Effects of placental transfusion in extremely low birthweight infants: meta-analysis of long- and short-term outcomes

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BACKGROUND: Risks and benefits of increasing placental transfusion in extremely preterm infants (extremely low birthweight [ELBW], <1000 g) are ill defined. We performed a meta-analysis to compare long- and short-term outcomes of ELBW infants in trials of enhanced placental transfusion regimens.

STUDY DESIGN AND METHODS: We conducted a meta-analysis of randomized controlled trials (RCTs) of delayed umbilical cord clamping or umbilical cord milking in compliance with PRISMA and Cochrane Collaborative guidelines for systematic reviews. We searched multiple databases for medical literature up to December 2012. Inclusion criteria were preterm infants less than 30 weeks and less than 1000 g birthweight, randomly assigned to enhanced placental transfusion (either delayed cord clamping or cord milking) versus immediate cord clamping. The primary outcome was standardized neurodevelopmental outcome at 18 to 24 months corrected age using a standardized scale. Several short-term outcomes were also evaluated as secondary variables.

RESULTS: We found 19 studies of which 10 studies could be included (n = 199). Three reported neurodevelopmental outcomes, none of which showed significant rates of disability. Two reported these at 18 to 24 months (n = 42) but used different scales preventing pooling. Short-term benefits of enhanced placental strategies included better blood pressure and hemoglobin on admission, along with reduced blood transfusions, a trend to reduced intraventricular hemorrhage, and episodes of late-onset sepsis.

CONCLUSIONS: Strategies to enhance placental transfusion may improve short-term outcomes of ELBW infants. However, paucity of data on neurodevelopmental outcomes and safety concerns tempers enthusiasm for these interventions. Appropriately designed RCTs to assess short-term and long-term outcomes are needed in ELBW infants.

Although Aristotle first advocated delayed umbilical cord clamping (DCC) in ancient Greece,[1] the current prevailing obstetric practice is for immediate cord clamping (ICC) in term and preterm infants. Recent recommendations from the American College of Obstetricians and Gynecologists now recommend a 1-minute delay for preterm infants "when feasible." In term infants, data strongly support the benefits of DCC, especially in the developing world, where

ABBREVIATIONS: BW = birthweight; DCC = delayed cord clamping; ELBW = extremely low birthweight; ICC = immediate cord clamping; IVH = intraventricular hemorrhage; NICU = neonatal intensive care unit; RCT = randomized controlled trial; UCM = umbilical cord milking.

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iron deficiency is a major health problem.[2,3] Correspondingly, DCC for 1 minute in term infants who do not require resuscitation is recommended by the 2011 International Consensus on Cardiopulmonary Resuscitation.[4] However the World Health Organization points out that "longer-term neonatal and infant outcomes, such as neurodevelopment, need to be evaluated."[3] A recent Cochrane review shows short-term benefits of DCC[5] for preterm infants less than 37 weeks. However, morbidities and outcomes vary greatly over this broad gestation age range. While some obstetricians and neonatologists support DCC for the larger and older preterm infants, many emphasize that the need for immediate support of the extremely low birthweight (ELBW) infant outweighs the potential benefits of DCC.[6]

A placental transfusion occurs during DCC when infants are held below the introitus or below the level of the uterus at cesarean section for a variable period, usually greater than 20 seconds. An alternative faster method of promoting placental transfusion is umbilical cord milking (UCM), which takes about 5 to 10 seconds.[7,8]

Since the birth of an ELBW infant less than 1000 g birthweight (BW) is often more emergent, compared to larger preterm infants, there is potential for serious short-term acuity. Moreover longer-term neurodevelopment impairment is significant. In a recent systematic review, the long-term range of serious neurodevelopment disability rates for surviving ELBW infants at 18 to 24 months ranges between 12.56 and 57.5%.[9] Placental transfusion via DCC or UCM increases hemoglobin (Hb) levels, which although not affecting short-term outcomes at discharge[10] may improve neurodevelopmental outcome.[11] Providing evidence that DCC or UCM could improve both short- and long-term outcomes for the ELBW neonate would strengthen the rationale for their use in the delivery room for the tiniest infants. We therefore wished to summarize in a meta-analysis available neurodevelopmental outcome of ELBW infants exposed to either DCC or UCM in a randomized controlled trial (RCT) compared to conventional ICC.

MATERIALS AND METHODS

Aims

Our primary aim was to obtain an estimate of long-term neurodevelopmental outcomes (as defined below) of DCC and/or UCM in ELBW (<1000 g at birth) preterm neonates (<30 weeks' gestation). A secondary aim was to examine shorter-term clinical outcomes during the neonatal intensive care unit (NICU) stay including the number of blood transfusions, Hb on admission, and number of days on a ventilator. DCC consisted of a greater than 20-second delay. UCM comprised of milking the cord toward the infant two to three times before clamping.

Design and methods

A systematic search was performed from May 2011 to December 2012 using the search engines MEDLINE, EMBASE, and CINAHL. The Cochrane Collaborative guidelines for systematic reviews and the PRISMA guidelines for meta-analyses were followed. No language restriction was adopted. Two independent investigators (SG, DB) used predetermined search terms, including "umbilical cord clamping and low birth weight," and "umbilical cord clamping and preterm or premature." The investigators also independently examined relevant cross-referenced papers. Additional information was requested from authors if necessary. Studies were eligible for inclusion if they were randomized or quasi-RCTs and enrolled preterm infants less than 30 weeks' gestation and less than 1000 g BW. Observational studies or those RCTs where weight-differentiated data were not available were excluded.

Data extracted and outcome measures

Two observers extracted data including type of delivery (cesarean section vs. vaginal delivery) and the experimental placental strategy maneuver used (DCC or UCM). Data were obtained for all neonates less than 30 weeks and less than 1000 g from authors in which studies included a mixed cohort of neonates (both eligible and noneligible neonates).

The primary outcome for this study was any standardized long-term neurodevelopmental outcome. We were primarily interested in studies at 18 to 24 months corrected age, allowing comparisons to a normative population. However, we did include studies that assessed neurodevelopment at an earlier assessment age. While the Bayley II or III was our preference,[12] we included studies using other standardized scales. Secondary outcomes were defined a priori and included Hb and hematocrit (Hct) on admission; number of blood transfusions; intraventricular hemorrhage (IVH); mean, systolic, and diastolic blood pressures; number of days on mechanical ventilation; and episodes of sepsis.

Statistical analysis

Statistical analysis was performed using the computer software (RevMan, Version 5.0 for Windows, Cochrane Collaboration, Oxford, UK). For continuous variables, the weighted mean differences and 95% confidence intervals (CIs) were calculated. For categorical variables, odds ratios (ORs) are reported.

RESULTS

Two searchers (SG, DB) identified 19 potential studies of which 10 could be included, with good agreement on inclusion and exclusion ($\kappa = 0.93$; Fig. 1). Of the nine excluded studies, three[13-15] did not recruit patients less than 1000 g. These excluded trials included 110 patients

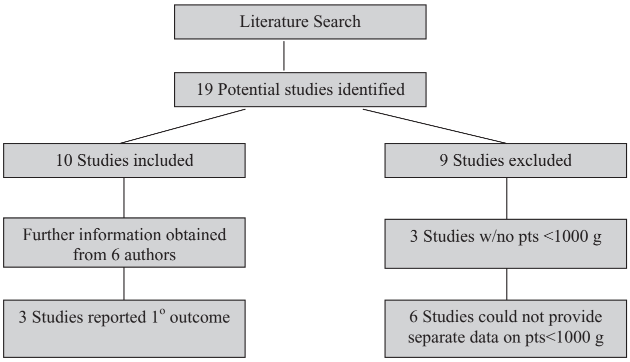


Fig. 1. Retrieval of relevant eligible articles: breakdown of all articles retrieved by the search.

and are not discussed further (see Appendix S1, available as supporting information in the online version of this paper). One study (n = 158 preterms)[16] did not analyze any data for infants less than 30 weeks' gestational age and was ineligible. Authors of five[17-21] additional studies did not separate data for infants less than 1000 g BW, and upon enquiry authors could not provide clarification. All excluded studies are listed in Appendix S1. Two authors[7,8,22,23] published secondary analyses of their original studies. Since they contained different outcomes, they are included here as four separate studies although infants are only counted once per outcome. We could only identify three studies[7,8,22,24] with data on our primary outcome of neurodevelopmental outcome, of which two evaluated this at 18 to 24 months of age. Ten studies[7,8,22-29] allowed secondary outcomes to be obtained; however, only a subset of 199 infants of a total of 360 infants were less than 1000 g BW. The characteristics of the included studies are described in Table S1 (available as supporting information in the online version of this paper).

Primary outcome

The primary outcome of neurodevelopmental status using a standardized scale was only assessed in three of 10 eligible studies (Fig. 3).[7,8,22,24] The total number of infants evaluated overall for the primary outcome is sparse, totaling 96. Although two studies[22,24] used the Bayley II scales of Infant Development, these were performed at different times. Mercer and colleagues[22] recorded Bayley II scores (BSID II) at 7 months for 54 infants (OR Mental Developmental Index, <70, 0.17; 95% CI 0.02-1.56; p = NS). This is too early a time point to be robust and was not repeated in these infants at a later age. Oh[24] evaluated 16 infants by the Bayley II, at 18-24 months corrected age (OR, 1.67; 95% CI, 0.23-12.22). Upon inquiry, we established that the RCT of cord milking by Hosono and colleagues[7,8] had followed 26 of 31 survivors (84%) to 24 months using the Tumori-Inage scale.[30] This standardized scale test for Japanese infants, developed in 1961, consists of 261 questions related to behavior, with a cutoff less than 2 SD below a normative mean. While this study does have high loss to follow-up, with resulting attrition bias, Hosono and colleagues found no significant differences in rates of disability (OR, 0.68; 95% CI, 0.12-3.87).[8] The study by Hosono and colleagues also cannot be pooled with either the studies by Mercer or Oh due to the different standardized test used. Since death may be a competing outcome, we note that we found no difference in the outcome for death (OR, 0.87; 95% CI, 0.28-2.73). There were no significant differences in the outcome of Mental Developmental Index of less than 70, according to sex in either of these three studies.[7,8,22,24] However, for even the largest study the very wide CIs make interpretations speculative (females OR, 5.57 [95% CI, 0.48-64.09]; males OR, 1.63 [95% CI, 0.13-19.99]).[22]

Secondary outcomes

Secondary outcomes could be extracted from 10 studies (Table 1, n = 199). Short-term outcomes favored DCC or UCM (Fig. 2). DCC at birth significantly reduced the number of blood transfusions given (95% CI −2.52 to −1.92; p < 0.001; n = 149) in ELBW patients. Mean blood pressure 4 hours upon admission (95% CI, 4.22-5.58; p < 0.001; n = 113) was higher with DCC or UCM. Hct (95% CI, 2.12-6.44; p < 0.001; n = 118) and initial Hb (95% CI, 3.11-3.74; p < 0.001; n = 137) were also higher after DCC or UCM. Infants exposed to DCC or UCM had lower rates of sepsis (95% CI, 0.18-081; p = 0.01; n = 154),[8,23,24,26-28] and there was a trend toward less IVH (95% CI, 0.29-1.07; p = 0.08; n = 196). There was no significant difference between the groups for number of days on ventilator. Funnel plots of studies reporting secondary outcomes suggested no clear publication bias (Appendix 1).

DISCUSSION

Considerable interest in enhancing placental strategy exists to reduce blood transfusion needs. However, we were unable to find clear evidence of safety and long-term benefit. Because of small sample size and inability to pool study outcomes there is inadequate evidence for improved neurodevelopmental outcome in the ELBW infants who received placental transfusion. This finding is consistent with the Committee Statement of the American College of Obstetricians and Gynecologists, which states that "large clinical trials are needed to investigate the effect of delayed umbilical cord clamping on infants delivered at less than 28 weeks gestation."[31]

A potential drawback of this meta-analysis is that we did not find unpublished materials in our analysis. Recent findings in a meta-analysis suggested that inclusion of unpublished materials narrows an otherwise positive

TABLE 1. Short-term outcomes of umbilical transfusion strategies

Outcome	Number of infants	Mean difference	95% CI	p value for overall effect
Hb on admission	137	3.42	3.11 to 3.74	<0.001
RBC transfusion requirement	149	–2.22	–2.52 to –1.92	<0.001
Admission blood pressure	113	4.9	4.22 to 5.58	<0.001
Days of mechanical ventilation	136	–3.92	–9.75 to 1.92	0.15
		OR	95% CI	
IVH	196	0.56	0.29 to 1.29	0.08
Episodes of late onset sepsis	154	0.39	0.18 to 0.81	0.01

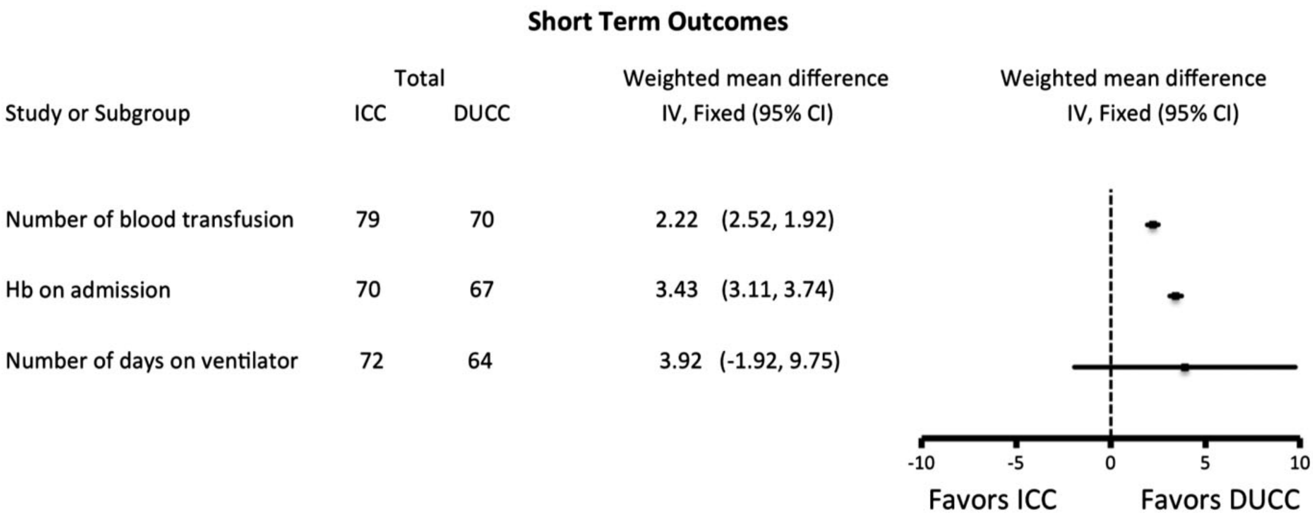


Fig. 2. Short-term outcomes. Forest plot shows some selected positive effects of the available studies, in terms of short-term outcomes. DUCC = delayed umbilical cord clamping.

finding.[32] However, this phenomenon is unlikely to apply in our case, since we have found a negative result. Moreover, funnel plots did not show major deviation indicating missed articles (Appendix S1). Finally our search did not miss any articles found during the Committee policy process in their statement.[31]

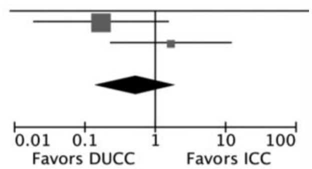
There is concern as to whether DCC or UCM is appropriate for the smallest of infants.[6] Few studies of placental transfusion have only recruited ELBW infants and no meta-analysis of data on placental transfusion in ELBW infants exists. Moreover, it is unclear how safe DCC is in the full resuscitation of ELBW infants. Available data do not include adequate details including condition of the infants on arrival in the NICU (including temperature on admission and SNAP scores). Since blood pressure was significantly improved in the DCC or UCM, this is a good surrogate for well-being of the infant on arrival to the NICU.

Regarding short-term outcomes, 199 ELBW babies are available for pooling of results. Meta-analysis of these suggests a potential benefit of DCC or UCM in this high-risk population. Infants with DCC or UCM had better admission Hb, reduced rates of late-onset sepsis, higher admission blood pressure, and a reduced need for blood transfusion during their hospital stay. These results suggest that DCC or UCM achieves an increase in blood volume that provides improved hemodynamic stability without compromising resuscitation in ELBW infants. In preterm infants, approximately half of the fetoplacental blood volume is in the placenta at the time of birth and contains potentially useful red blood cells (RBCs) and stem cells as well as volume. A delay of between 30 and 180 seconds in cord clamping and cord milking appears able to deliver adequate blood to the newborn.[17] The observed pooled reduced sepsis rate may reflect enhanced delivery of stem cells from placental transfusion.

Concern has been raised regarding acute blood volume expansion in preterm infants and associated increase in morbidity and mortality with placental transfusion.[33,34] Theoretically, placental transfusion with DCC of more than 30 to 180 seconds, and an even faster rate of blood volume expansion by UCM may be counterproductive for ELBW infants. However, the apparent improved short-term outcomes negate this concern, especially given the trend to a lower incidence of IVH. This may be due to hemodynamic advantage provided by placental transfusion with better perfusion and blood pressure. We note that preliminary evidence suggests that maintaining

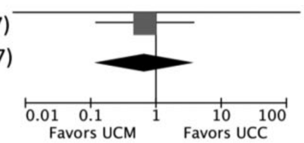
Neurodevelopmental Outcomes

	DUCC		ICC			OR
Study or Subgroup	Events	Total	Events	Total	Weight (%)	M-H, Fixed (95% CI)
MDI<70						
Mercer 2010[22]	1	27	5	27	76.2	0.17 (0.02, 1.56)
Oh 2011[24]	4	8	3	8	23.8	1.67 (0.23,12.22)
Total (95% CI)		35		35	100	0.52 (0.14, 1.98)
Total Events	5		8			



Heterogeneity: Chi^2=2.29 P=0.13 I^2=56%
Test for overall effect: Z=0.95 (p=0.34)

	UCM		UCC			OR
	Events	Total	Events	Total	Weight (%)	M-H, Fixed (95% CI)
Tumori-Inage						
Hosono 2008[7]	3	13	4	13	100	0.68 (0.12,3.87)
Total (95% CI)		13		13	100	0.68 (0.12,3.87)



Test for overall effect Z=0.44 (P=0.66)

Fig. 3. Neurodevelopmental outcomes at 24 months. The only available data on the long-term outcomes seen in three trials are displayed. Note that the Mercer 2010 trial followed infants only to 7 months, while the remaining two trials followed patients out to 24 months corrected age. In addition all are reported as results more than 2 SD below the mean. DUCC = delayed umbilical cord clamping; UCC = umbilical cord clamping.

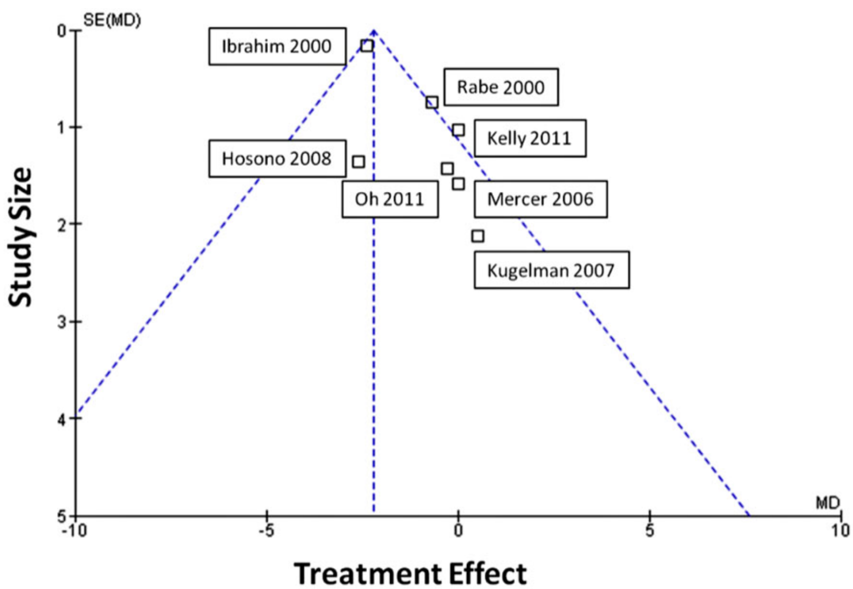
higher Hb levels in the newborn period may improve neurodevelopmental outcome.[11,35] If this is confirmed by larger trials,[36] such positive effects may be due to better cerebral oxygenation and perfusion.[37]

The new International Consensus on Cardiopulmonary Resuscitation[4] recommendations for healthy term infants include a delay in cord clamping of at least 1 minute.[38] This practice may also increase systemic blood pressure during resuscitation. Although the American College of Obstetricians and Gynecologists acknowledges an emerging body of evidence that DCC may decrease the need for blood transfusions and incidence of IVH in preterm infants, it did not recommend it as routine in ELBW infants because of a lack of sufficient evidence.[31] There are currently several active trials investigating the effects of enhanced placental transfusion in ELBW patients. We anticipate that more data will be available to establish the appropriate practice of the strategies in this population.

In conclusion, DCC or cord milking offers some improvement in hemodynamic status in ELBW infants. Considering the small number of patients with long-term outcomes, more studies are needed to fully appreciate long-term implications of delayed umbilical cord clamping on neurodevelopmental outcomes of ELBW infants.

APPENDIX 1

Funnel plot of included studies, showing no clear publication bias



CONFLICT OF INTEREST

The authors report no conflicts of interest or funding sources.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Characteristics of included studies
Appendix S1. Excluded studies