCTs assessing the impact of UCM on clinical outcomes are necessary to reach higher confidence in these beneficial effects.

AUTHOR CONTRIBUTIONS

J.J.B. and A.V.H.: conception and design of the study, acquisition of data, analysis and interpretation of data, writing of the article, critical review of the article, approval of the final version. L.A.-F., M.R.-M., J.R.-H., J.C.-A., and V.P.: acquisition of data, critical review of the article, approval of the final version.

ADDITIONAL INFORMATION

The online version of this article (https://doi.org/10.1038/s41390-020-0902-x) contains supplementary material, which is available to authorized users.

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