Delayed vs Early Umbilical Cord Clamping in 100 Preterm Infants: an RCT from Bhavnagar, Gujarat

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Abstract

Objective: To investigate the safety, feasibility and efficacy of delayed cord clamping (DCC) compared with early cord clamping (ECC) at delivery among preterm infants born before completed 37 weeks' gestation.

Methods: This is a randomized, controlled trial in which women in labor with 100 singleton pregnancies before completed 37 weeks gestation were randomly assigned to ECC (cord clamped before 30sec) or DCC (cord clamped after 120 sec) whether vaginal (84) or cesarean (16) deliveries.

Results: There were no significant difference in morbidities like Respiratory distress (p=0.45), Necrotising enterocolitis (p=0.31), Intraventricular hemorrhage (p=0.31), duration of hospital stay (p=0.22) between two randomization groups of DCC and ECC. There is no significant difference in mortality rate (p=0.6). DCC significantly reduced the requirement of blood transfusion and incidence of anemia at birth, at 1 and 4 months of age in preterm.

Conclusion: The requirement of blood transfusion is reduced with delayed cord clamping upto the first four month of age significantly with improvement in hemoglobin and mean corpuscular volume. Infant morbidity was not affected by delayed vs early cord clamping, neither when regarding the neonatal period (hyperbilirubinaemia/ jaundice, respiratory symtoms, polycythemia), nor at the first 4 months of life (infection symptoms, gastro intestinal problems, contact with doctors).

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What is already known
DCC reduces incidence of anemia and blood requirement and also morbidities like NEC and RDS in full term newborns. Risk of IVH and polycythemia is associated with DCC.

What this study adds
For a preterm child between 28 to <37 weeks of gestation
Hb at Birth, 1 and 4 months, and MCV at 4 months are significantly higher in DCC delayed (120 sec) cord clamping group. Infant morbidities like RDS, NEC, and IVH were not significantly different between DCC and ECC. Incidence of jaundice requiring phototherapy and symptomatic polycythemia was not increased significantly by DCC.

Abbreviations

DCC Delayed umbilical cord clamping; *ECC* early cord clamping; *IVH* intra-ventricular hemorrhage; *MCV* mean corpuscular volume; *NEC* Necrotizing Enterocolitis; *RDS* Reparatory distress syndrome; *TfR* transferrin receptor; *TS* transferrin saturation.

Introduction

The optimal timing of umbilical cord clamping has been debated in the scientific literature for over a century. “Early” cord clamping is generally carried out in the first 30 seconds after birth (generally within the first 15–30 seconds), whereas “delayed” umbilical cord clamping is carried out more than 1 min after the birth or when cord pulsation has ceased.

Cord clamping is part of the third stage of labour, which is the time between the delivery of the infant and the placenta. The cord is usually clamped by applying two clamps and cutting in between the two clamps, without blood loss for either the infant or the mother, through the placenta. During the first 5 to 15 seconds after the delivery, blood volume increases by 5 to 15 ml/kg as a result of uterine contractions. This early placental transfusion does not occur if the cord is clamped immediately after the birth or if the uterine contraction does not occur (Figure 1).[1] The time to umbilical cord clamping may have an important impact on a population’s health, as shown by the results in this study and previous data. Even small effects on each individual may have a great impact when multiplied in a large population.

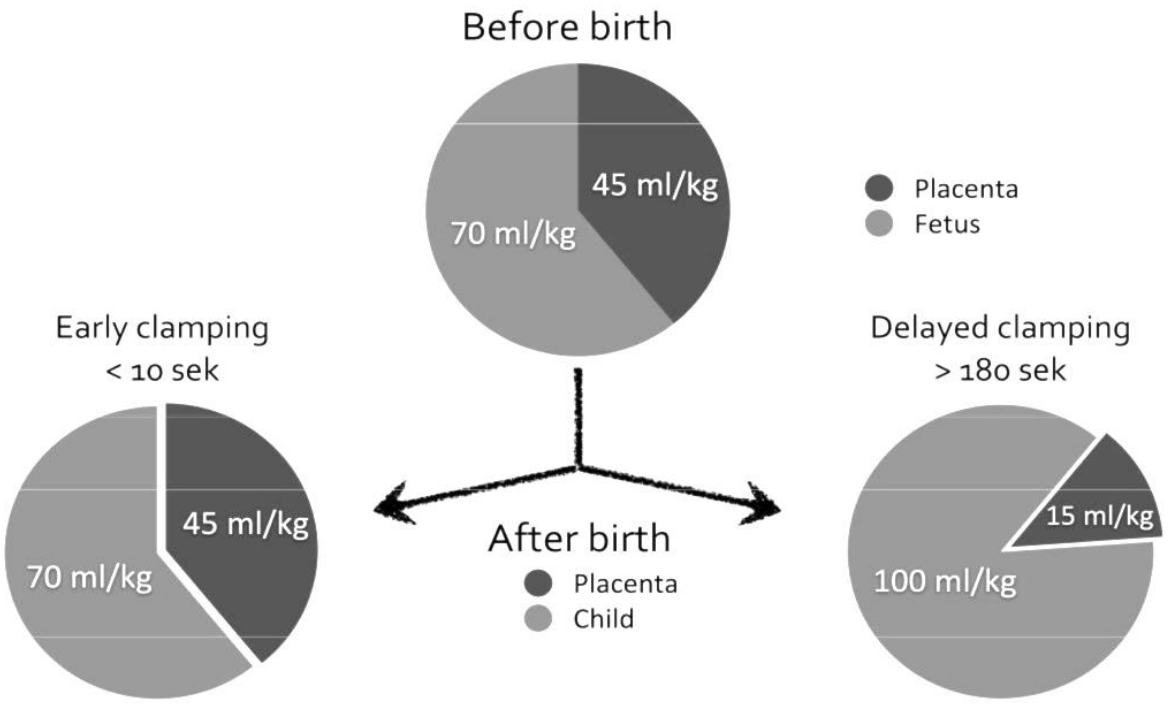

Figure 1. Effects of Delayed versus Early Cord Clamping on Healthy Term Infants

Blood volume in the placenta (dark) and fetus before birth and infant after birth, after early and delayed cord clamping (reproduced from Ola Andersson [1])

sek seconds

Advantages of delaying clamping of the umbilical cord and subsequent increase in placental transfusion include higher haematocrit levels, higher red blood cell flow, lower risk of intra-ventricular haemorrhage, less respiratory distress, less need for blood transfusion and less requirement for respiratory support, lower risk of Necrotizing Enterocolitis, lower risk of late-onset sepsis.[2]

The placental transfusion model (Figure 2).

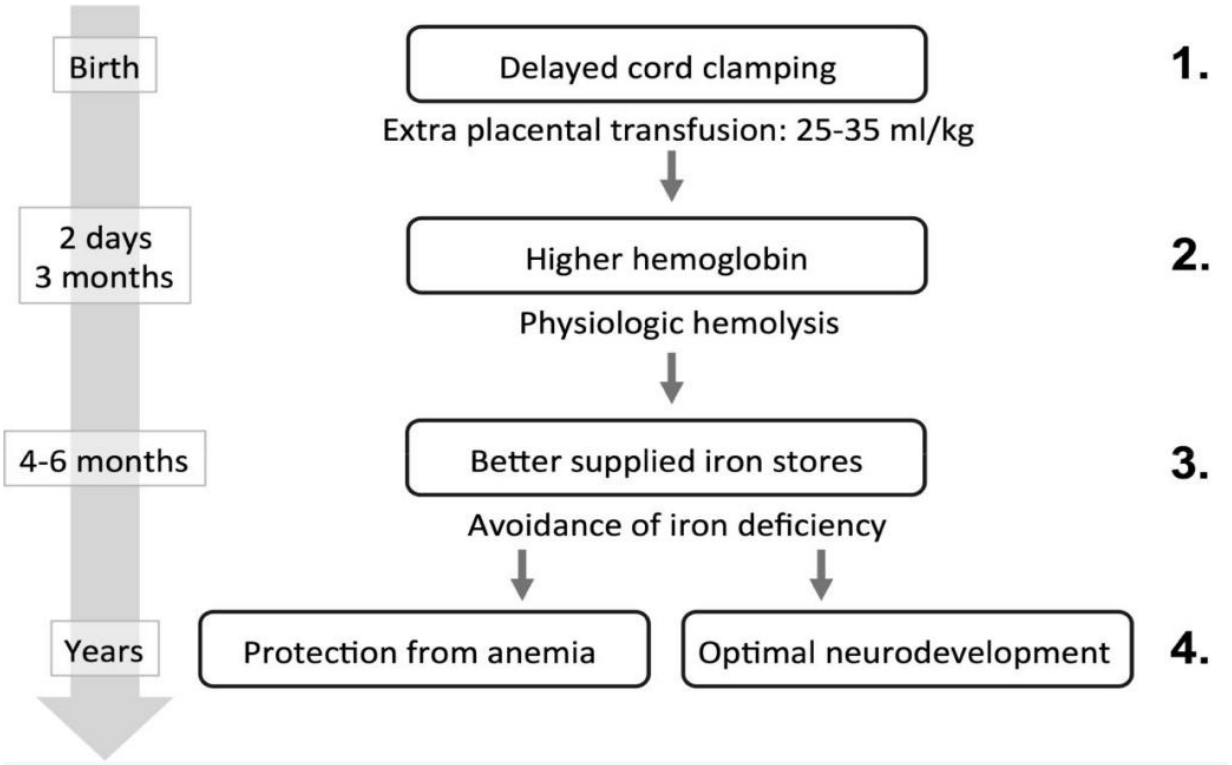

Figure 2. The placental transfusion model (reproduced from Ola Andersson [1])

1. DCC contributes to a net transfusion of umbilical cord blood.
2. This placental transfusion adds to elevated hemoglobin in the newborn period and at two months of age.
3. As the physiologic hemolysis occurs during the first months of life, hemoglobin is metabolised and transferred as iron stores throughout the body, reflected in higher levels of ferritin, transferrin saturation (TS), and lower levels of soluble transferrin receptors (TfR).
4. It also postulated that the excess iron received by placental transfusion could prevent iron deficiency and as a result of this protects from iron deficiency anemia and iron deficiency-associated neurodevelopmental and behavioral deficits later on.

Vikram[3] reported significantly better short-term neuro-behavioral outcome at 37 weeks post- conception age using the Neurobehavioral Assessment of Preterm Infants (NAPI) in motor development and vigor, and alertness and orientation.

The disadvantages may include delay in resuscitation, hypothermia, polycythemia, hyper-bilirubinemia needing treatment. Only Geethanath [4] found that the iron stores at 3 months in term infants are not influenced by timing of cord clamping at birth.

Despite significant proposed benefits, delayed umbilical cord clamping (DCC) is not practiced widely in full-term and preterm infants largely because the habits do not change fast enough and the feasibility of the procedure ie how to co-ordinate with the obstetrics team and carry out it actually are the mental blocks remain to be uncovered by more training and more validation of the benefits.

Another benefit of DCC is that along with hemoglobin the Oxygen is also received by the baby and so asphyxia is prevented or minimized. This is seen as ‘intact cord resuscitation’ studies for asphyxia babies being carried out now.

Aims and Objectives

Primary Objective

To determine the selected hematological effects of delayed cord clamping and placental transfusion on premature (<37 weeks) neonates after birth, and at one and 4-month follow-up.

Methods

Ethics committee and Institution Review Board approval obtained [Regd. with: Directorate General Health Services, Drugs Controller General (India)] ECR/557/Inst/GJ/2014, 29/04/ 2014, Government Medical College, Bhavnagar. Patient consent was obtained.

Duration: January 2016 to June 2016 at Gopinath Maternity ward and NICU of Sir T G hospital, Bhavnagar.

Trial Design

Randomised controlled trial (parallel-group study with 1:1 randomisation) comparing delayed cord clamping (DCC) with early cord clamping (ECC). Randomisation was performed by one of the investigators in advance by computer in blocks of 20 using the random number generator in MS Excel.

Sample size calculation

There are about 1300 deliveries during the study period. And 30% are preterm, so expected preterm would be 390, of whom healthy preterm would be 260. At 95% confidence level, the confidence interval of 8, the sample size would be 95. We included 100 subjects for the study.

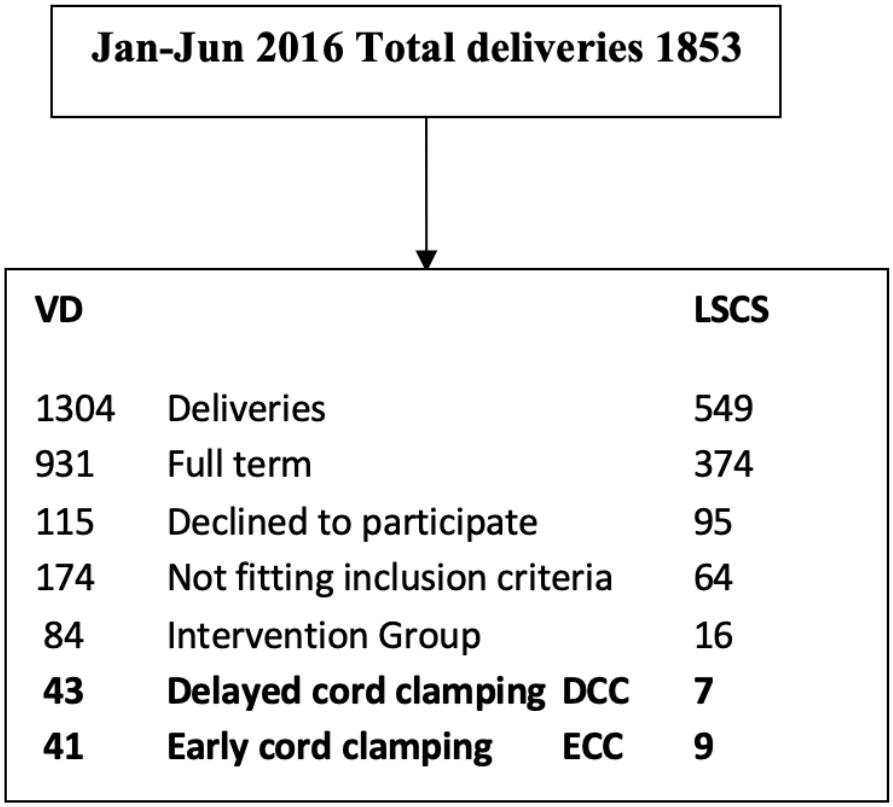

Figure 3. Flowchart 1 Delivery distribution and allocation

VD vaginal delivery; LSCS lower segment cesarean section

Inclusion Criteria:

Preterm infants born before 37 completed gestational weeks, vaginal or cesarean section, single pregnancy.

Exclusion Criteria:

Term infants >37 weeks, fetal distress, fetal hydrops, fetal malformations, instrumental delivery, meconium stained liquor, autoimmune hemolytic anemia, antepartum hemorrhage, birth weight less than 1 kg, multiple pregnancies, congenital heart disease.

Those fulfilling the inclusion criteria at the time of admission to the delivery ward were again informed about the study by the attending midwife. Written informed consent was obtained before delivery from the pregnant woman, and when possible, from both parents.

Intervention and Blinding:

When delivery was imminent (expected within 10 min), the midwife opened a sealed numbered opaque envelope containing the treatment allocation. The intervention in the DCC group consisted of delayed clamping of the umbilical cord (≥ 120 sec) and the ECC group consisted of early clamping of the umbilical cord (≤ 30 sec). In both randomisation groups,

the midwife was instructed to hold the newborn infant at a level around 20 cm below the vulva for 30 sec, and then place the baby on the mother's abdomen. Although, Grajeda[2] had reported slightly better results, with the infant placed at the level of the placenta. All aspects of obstetric care were managed according to standard practice at the hospital. The midwives were also instructed to perform controlled cord traction. All staff in the delivery unit was trained in the study procedures before the trial started. Early cord clamping was the clinical standard procedure in the hospital before and during the study.

Blinding

Due to the study design, neither the mother giving birth nor the midwife performing the intervention could be blinded. Physicians performing neonatal examinations, staff members responsible for the collection of blood samples and background data, and laboratory staff performing analyses of blood samples were blinded to the infant allocation groups. Staff performing the follow-up was blinded to randomisation group, and the parents were asked not to tell the randomisation group to the staff.

Data collection

The midwife's assistant measured the time from complete delivery of the baby to the first clamp on the umbilical cord with a stopwatch.

The infant was assessed at 1 and 6 h by the midwife nurse, who recorded if the baby had been breastfed and the presence of respiratory symptoms, i.e. respiratory rate above 60, presence of nostril flaring, grunting or intercostal re-tractions.

All neonatal diagnoses were reported in the study protocol. At 48-72 h after birth, a midwife or a neonatal nurse collected study samples in conjunction with routine venous blood sampling for metabolic screening. All blood samples were analysed for 'complete blood count': Hb, MCV, in particular. A physician reviewed the results from study samples once a week, and appropriate action was taken if necessary.

1 and 4 month data collection

At 1 and 4 months of age, infants were scheduled for a follow up visit including blood sampling, weight and length measurements. Venous blood sampling was performed after consent. Before discharge from the postnatal ward, the family was asked to regularly record data regarding their infant's health until the last visit at 4 months (the morbidity questionnaire). In the morbidity questionnaire, parents were asked to note, on a daily basis, if the child had: symptoms of infection (fever 38.0ºC or more), abdominal problems (watery diarrhea, loose or hard stools, abdominal pain, vomiting), airway problems (cough, breathing difficulties, rhinorrhea/ runny nose, nasal congestion), other problems (ear discharge, rash, excessive crying, less active), visiting a doctor (pediatrician, other doctor), if the child had antibiotics, and if the child had been admitted to hospital.

Results

Table 1. Baseline characteristics

Baseline	DCC (n=50)	ECC (n=50)	p value
Gestational Age (Weeks)	32.86	32.94	0.84
Birth Weight (Grams)	1698	1598	0.2
Birth Length (Cm)	42.6	42.5	0.23
Head Circumference (Cm)	32.6	32.2	0.32
1 Min Apgar Score	47 (94%)	45 (90%)	0.56
Male Gender	28 (56%)	26 (52%)	0.84
Vegetarian Mother	9 (18%)	11 (22%)	0.8
Iron tablet antenatally	46 (92%)	44 (88%)	0.24

DCC delayed cord clamping; ECC early cord clamping.

Table 1 No differences in infant characteristics (gestational week, birth weight, length, HC, 1 min Apgar score) between the two groups were observed at the start of the study.

Table 2. Various parameters post-intervention

Parameter	unit	DCC group	ECC group	p, X2
RDS	n	8	12	0.45, 0.56
Phototherapy	n	6	4	0.11, 0.73
IVH	n	1	0	0.31, 1.01
NEC	n	0	1	0.31, 1.01
Duration of stay	days	5.3	6.3	0.22
Deaths number	n	1	3	0.60, 0.26
Anemia 1 month	n	1	6	0.10, 2.58
Anemia 4 month	*n*	*2*	*10*	***0.01, 5.54***
Transfusions	*n*	*2*	*9*	***0.031, 4.63***
Hb birth	*g/dl*	*14.59*	*13.52*	***0.0035***
Hb 1 month	*g/dl*	*12.80*	*11.95*	***0.0044***
Hb 4 month	*g/dl*	*13.23*	*11.75*	***0.0001***
MCV 4 month	*fl*	*81.21*	*73.58*	***0.0001***

DCC delayed cord clamping; ECC early cord clamping; RDS respiratory distress syndrome; IVH intraventricular haemorrhage; NEC necrotizing enterocolitis; Hb haemoglobin; MCV mean corpuscular volume.

Table 2 There was statistically no difference in the incidence of RDS (p=0.45), phototherapy for hyperbilirubinemia

(p=0.11), anemia at 1-month of age (p=0.10), IVH (p=0.31), NEC (p=0.31), duration of stay (p=0.22), mortality rate (p=0.60), between both DCC and ECC groups.

There was a *significant* difference, in the incidence of anemia (reduced) and MCV (increased) at 4-month of age (in DCC group, *p=0.01, 0.00*), in the requirement of blood transfusion (reduced by delayed clamping, in the DCC group*p=0.03*), and in the mean hemoglobin at birth (higher in the DCC group, p=0.0**)** between two groups DCC and ECC. In our study, no case of *polycythemia* was noted in either group.

Follow-up and other results of the trial are summarized in figures 4 and 5 (flowchart 2, 3).

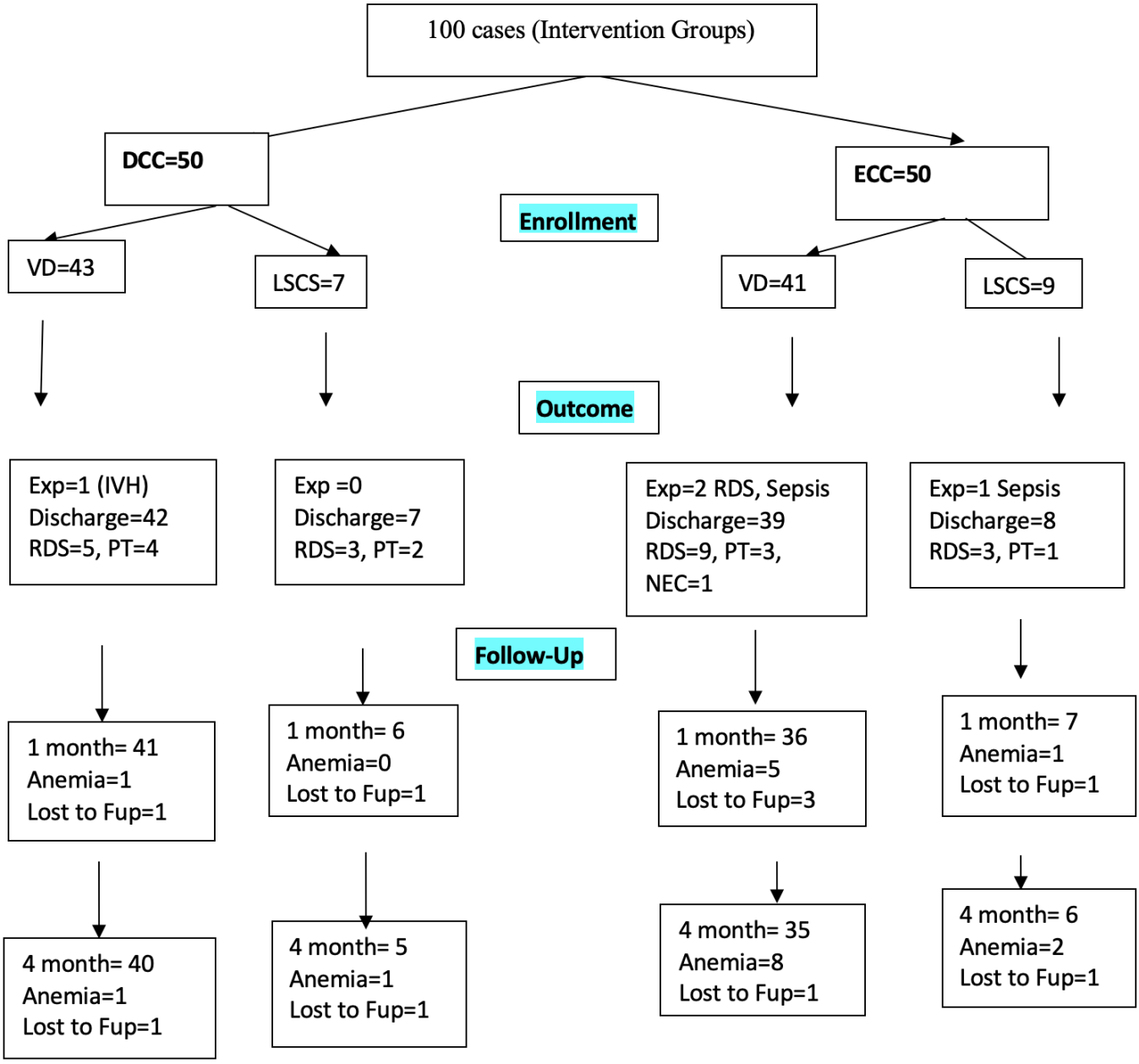

Figure 4. Flowchart 2 Follow-up and morbidity chart

DCC delayed cord clamping; ECC early cord clamping; VD vaginal delivery; LSCS lower segment cesarean section; IVH intra-ventricular hemorrhage; PT phototherapy given; Fup follow up; Exp Deaths

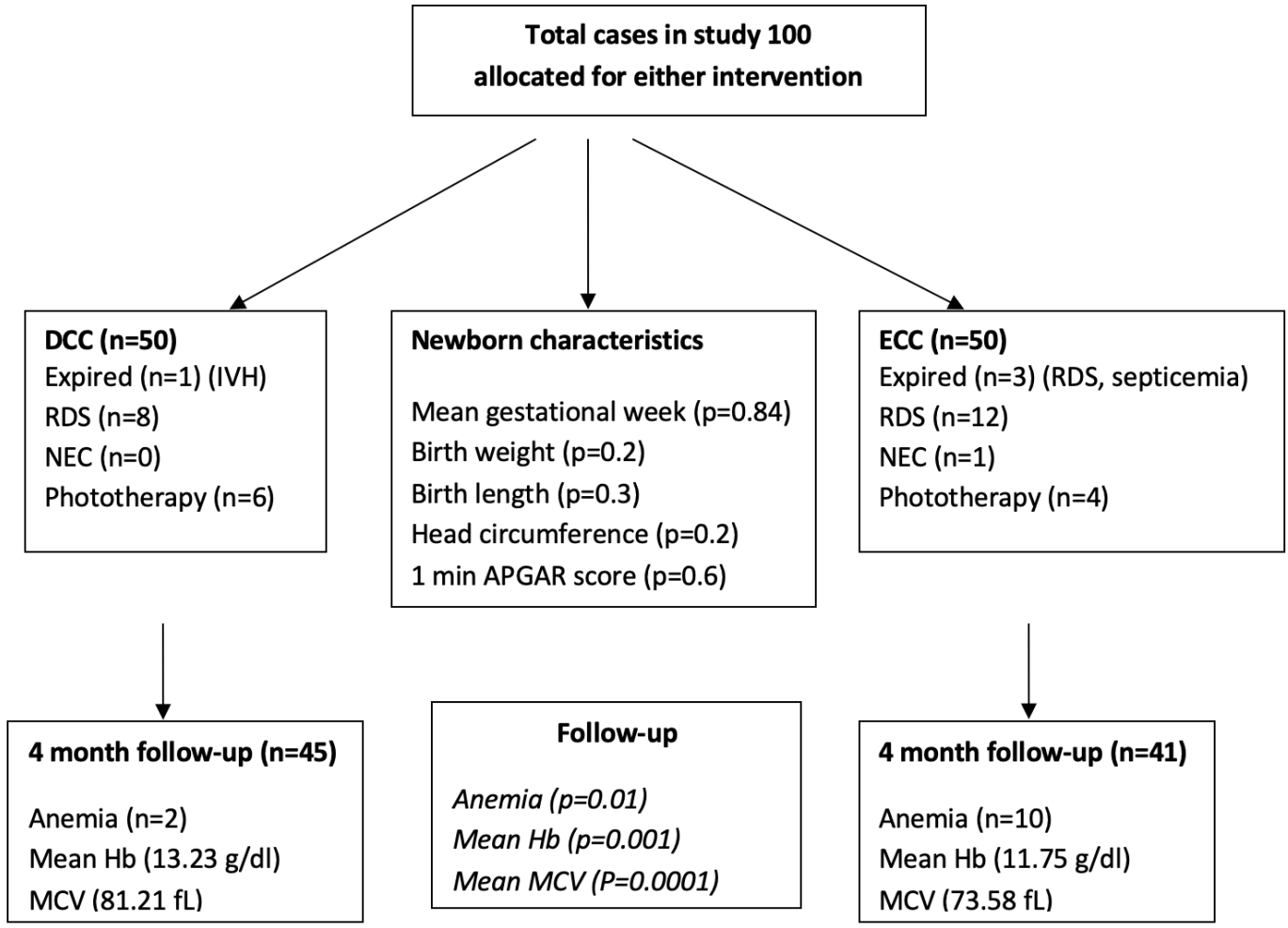

Figure 5. Flowchart 3 Comparison between DCC and ECC

DCC delayed cord clamping; ECC early cord clamping; IVH intra-ventricular hemorrhage; RDS respiratory distress syndrome; NEC necrotizing enterocolitis; MCV mean corpuscular volume.

VD vaginal delivery; LSCS lower segment cesarean section

Discussion

Follow-up We have showed a longer follow-up than previous studies and included measures of MCV (at 4 months, 81.2 vs 73.6) as a proxy for iron deficiency.

Several issues regarding the effects of DCC as compared to ECC have shown contradictory results, such as risks for maternal PPH, and infants' risk for polycythemia and jaundice. Possible benefits of improved iron status in a high-income

country where iron stores are usually adequate are not known. The main proposed disadvantages of DCC in newborn infants are associated with events occurring close to birth, such as polycythemia, respiratory distress, and hyperbilirubinemia, and the need for phototherapy. Reasons for ECC in obstetric practice are decreased maternal post-partum hemorrhage and to facilitate umbilical artery blood gas sampling.

Hemoglobin, iron stores- As our main outcome for the study, and also the base for the sample size estimation, hemoglobin level at 4-month was chosen. As a theoretical framework, we chose the 'placental transfusion model' (see Introduction, Figure 2) for the possible advantages of DCC. The increased placental transfusion associated with DCC will result in elevated neonatal hemoglobin, and probably persisting higher hemoglobin during the first four months of age. Through the normal turnover of red blood cells, hemoglobin is metabolised and transferred to iron stores.

Increased hemoglobin would then result in increased iron stores, and could thus prevent iron deficiency, and as a consequence also protect infants from iron deficiency anemia and iron deficiency-associated neurodevelopmental and behavioral deficits.

Polycythemia, usually defined as venous hematocrit above 65%, and increased blood viscosity, Hutton[5] did find significantly higher rates of polycythemia associated with DCC, although they commented that no infant in any of the included studies in their review had been symptomatic. In the Cochrane report, the risk ratio of polycythemia by ECC compared to DCC was estimated to 0.39 (95% CI 0.12 - 1.27). [6] In our study, no case of polycythemia was noted in either group, suggesting that neonatal polycythemia may be more of a problem in risk groups associated with high intrauterine hematocrit such as maternal diabetes and intrauterine growth restriction.

Hyperbilirubinemia There are conflicting results, also in the meta-analysis, regarding the risks after DCC. In a meta-analysis from 2007, Hutton[5] concluded that DCC was not associated with a higher mean of bilirubin, or a higher risk for, clinical jaundice (8 studies) or use of phototherapy (3 studies), in contrast to results published in another meta-analysis, by van Rheenen [7] three years earlier, demonstrating a higher risk of hyperbilirubinemia after DCC (4 studies). The Cochrane analysis 2008, updated 2013, [6] suggested that DCC was associated with increased risk for jaundice requiring phototherapy but not for clinical jaundice (5 studies). In this Cochrane analysis also unpublished data were included, contributing to over 50% of the data forming the basis for the conclusions. Panda [8] also found an increase of phototherapy and reduction of morbidities and mortalities. In the present study, we did not find any indications of either higher bilirubin or of the proportion of infants having hyperbilirubinemia or the use of phototherapy in the DCC group significantly (p=0.73). However, our population is a selected population of preterm infants without complications, and even then very few preterm infants needed phototherapy.

Respiration A transiently higher respiratory rate after DCC was shown by Yao[9] in 1971, but neither Hutton nor the Cochrane report did find any significantly higher risks of respiratory symptoms associated with DCC. In our study, we observed infants for signs of respiratory distress at 1 and 6 hours, and did not find any significant difference in RDS between the two groups (p=0.45).

Rabe has found DCC feasible in preterm, cesarean, and found that it decreases transfusion needs till the postnatal age of

six weeks. [10]

IVH Mercer found that IVH and LOS were less and haematocrit were higher in very preterm DCC group.[11] Modi found less deaths in preterm DCC group.[12] Ranjit found higher haematocrit, ferritin and more need of phototherapy in preterm DCC group.[13] Duley found some benefits in neurobehavioral outcomes in DCC group.[14]

Conclusions

In the population studied in this trial, preterm infants born after an uncomplicated pregnancy by healthy mothers, delayed cord clamping improved iron stores as inferred from MCV level at 4 months of age. The requirement of blood transfusion was reduced with delayed cord clamping upto 4 months of age significantly. Infant morbidity was not affected between delayed as compared to early cord clamping, either during the neonatal period (hyperbilirubinemia/ jaundice, respiratory symptoms, polycythemia) or at the 4-month of life (infection symptoms, gastrointestinal problems, contact with doctors).

We conclude that delaying umbilical cord clamping for upto 120 sec is a safe and feasible alternative when handling uncomplicated preterm birth. Iron status as inferred from MCV was significantly increased at 4 months of age.

The effects on neurodevelopment are to be seen at 6 to 12 months; therefore it was not studied as the follow-up was of four months.

Benefits and Limitations

This study's major benefit is a long follow-up trying to cover both Hb and blood transfusion requirement. Using several different measurements on iron stores could cause contradictory results, but when all indicators point in the same direction, we see this rather as strengthening the conclusion that DCC enhances iron stores at 4 months.

Data concerning maternal outcomes and the newborn postnatal morbidity were observed and reported by midwives on the obstetric and postnatal ward. Although we do not find it likely, it cannot be ruled out with certainty that the midwife, even if not present at the birth of the baby and witnessing the intervention, still had knowledge of what intervention the specific newborn had undergone, and thus might have been biased in their assessments.

Declarations

Author Contributions

Dr Gohil conceptualized the study and with Dr Minesh prepared the study design. Dr Minesh and Dr Shivani carried out the study. Dr Minesh analysed the results. Dr Gohil and Dr Minesh prepared the first draft. Dr Minesh recorded the results and carried out the statistical analysis. All authors revised the first draft and final draft was prepared and approved by all

authors.

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No finance received. There are no financial disclosures by any authors.

COI There is no conflict of interest by any authors.

Ethics

Ethics and Institutional review board approval obtained[Regd. with: Directorate General Health Services, Drugs Controller General (India)] ECR/557/Inst/GJ/2014/29/04, Government Medical College, Bhavnagar.

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