Effect of Delayed *Versus* Early Cord Clamping on Improving Anemia in Term Infants Aged Two Months or Older - *A Meta-analysis*

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Objective: To assess the effects of delayed cord clamping (DCC) on hemoglobin (Hb), mean corpuscular volume (MCV) and ferritin level in infants 2 months or older.

Evidence acquisition: Meta-analysis of randomized control trials searched systematically from PubMed, Cochrane and Web of science. Trials published from Jan 1,1975 to Mar 12, 2018, no language and country restrictions. Twelve studies were included in this meta-analysis. In total, 993 infants were treated with DCC, while 989 cases received early cord clamping. Delayed cord clamping was defined as umbilical cord clamping time greater than 60s after delivery. Outcomes assed were (*i*) hemoglobin (Hb), (*ii*) mean corpuscular volume (MCV) and ferritin level.

Results: The results show that DCC increased hemoglobin level (SMD=0.4678 95%CI: [0.1515, 0.7841]), Ferritin level (SMD=2.1450 95%CI: [1.0431, 3.2470]) and MCV (SMD=0.5751 95%CI: [0.1637, 0.9865]) in infants between 2-12 months compared to ECC subject analysis noted the effects of Hb increase was greater in Asian infants.

Conclusions: Delayed cord clamping improved the Hb, MCV and ferritin level of infants after birth.

Keywords: *Hemoglobin, Infant, Meta-analysis, Umbilical cord*.

The appropriate timing of umbilical cord clamping has been a matter of debate for long. Early umbilical cord clamping (ECC) was standard practice but with emerging evidence it has started to shift to delaying cord clamping (DCC) to beyond 30-60 secs. In term infants, placental transfusion contributes between one-quarter and one-third of total potential blood volume at birth [1]. At 1-minute, newborn infants receives about 80 mL of blood while at 2-3 minutes it is about 100 mL [2].

The American Association of Obstetricians guideline, 2017, states that DCC can increase hemoglobin levels at birth, and early iron stores [3]. The guideline also recommends a delay in umbilical cord clamping in vigorous term and preterm infants for at least 30–60 seconds after birth. In addition, it can also benefit the preterm infants by decreasing the need for blood transfusion, lowering incidence of necrotizing enterocolitis and intraventricular hemorrhage. Previous systematic reviews [4,5] have reported the advantages of DCC, but mainly as a dichotomous variable, and mainly during the neonatal period [6]. The present systematic review and meta-analysis reports change in hemoglobin between ECC and DCC in infants 2 months or older.

METHODS

All relevant studies published between January 1, 1975 and March 8, 2018 were identified by searching PubMed, Cochrane reviews and Web of science. The Search strategy used the terms (((delayed cord clamping [Title/Abstract]) OR delayed cord ligation [Title/Abstract])) OR ((late cord clamping [Title/Abstract]) OR late cord ligation [Title/Abstract]))) Filters: Randomized Controlled Trial. There was no language limitation in the selection.

Accompanying commentary: Pages 791-92.

Studies were screened and selected by the following criteria: (*a*) randomized controlled trials (except quasi randomized study); (*b*) singleton newborns, no developmental deformity, no gestational age limit; (*c*) clinical trial data included hemoglobin, mean corpuscular volume (MCV) and ferritin; (*d*) delayed cord clamping was in intervention group, and early cord clamping was in control group; (*e*) the outcomes' were measured at 2 months or more after birth. Articles were excluded if it was a conference summary; had Incomplete data; presence of maternal complications (antepartum blood loss, pregnancy-induced hyper-tension, pre-eclampsia and gestational diabetes); history of post-partum hemorrhage (PPH), there was need for neonatal resuscitation, or history of fetal distress.

The following data were extracted from each selected study: Region where study was performed, total number of participants, gestational age, follow-up time, and the effect of DCC versus ECC beyond 2 months were also compared; hemoglobin as the main outcome, MCV or ferritin as a secondary outcome.

For meta-analysis, RevMan 5.3 of the Cochrane Collaboration and stata 12.0 was used [6]. The Cochrane risk bias assessment tool was used to assess the bias in the included studies. Clinical and methodological heterogeneity of the included studies were analyzed, and subgroup analysis were conducted according to clinical and methodological heterogeneity. The I^2 index was calculated to assess the degree of heterogeneity. In the absence of heterogeneity ($P \geq 0.05$; $I^2 \leq 50\%$), a fixed effect model was used; if there was heterogeneity between studies ($P<0.05$; $I^2>50\%$), a random effects model was used. Sensitivity analysis was used to assess the stability of the results. Continuous data were expressed as Standard mean difference (IV, Random, 95% CI). Funnel plots was used to analyze for possible publication bias. Funnel plot asymmetry was assessed using Egger tests, and significant publication bias was defined as a P value<0.1. If publication bias existed, the trim-and-fill computation was used to estimate the effect of publication bias on the interpretation of the results.

The entire process was completed by two independent investigators, and the disagreement if any, was resolved by a third investigator.

RESULTS

A total of 325 studies was identified, with 13 publications fulfilling eligibility for inclusion. [7-19] (***Fig. 1***). Two articles written by Andersson, *et al*. [9,19] have the same patients but the follow-up time and outcomes were different. So these two articles were regarded as one trial and outcomes extracted accordingly. The characteristics of all included trials is presented in ***Table* I**. Follow-up time was between 2 months and 12 months. The effect of ECC and DCC on hemoglobin was assessed in 12 trials, ferritin in 10 trials and MCV in 5 trials. In total, 993 infants were treated with DCC, while 989 cases received

Table I Characteristics of Included Studies Comparing Early and Delayed Cord Clamping

Study; place, year	*Sample (DCC/ECC)*	*Gestational age (DCC/ECC)*	*Intervention method DCC/ECC*	*Outcomes*
KC, *et al.* [7]; Nepal, 2017	212/188	38/38 median	≥180s/≤60s	Hb and ferriten level at 8-mo
Tiemersma, *et al*. [8]; South Africa, 2015	35/38	38/38 median	120-180 s/≤30s	Hb level at 2-3 mo
Andersson, *et al*.* [9]; Sweden, 2011-2014	168/175 150/144	40.0/40.1 mean	≥180s/≤10s	Hb and MCV level at 4-mo Ferritin level at 12-month
Ceriani Cernadas, *et al*. [10]; Argentina, 2010	83/86	39/39 median	180s/<15s	Hb and MCV level at 6-mo Ferritin level at 6-mo
Chaparro, *et al*. [11]; Mexico, 2006	171/157	38.8/39.0 mean	120s/around 10s	Hb and MCV level at 6-mo Ferritin level at 6-mo
Geethanath, *et al*. [12]; India, 1997	59/48	Term infants	Placenta into vagina/ICC	Hb level at 3-mo Ferritin level at 3-mo
Li, *et al*. [13]; China, 2012	64/94	38.6/38.7 mean	60s/15s	Hb and MCV level at 4-mo Ferritin level at 4-mo
Nesheli, *et al*. [14]; Iran, 2014	30/30	40/40 mean	50-60s/ICC	Hb, ferritin and MCV level at 6-mo
Venâncio, *et al*. [15]; Brazil, 2008	115/109	39.3/39.3 median	60s/ICC^h	Hb level at 3-mo Ferritin level at 3-mo
van Rheenen, *et al*. [16]; Zambia, 2007	39/39	40/40 mean	>60s/20s	Hb level at 4-mo
Gupta, *et al*. [17]; India, 2002	29/29	39.1/39.4 mean	Placenta into vagina/ICC	Hb level at 3-mo
Grajeda, *et al*. [18]; Guatemala, 1997	26/21	38.8/38.5 mean	Cord stopped pulsating/ICC	Hb level at 2-mo Ferritin level at 2-mo

**Includes two articles with the same patients, the sample 168/175 at 4-month, the other at 12-month; DCC-delayed cord clamping; ECC-early cord clamping; ICC-cords clamped immediately after the birth ; Hb-hemoglobin; MCV-mean corpuscular volume.*

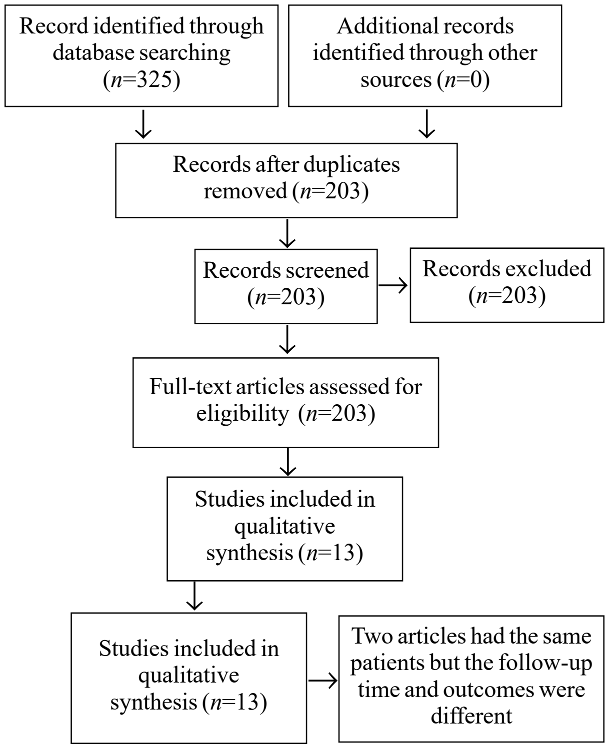

Fig.1 *Study selection for the meta-analysis.*

ECC. All of these infants were term infants. These trials used different definition of DCC, but all were pooled, and DCC was redefined as umbilical cord clamping time greater than 60s after delivery.

***Web Fig*. I** depicts the assessment of risk of bias in the included trials. Eight studies [7-12,13,16,17] clearly indicated the method of randomization, 9 studies [7,8,12-18] did not indicate if the study was blinded.

There was little publication bias on funnel plot (***Fig*. 2**) and Egger test (P=0·073) in this analysis. However, further analysis with trim-and-fill test indicated that this publication bias could not impact the estimates (no trimming done because data was unchanged).

To study the effect of DCC compared to ECC on hemoglobin level the sample size varied significantly among the included studies and there was heterogeneity (I^2=91%), so a random effects model was used to analyze the results. One trial in our study did not mention the unit [16], so outcomes have taken SMD to analyze. The results obtained show that DCC resulted in higher hemoglobin levels compared to ECC (SMD=0.47; 95% CI: 0.15, 0.78) (***Fig*. 3**). DCC resulted in significantly higher ferritin levels compared to ECC (SMD=2.14; 95% CI: 1.04, 3.25) (***Fig*. 3**). Similarly DCC resulted in significantly higher MCV levels compared to ECC (SMD=0.57; 95% CI: 0.16, 0.99) (***Fig*. 2**).

Subgroup analysis on effect of DCC and ECC on hemoglobin was performed by race (***Web Fig*. 2.1**), timing of DCC (120s as the critical value) (***Web Fig*. 2.3**) and the follow-up time of DCC (6 months as the critical value) (***Web Fig*. 2.2**). DCC improved Hb significantly compared to ECC in Asian studies, when follow-up was more than 6 months and when timing cord clamping was not beyond 120 secs. Accordingly, the race of participants, timing and follow-up time of DCC can be regarded as a source of heterogeneity.

DISCUSSION

The results obtained show that DCC could increase the level of hemoglobin, MCV and especially ferritin when compared with ECC. The influence could be different based on participants' regional distribution, timing of umbilical cord clamping and the age of infants. The optimal time to delay umbilical cord ligation which impacted hemoglobin levels is about 60-120s.

Some studies have indicated that the differences in hematologial variables between DCC and ECC became smaller with the increased follow-up time [7,9]. A randomized controlled trial in Sweden demonstrated that DCC significantly increased stored iron at 4 months, but the effect on hemoglobin was not significantly different from ECC. When the follow-up reached 12 months, the beneficial effect on iron storage disappeared. This might be related to the postnatal iron supplementation. A previous study [11] showed that during the three-month follow-up, hematologic improvement was enhanced in iron-deficient mothers, infants with infant birth weights between 2500 and 3000 grams, and infants who did not receive infant formula or iron fortified milk. A previous meta-analysis including 6 trials about hemoglobin level showed no significant difference in the hemoglobin levels within 6 months.

The study has some limitations. Firstly, the timing of cord clamping varied from 60 seconds till descent of placenta into vagina or cord stopped pulsating, and in the latter the means used were approximate estimates. Secondly, all studies had loss to follow-up. Since acute inflammatory process could increase the ferritin concentration, there might be an error in the result of ferritin.

There is also a long way to go in the optimization of umbilical cord ligation. In addition, countries should develop DCC guidelines based on race, gender, and physical status of pregnant women in order to improve the blood volume and iron storage of newborns more effectively.

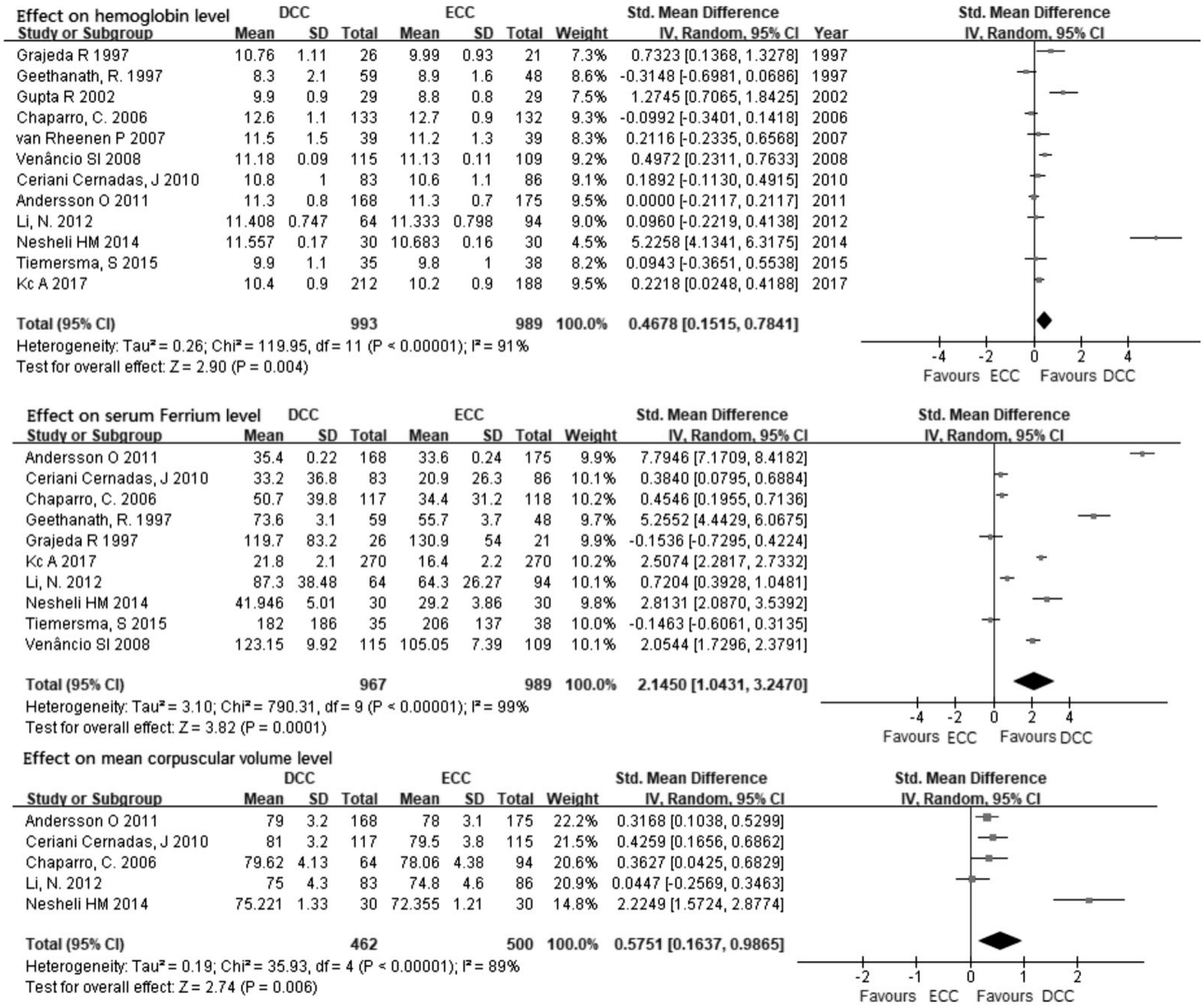

Fig. 2 *Forest plots comparing effect of early and delayed cord clamping on various hematological parameters.*

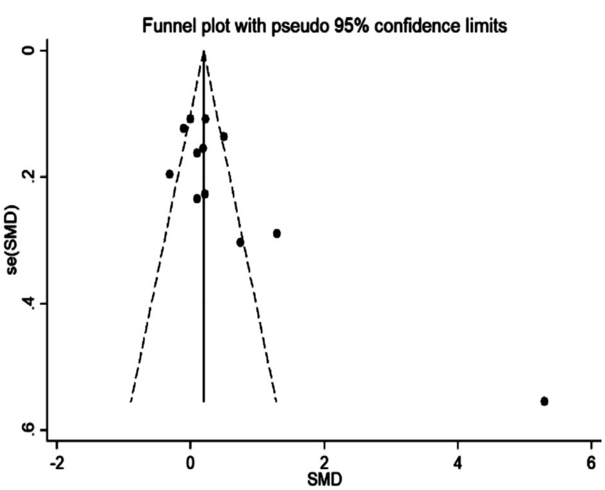

Fig. 3 *Funnel plot of studies comparing early and delated cord clamping.*

As there is a high incidence of anemia and low iron stores in Asian and African infants [7,12,16], DCC might be an effective intervention to prevent anemia and iron deficiency in developing countries.

Contributors: XF: contributed to conception and design, acquisition, analysis, and interpretation; DD: contributed to conception and design, acquisition and interpretation; SL: contributed to conception and design, acquisition; ZX: contributed to conception and design, analysis; HW: contributed to conception and design, acquisition, analysis, and interpretation. All authors drafted manuscript, critically revised manuscript, gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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WHAT IS ALREADY KNOWN?

- Delayed cord clamping provides adequate blood volume and birth iron stores, thus decreasing the risk of iron deficiency anemia during infancy

WHAT THIS STUDY ADDS?

- The optimal time to delay umbilical cord ligation is about 60-120s and it will be more conducive to the growth of hemoglobin than the longer umbilical clamping time. In contrast, Asians might gain more benefits from delayed umbilical clamping.

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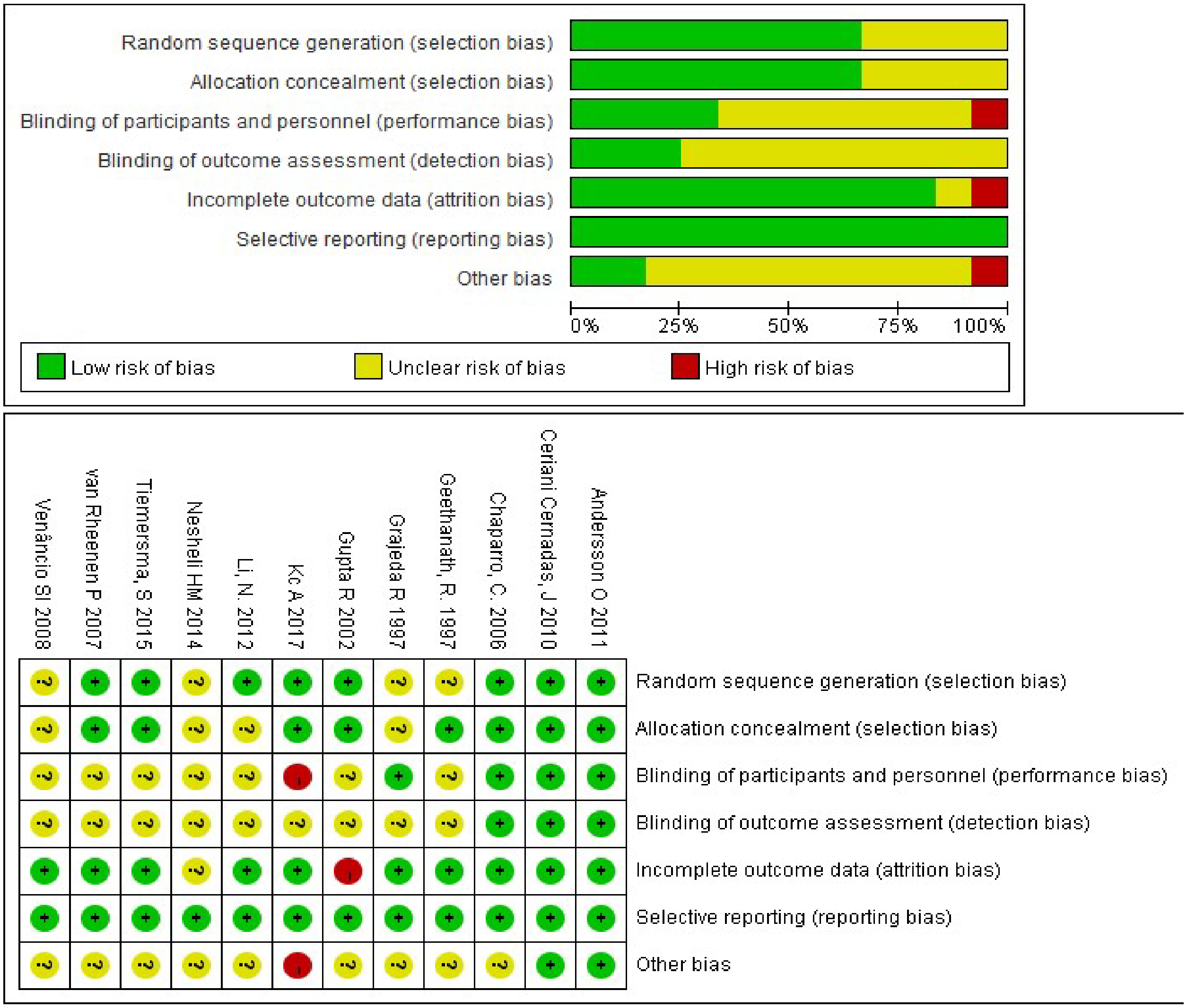
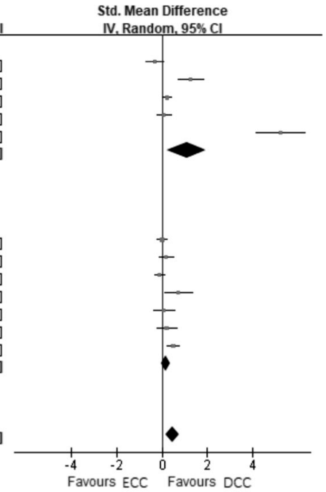


Web Fig. 1 *Assessment of Risk Bias.*

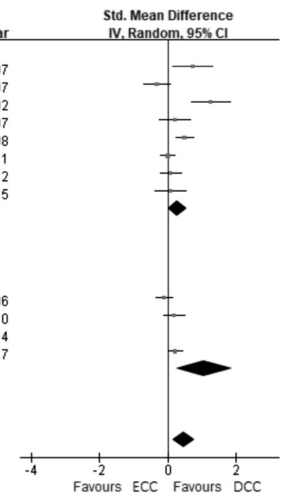
1

Study or Subgroup	DCC Mean	DCC SD	DCC Total	ECC Mean	ECC SD	ECC Total	Weight	Std. Mean Difference IV, Random, 95% CI
Asia								
Geethanath, R. 1997	8.3	2.1	59	8.9	1.6	48	8.6%	-0.3148 [-0.6981, 0.0686]
Gupta R 2002	9.9	0.9	29	8.8	0.8	29	7.5%	1.2745 [0.7065, 1.8425]
Kc A 2017	10.4	0.9	212	10.2	0.9	188	9.5%	0.2218 [0.0248, 0.4188]
Li, N. 2012	11.408	0.747	64	11.333	0.798	94	9.0%	0.0960 [-0.2219, 0.4138]
Nesheli HM 2014	11.557	0.17	30	10.683	0.16	30	4.5%	5.2258 [4.1341, 6.3175]
Subtotal (95% CI)			**394**			**389**	**39.2%**	**1.1027 [0.2418, 1.9636]**
Heterogeneity: Tau² = 0.88; Chi² = 101.49, df = 4 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 2.51 (P = 0.01)								
Outside Asia								
Andersson O 2011	11.3	0.8	168	11.3	0.7	175	9.5%	0.0000 [-0.2117, 0.2117]
Ceriani Cernadas, J 2010	10.8	1	83	10.6	1.1	86	9.1%	0.1892 [-0.1130, 0.4915]
Chaparro, C. 2006	12.6	1.1	133	12.7	0.9	132	9.3%	-0.0992 [-0.3401, 0.1418]
Grajeda R 1997	10.76	1.11	26	9.99	0.93	21	7.3%	0.7323 [0.1368, 1.3278]
Tiemersma, S 2015	9.9	1.1	35	9.8	1	38	8.2%	0.0943 [-0.3651, 0.5538]
van Rheenen P 2007	11.5	1.5	39	11.2	1.3	39	8.3%	0.2116 [-0.2335, 0.6568]
Venâncio SI 2008	11.18	0.09	115	11.13	0.11	109	9.2%	0.4972 [0.2311, 0.7633]
Subtotal (95% CI)			**599**			**600**	**60.8%**	**0.1882 [-0.0141, 0.3904]**
Heterogeneity: Tau² = 0.04; Chi² = 16.43, df = 6 (P = 0.01); I² = 63%								
Test for overall effect: Z = 1.82 (P = 0.07)								
Total (95% CI)			**993**			**989**	**100.0%**	**0.4678 [0.1515, 0.7841]**
Heterogeneity: Tau² = 0.26; Chi² = 119.95, df = 11 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 2.90 (P = 0.004)								
Test for subgroup differences: Chi² = 4.11, df = 1 (P = 0.04), I² = 75.7%								



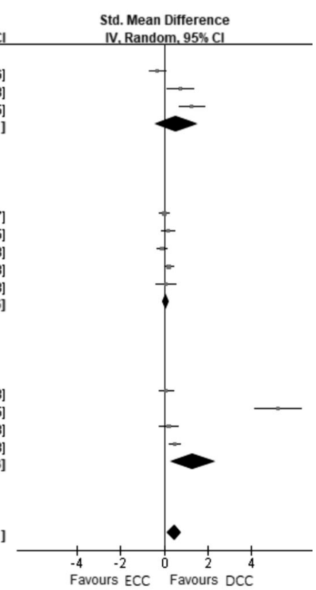
2

Study or Subgroup	DCC Mean	DCC SD	DCC Total	ECC Mean	ECC SD	ECC Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
within 6 mo									
Grajeda R 1997	10.76	1.11	26	9.99	0.93	21	7.3%	0.7323 [0.1368, 1.3278]	1997
Geethanath, R. 1997	8.3	2.1	59	8.9	1.6	48	8.6%	-0.3148 [-0.6981, 0.0686]	1997
Gupta R 2002	9.9	0.9	29	8.8	0.8	29	7.5%	1.2745 [0.7065, 1.8425]	2002
van Rheenen P 2007	11.5	1.5	39	11.2	1.3	39	8.3%	0.2116 [-0.2335, 0.6568]	2007
Venâncio SI 2008	11.18	0.09	115	11.13	0.11	109	9.2%	0.4972 [0.2311, 0.7633]	2008
Andersson O 2011	11.3	0.8	168	11.3	0.7	175	9.4%	0.0000 [-0.2117, 0.2117]	2011
Li, N. 2012	11.408	0.747	64	11.333	0.798	94	9.0%	0.0960 [-0.2219, 0.4138]	2012
Tiemersma, S 2015	9.9	1.1	35	9.8	1	38	8.2%	0.0943 [-0.3651, 0.5538]	2015
Subtotal (95% CI)			**535**			**553**	**67.6%**	**0.2793 [0.0001, 0.5586]**	
Heterogeneity: Tau² = 0.12; Chi² = 32.57, df = 7 (P < 0.0001); I² = 79%									
Test for overall effect: Z = 1.96 (P = 0.05)									
beyond 6 mo									
Chaparro, C. 2006	12.6	1.1	133	12.7	0.9	132	9.3%	-0.0992 [-0.3401, 0.1418]	2006
Ceriani Cernadas, J 2010	10.8	1	83	10.6	1.1	86	9.1%	0.1892 [-0.1130, 0.4915]	2010
Nesheli HM 2014	11.557	0.17	30	10.683	0.16	30	4.6%	5.2258 [4.1341, 6.3175]	2014
Kc A 2017	10.4	0.9	164	10.2	0.9	179	9.4%	0.2217 [0.0092, 0.4342]	2017
Subtotal (95% CI)			**410**			**427**	**32.4%**	**1.0692 [0.2322, 1.9062]**	
Heterogeneity: Tau² = 0.66; Chi² = 87.36, df = 3 (P < 0.00001); I² = 97%									
Test for overall effect: Z = 2.50 (P = 0.01)									
Total (95% CI)			**945**			**980**	**100.0%**	**0.4706 [0.1508, 0.7905]**	
Heterogeneity: Tau² = 0.27; Chi² = 119.93, df = 11 (P < 0.00001); I² = 91%									
Test for overall effect: Z = 2.88 (P = 0.004)									
Test for subgroup differences: Chi² = 3.08, df = 1 (P = 0.08), I² = 67.5%									



3

Study or Subgroup	DCC Mean	DCC SD	DCC Total	ECC Mean	ECC SD	ECC Total	Weight	Std. Mean Difference IV, Random, 95% CI
unclear								
Geethanath, R. 1997	8.3	2.1	59	8.9	1.6	48	8.6%	-0.3148 [-0.6981, 0.0686]
Grajeda R 1997	10.76	1.11	26	9.99	0.93	21	7.3%	0.7323 [0.1368, 1.3278]
Gupta R 2002	9.9	0.9	29	8.8	0.8	29	7.5%	1.2745 [0.7065, 1.8425]
Subtotal (95% CI)			**114**			**98**	**23.4%**	**0.5460 [-0.4581, 1.5501]**
Heterogeneity: Tau² = 0.72; Chi² = 23.21, df = 2 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 1.07 (P = 0.29)								
⩾120s								
Andersson O 2011	11.3	0.8	168	11.3	0.7	175	9.5%	0.0000 [-0.2117, 0.2117]
Ceriani Cernadas, J 2010	10.8	1	83	10.6	1.1	86	9.1%	0.1892 [-0.1130, 0.4915]
Chaparro, C. 2006	12.6	1.1	133	12.7	0.9	132	9.3%	-0.0992 [-0.3401, 0.1418]
Kc A 2017	10.4	0.9	212	10.2	0.9	188	9.5%	0.2218 [0.0248, 0.4188]
Tiemersma, S 2015	9.9	1.1	35	9.8	1	38	8.2%	0.0943 [-0.3651, 0.5538]
Subtotal (95% CI)			**631**			**619**	**45.6%**	**0.0788 [-0.0511, 0.2086]**
Heterogeneity: Tau² = 0.00; Chi² = 5.17, df = 4 (P = 0.27); I² = 23%								
Test for overall effect: Z = 1.19 (P = 0.23)								
<120s								
Li, N. 2012	11.408	0.747	64	11.333	0.798	94	9.0%	0.0960 [-0.2219, 0.4138]
Nesheli HM 2014	11.557	0.17	30	10.683	0.16	30	4.5%	5.2258 [4.1341, 6.3175]
van Rheenen P 2007	11.5	1.5	39	11.2	1.3	39	8.3%	0.2116 [-0.2335, 0.6568]
Venâncio SI 2008	11.18	0.09	115	11.13	0.11	109	9.2%	0.4972 [0.2311, 0.7633]
Subtotal (95% CI)			**248**			**272**	**31.0%**	**1.3070 [0.2636, 2.3503]**
Heterogeneity: Tau² = 1.04; Chi² = 79.51, df = 3 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 2.46 (P = 0.01)								
Total (95% CI)			**993**			**989**	**100.0%**	**0.4678 [0.1515, 0.7841]**
Heterogeneity: Tau² = 0.26; Chi² = 119.95, df = 11 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 2.90 (P = 0.004)								
Test for subgroup differences: Chi² = 6.00, df = 2 (P = 0.05), I² = 66.6%								



Web Fig. 2 *Subgroup analysis on effect of delayed (DCC) and early cord clamping (ECC) on hemoglobin.*