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Meta Analysis
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Meta-Analysis the Effect of Cord Clamping Time on Hemoglobin Elevation in Newborn Infants

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ABSTRACT

Background: Fulfillment of iron needs is very important in the first 1000 days of human life, with sufficient amounts of iron can determine the quality of life in the future, to produce a healthy and quality generation. Delaying clamping and cutting the umbilical cord for about 1-2 minutes can increase the amount of blood flowing to the newborn so as to prevent low hemoglobin in the neonatal period. This study aims to analyze the effect of delayed cord cutting on hemoglobin levels in newborns.

Subjects and Method: This study was a systematic study and meta-analysis, with the following PICO Population= term newborn at 48 hours after birth. Intervention= Time delay of clamping the umbilical cord (≤60 seconds). Comparison= Immediate cord clamping time (≤15 seconds). Outcome= Hemoglobin Level. The articles used in this study were obtained from several databases including PubMed, Science Direct and Google Scholar. The keywords used were: "umbilical cord and infant", "Delayed Cord Clamping", "Delayed Cord Clamping and Immediate Cord Clamping" "DCC and Hemoglobin "DCC and Anaemia". Inclusion criteria were full-text articles of randomized controlled experimental study design. trial (RCT) Articles were collected using PRISMA flow diagrams Articles were analyzed using the Review Manager 5.3 application.

Results: Based on the results of a meta-analysis of 9 primary studies on the effect of cord clamping time on increasing newborn hemoglobin levels originating from Pakistan, China, Thailand, India, Bangladesh, the United States, and Nigeria, it can be concluded that delayed cord clamping in newborns birth increased the hemoglobin level by 0.81 units compared to clamping the cord immediately after birth, and this result was statistically significant (SMD= 0.81; 95% CI= 0.30 to 1.32; p=0.002).

Conclusion: Delay in cutting the umbilical cord can increase hemoglobin in full-term newborns without indications.

Keywords: delayed cord clamping, hemoglobin.

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BACKGROUND

Anemia in infants can cause irreversible disturbances in physical, cognitive, motor and behavioral development. Incidence of anemia and lower iron levels were found in infants with immediate umbilical cord cutting, because these infants did not receive an additional 40% blood volume from placental transfusions (Hutchon, 2012)

Delayed Cord Clamping (DCC) or delayed clamping of the umbilical cord can significantly increase iron reserves and increase the transfer of stem cells (stem cells) in newborns (Tolosa et al., 2010)

According to WHO, (2012) Delaying clamping of the umbilical cord for 1 to 3 minutes is recommended to improve the health and nutrition of the baby. Placental transfusion related to DCC can add 30% blood volume and 60% red blood cells which are used as a source of iron for the baby (Garabedian et al., 2016).

The advantages of DCC include preventing anemia, increasing hematocrit levels, reducing the incidence of postpartum hemorrhage, optimizing oxygen transfer to the baby, increasing the closeness of mother and baby and increasing the growth of the baby's brain (Astuti, 2018).

The incidence of anemia and lower iron levels was found in infants with immediate umbilical cord cutting, because these infants did not receive an additional 40% blood volume from placental transfusions (Hutchon, 2012). Neonatal anemia is an important problem that can have long-term impacts on the neurological, emotional, and behavioral development of newborns (Lozoff and Georgieff, 2006; Songthamwat et al., 2020). Anemia is a symptom that must be found for the cause and its handling is carried out according to the cause (Briawan, 2014)

Various studies have been carried out with varying results around the world, but further analysis needs to be done in order to get a more convincing conclusion. Therefore, researchers are interested in analyzing using a systematic approach to relevant studies by conducting a meta-analysis to identify the magnitude of the effect of delayed cord cutting on hemoglobin levels in newborns.

Conducting a meta-analysis to clearly identify the magnitude of the influence of bullying on the risk of suicide in adolescents.

SUBJECTS AND METHOD

1. Study Design

This study was a systematic study and meta-analysis, with the following PICO Population = term newborn at 48 hours after birth. Intervention= Time delay of clamping the umbilical cord (≤60 seconds). Comparison = Immediate cord clamping time (≤15 seconds). Outcome = Hemoglobin Level. The articles used in this study were obtained from several databases including PubMed, Science Direct, and Google Scholar. The keywords used were: “umbilical cord and infant”, “Delayed Cord Clamping”, “Delayed Cord Clamping and Immediate Cord Clamping” “DCC and Hemoglobin “DCC and Anaemia”. Inclusion criteria were full-text articles of randomized controlled experimental study design. trial (RCT) Articles were collected using PRISMA flow diagrams Articles were analyzed using the Review Manager 5.3 application.

2. Steps of Meta-Analysis

The meta-analysis was carried out through 5 steps as follows:

1) Formulating research questions using the PICO model.
2) Searching primary study research articles from electronic databases, such as PubMed, Science Direct, and Google Scholar.
3) Conducting screening and quality assessment of primary research articles.
4) Extracting and analyzing data into the RevMan 5.3 application.
5) Interpreting the results and draw conclusions.

3. Inclusion Criteria
The inclusion criteria in this study were the full paper articles of the RCT study design with the outcome of hemoglobin levels.

4. Exclusion Criteria
Exclusion criteria were articles with quasy experimental, cohort, case control and cross-sectional study designs, articles that were not full-text and used languages other than English and Indonesian.

5. Operational Definition of Variable
Anemia is a condition when the number of red blood cells or the concentration of oxygen carrier in the blood is insufficient for the body's physiological needs.

Hemoglobin is an erythrocyte tetrameric protein that binds to a non-protein molecule, namely an iron porphyrin compound called heme. Hemoglobin has two important transport functions in the human body, one of which is the transport of oxygen from the respiratory organs to peripheral tissues.

6. Instrument
The study was guided by the PRISMA flowchart and the quality assessment used an assessment from a randomized controlled trial (RCT) published by CEBM (Centre for Evidence-Based Medicine).

7. Data Analysis
The data in the study were analyzed using the Review Manager application (RevMan 5.3). Forest plots and funnel plots are used to determine the size of the relationship and the heterogeneity of the data. The fix effect model is used for homogeneous data, while the random effect model is used for heterogeneous data across studies.

RESULTS
The initial search process on the database yielded 863 articles. After the process of deleting published articles, it was found that 9 of them met the requirements for a full text review.

Figure 2 shows research related to the effect of delaying cord clamping on hemoglobin levels in full-term infants, namely Asia and Africa. There were 9 studies originating from the Asian continent (5 studies from Pakistan, China, Thailand, India, Bangladesh) 3 studies from the Americas, 1 study from the African continent (Nigeria).

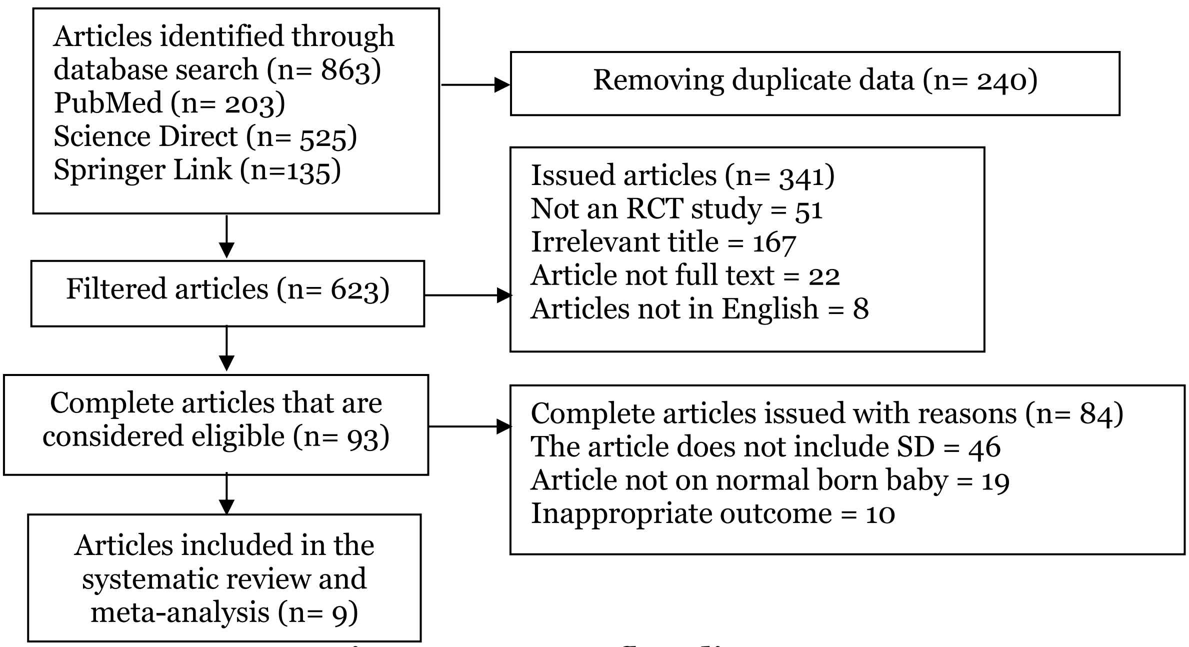

Figure 1. PRISMA flow diagram

Figure 2. Map of the research area of delay of cord cutting on hemoglobin levels

Table 1. The results of the quality assessment of the RCT study on of delay of cord cutting on hemoglobin levels

Author (Year)	Questions Criteria												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Erickson et al. (2012)	2	2	2	2	2	2	2	2	2	2	2	2	24
Ofojebe et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	24
Akram et al. (2019)	2	2	2	2	2	2	2	2	2	2	1	2	23
Shao et al. (2021)	2	2	2	2	2	2	2	2	2	2	1	2	23
Mercer et al. (2016)	2	2	2	2	2	2	2	2	2	2	2	2	24
Mercer et al. (2020)	2	2	2	2	2	1	2	2	2	2	2	2	23
Jaiswal et al. (2015)	2	2	2	2	2	2	2	2	2	2	2	2	24
Mitra et al. (2009)	2	2	2	2	2	2	0	2	2	2	2	2	22
Tanmoun et al. (2013)	2	2	2	2	2	2	2	2	2	2	2	2	24

Question description:

1) Does the research address a clear research focus?
2) Is the RCT research method suitable for answering research questions?
3) Were there enough subjects in the study to establish that the findings were not accidental?
4) Were subjects randomly divided into experimental and control groups? If not, could this introduce bias?
5) Does the study use inclusion/exclusion criteria?
6) Were the two groups comparable at study entry?
7) Are the outcome criteria objective and unbiased?
8) Is the measurement method used objective and valid to measure the results? If not, was there blinding in the study?
9) Is the effect size practically relevant?
10) Are the effect estimates correct? Is there a degree of confidence interval?
11) Are there any confounding factors that have not been taken into account?
12) Can the results be applied to your research?

Description of the answer score:

0 = No
1 = Hesitant
2 = Yes

Table 2 Description of primary studies on delayed cord cutting in newborns

Author (year)	Country	Study Design	Sample	P Population	I Interven tion	C Compa rison	O Outcome
Erickson et al. (2012)	The USA	RCT	DCC =12 ICC=12	Full term baby 48 hours old	DCC ≥1 minute	ICC <15 seconds	Blood volume, Hemoglobin* level, hematocrit level.
Ofojebe et al. (2021)	Nigeria	RCT	DCC = 102 ICC = 102	Full term baby 48 hours old	DCC ≥1 minute	ICC <15 seconds	Hemoglobin* level, bilirubin level, postpartum hemorrhage,
Akram et al. (2019)	Pakistan	RCT	DCC = 111 ICC = 111	Full term baby 48 hours old	DCC ≥180 sec	ICC <10 seconds	Hemoglobin* level, hematocrit level, serum ferritin level
Shao et al. (2021)	China	RCT	DCC = 25 ICC = 11	Full term baby 48 hours old	DCC ≥ 61-120 seconds	ICC ≤ 30-60 seconds	Bilirubin level, hemoglobin* level, hematocrit level
Mercer et al. (2016)	The USA	RCT	DCC = 37 ICC = 36	Full term baby 48 hours old	DCC ≥5 minutes	ICC <20 seconds	Bilirubin level, hemoglobin* level, hematocrit level
Mercer et al. (2020)	The USA	RCT	DCC = 21 ICC = 20	Full term baby 48 hours old	DCC ≥5 minutes	ICC <20 seconds	The amount of postpartum hemorrhage, Apgar score, hemoglobin*, hematocrit, total serum bilirubin
Jaiswal et al. (2017)	India	RCT	DCC = 93 ICC = 92	Full term baby 48 hours old	DCC ≥60 sec	ICC < 30 seconds	Hemoglobin* level, serum ferritin
Mitra et al. (2009)	Banglades h	RCT	DCC = 48 ICC = 50	Full term baby 48 hours old	DCC ≥60 sec	ICC <15 seconds	Hemoglobin* level, hematocrit level, bilirubin level
Tanmoun et al. (2013)	Thailand	RCT	DCC = 76 ICC = 72	Full term baby 48 hours old	DCC ≥120 sec	ICC <10 seconds	Hemoglobin* level, hematocrit level, bilirubin level

The forest plot in Figure 3 shows that a longer delay in clamping the umbilical cord can increase Hemoglobin levels in newborns. Infants with longer cord clamping delays had hemoglobin levels 0.81 units higher than infants who underwent immediate cord clamping, and these results were statistically significant (SMD=0.81; 94% CI= 0.30 to 1.32; p=0.002). The heterogeneity of research data showed I2 = 94%, which means that the effect estimates between primary studies in this meta-analysis varied greatly. Thus, the calculation of the average effect estimate is carried out using the random effect model approach.

The funnel plot in Figure 4 shows that the distribution of effect estimates from the primary study meta-analysis lies more to the right of the estimated average vertical line than to the left, which indicates publication bias. Because the publication bias tends to be to the right of the average vertical line in the same direction as the location of the diamond shape in the forest plot, this publication bias tends to increase the effect of cord clamping time on Hb levels (overestimate).

Table 3. Adjusted Odds Ratio (aOR) the effect of bullying on suicide risk

Author (Year)	ICC		DCC	
	Mean	SD	Mean	SD
Erickson et al. (2012)	19.4	2.2	17.2	2.1
Ofojebe et al. (2021)	16.51	1.71	15.16	2.27
Akram et al. (2019)	16.45	0.84	14.32	1.08
Shao et al. (2021)	205.07	21.52	203.32	17.4
Mercer et al. (2016)	19.5	2.1	17.7	1.8
Mercer et al. (2020)	19.6	1.9	17.6	2
Jaiswal et al. (2017)	15.8	2	16.2	2.4
Mitra et al. (2009)	16.3	0.9	15.6	0.9
Tanmoun et al. (2013)	17.8	2	16.1	1.7

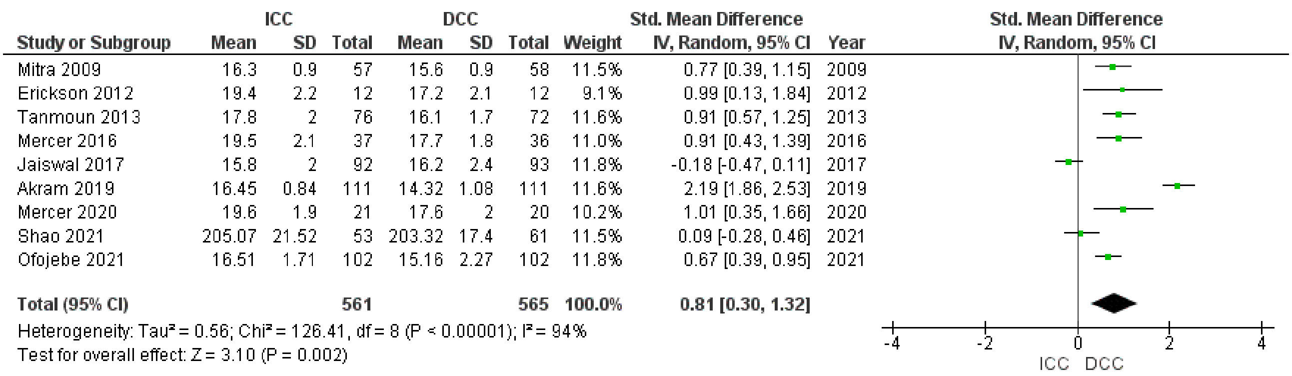

Figure 3. Forest plot of Delay of Cord Cutting on Hemoglobin Levels

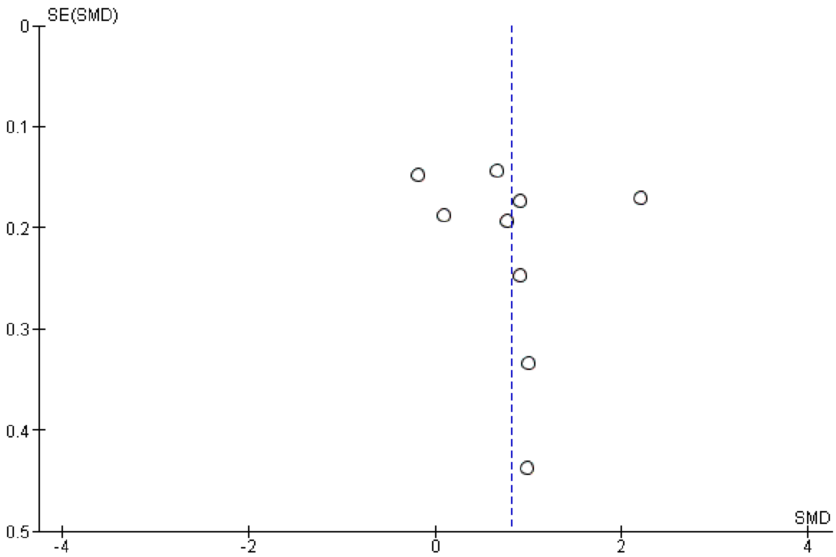

Figure 4. Funnel plot of delay of cord cutting on hemoglobin levels

DISCUSSION

A systematic review and meta-analysis in this study was conducted with the aim of increasing the generalizability of the findings and obtaining convincing conclusions from the results of similar studies regarding the effectiveness of cord clamping on newborn hemoglobin levels. Primary studies on the timing of clamping the umbilical cord with increased hemoglobin levels in newborns who met the criteria totaled 9 articles from 5 Asian continents, 3 from the Americas, 1 from the African continent.

A total of 9 experimental research articles with RCT as a source of meta-analysis of the effect of cord clamping time on increasing newborn hemoglobin levels. This study shows that delayed cord clamping can increase hemoglobin levels in newborns, and this is statistically significant. The results of the forest plot showed that newborns with delayed clamping of the umbilical cord could increase hemoglobin levels by more than 0.81 units and these results were statistically significant (SMD= 0.81; 94% CI= 0.30 to 1.32; p=0.002).

Delaying cord clamping can increase hemoglobin levels in newborns, in addition, according to (Buckley, 2011) one of the benefits of delaying cord clamping is that the hemoglobin level in infants who are immediately clamped by the cord is 16.2 g/dL, while in Infants with delayed clamping of the umbilical cord were 18.3 g/dL (Lubis, 2008). Delayed clamping of the umbilical cord can also increase iron storage at birth so as to prevent iron deficiency anemia in newborns (Dianty et al., 2012).

The results of this study indicated that delayed cord clamping increased hemoglobin levels by 0.81 times compared to immediate cord clamping (Ofojebe et al., 2021) The results of this study concluded that at 48 hours of birth, the mean hemoglobin concentration was significantly higher in the delayed clamping group than the immediate clamping group. Hb levels are not affected until iron stores decrease. Delaying cord clamping for three minutes provides an additional 100 mL of blood volume. This blood volume can add 40-50 mg/kg of iron to the 75 mg/kg of iron that is already present in the body of a full-term newborn, bringing the total iron to about 115-120 mg/kg. So, with the addition of this amount can prevent iron deficiency for up to one year of life (Cernadas et al., 2006)

Research Tanmoun (2013) also stated that at the beginning the two groups had similar demographic characteristics of moers. At 48 hours after delivery, the infant's hemoglobin and hematocrit were statistically significantly higher in delayed cord clamping than in early cord clamping. The prevalence of neonatal anemia in early cord clamping is relatively higher than delayed cord clamping.

AUTHOR CONTRIBUTION

Rynda Arum Dilafa is the main researcher who selects topics, explores and collects data. Setyo Sri Rahardjo and Bhisma Murti played a role in analyzing the data and reviewing research documents.

FUNDING AND SPONSORSHIP

This study is self-funded.

CONFLICT OF INTERESTS

There is no conflict of interest in this study.

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