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Original Research Article

A Prospective Study to Determine the Effectiveness of Delayed Umbilical Cord Clamping in Preterm Infants in a Tertiary Care Hospital

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Conflict of interest: Nil

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.

Study Design: This is randomized, controlled trial in which women in labor with singleton pregnancies before completed 37 weeks' gestation were randomly assigned to ECC (cord clamped before 30sec) or DCC (cord clamped after 120sec).

Results: When analyzing the 100 cases performes per protocol, there were no significant difference in morbidities like RDS (p=0.45), NEC (p=0.31), IVH(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) as well. DCC significantly reduces requirement of blood transfusion and incidence of anemia at birth, at 1 month of age and at 4 months of age.

Conclusion: The requirement of blood transfusion is reduced with delayed cord clamping up to 4 month of age significantly. Infant morbidity was not affected of delayed as compared to early cord clamping, neither when regarding the neonatal period (hyperbilirubinaemia/jaundice, respiratory symptoms, polycythemia), nor the first 4 months of life (infection symptoms, gastro intestinal problems, contact with doctors) It offers hematological and circulatory advantages compared with ECC. A more comprehensive appraisal of this practice is needed.

Keywords: DCC, ECC, Hematological, Preterm, Placenta.

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 [1,2]. In the early 19th century, the English physician, Erasmus Darwin mentioned "another thing very injurious to the child is the tying and cutting of the navel string too soon, which should always be left till the child has not only repeatedly breathed but till all pulsation in the cord ceases. As otherwise the child is much weaker" [3].

Cord clamping is part of third stage of labor, which is the time between 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 [4].

Suggested 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 intraventricular hemorrhage, less respiratory distress, less need for blood transfusion and less requirement for respiratory support, lower risk of necrotizing enetrocolitis, lower risk of late onset sepsis. Potential disadvantages include delay in resuscitation, hypothermia, polycythemia, hyperbilirubinemia needing treatment [5,6]. For developing countries with limited resources and a high risk of transmitting infection through blood transfusion, the potential value of reduced need of blood transfusion would be of particular interest. This study will be of interest to obstretician, midwives, neonatologist as well as pregnant woman [7].

Material and Methods

Study design: Randomised controlled trial (parallel-group study with 1:1 randomisation) comparing delayed cord clamping (DCC) with early cord clamping (ECC). The study was conducted between January 2016 to June 2016 at NICU and Gopnath Maternity Home at Sir-T Hospital, Bhavnagar in 6 months of duration.

Inclusion Criteria

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

Exclusion Criteria

1. Term infants >37 weeks
2. Severe fetal distress
3. Fetal hydrops
4. Fetal malformations
5. Instrumental delivery
6. Meconium stained liquor
7. Autoimmune hemolytic anaemia
8. Antepartum haemorrhage
9. Baby birth weight less than 1 kg
10. Multiple pregnancies
11. 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.

All blood samples were analysed for 'complete blood count': Hb, Hct, MCV, mean cell haemoglobin concentration (MCHC), reticulocyte count (Rtc), and reticulocyte haemoglobin (RetHE).

Definitions and reference range for anaemia and iron status indicators used for defining iron deficiency are presented below Table 1.

Table 1: Definitions of anaemia and iron deficiency at different ages, and poly-cythemia and hyperbilirubinaemia at 2-3 days. Iron deficiency was defined as at least two (out of four) iron store indicators (MCV) outside reference range.

Table 1: Reference value of hematology system

Condition	Test	2-3 days	1 month	4 month
Anemia	Hb(g/dl)	< 14.5[53]	< 10.5[54]	< 11[55]
Iron deficiency	MCV(fL)	<95	< 91[54]	< 73[55]
Polycythemia	Hct(%)	>65	-	-
Hyperbilirubinemia	Bilirubin(micromol/l)	>20[22]	-	-

Results

Maternal characteristics

There were no significant differences in maternal characteristics between the DCC and ECC groups. Neither did maternal characteristics differ between the randomisation groups among those who continued participation in the study with follow up at 1 and 4 months, respectively.

Not reported elsewhere is maternal dietary preferences and use of iron supplementation during pregnancy: a total of 20 women stated that they were vegetarians, 09(18%) in the DCC group and 11 (22%) in the ECC group, p=0.8. A majority of women had taken iron supplements during pregnancy, 46 (92%) in the DCC group and 44 (88%) in the ECC group, p=0.24.

Newborn characteristics

Randomisation was successful as groups were comparable in most aspects. Data on newborn characteristics are presented in Table 2.

The differences between the two groups in birth weight, Hb and Hct were not expected, and a probable explanation is offered in the discussion. Per protocol analysis of background characteristics When analysing the 100 cases performed per protocol, there were no significant differences in maternal background data, and the differences between the randomisation groups in birth weight (p=0.2), gestational age(p= 0.84) were all strengthened.

Table 2: Comparison of Characteristics of Newborn

	Dcc(N=50)	Ecc(N=50)	P Value
Gestational Age(Weeks)	32.86	32.94	0.84
Birrth Weigjht(Grams))	1698	1598	>00.5
Birth Lengths(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

No differences in infant characteristics between the two groups were observed (Table 2)

Outcome Measures

Respiratory System

Table 3: Comparison of respiratory distress syndrome in both groups

	Frequency of RDS		
	Yes	No	Total
DCC	8	42	50
ECC	12	38	50
X2 Value 0.56 P Value 0.45			

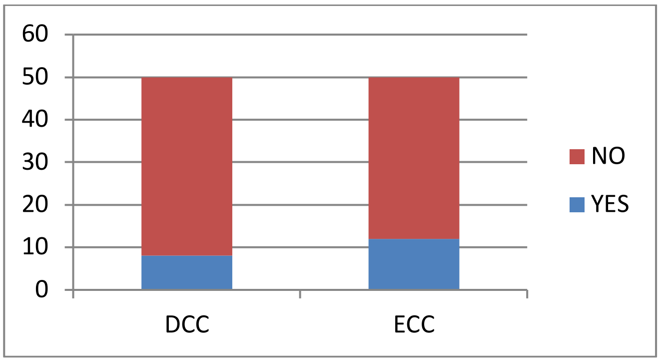

Figure 1: Frequency of RDS in DCC and ECC groups

There is statistically no significant difference (p=0.45) in the incidence of RDS in both DCC and ECC groups (chi square test).

Hematological System

Table 4: Comparison of phototherapy requirements in DCC and ECC groups

	Requirement of Phototherapy		
	Yes	No	Total
DCC	6	44	50
ECC	4	46	50
X2 Value 0.73 P Value 0.11			

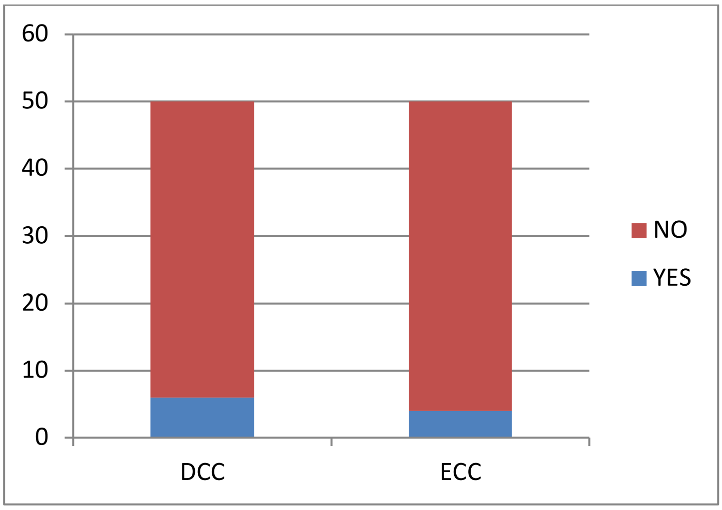

Figure 2: Comparisons of phototherapy requirements in DCC and ECC groups

There is statistically no significant difference (p=0.11) in the phototherapy for hyperbilirubinemia in both DCC and ECC groups (chi square test).

Table 5: Comparison of frequency of anemia at 1 month in DCC and ECC groups

	Frequency of Anemia at 1 Month		
	Yes	No	Total
DCC	1	45	46
ECC	6	37	43
X2 Value 2.58 P Value 0.10			

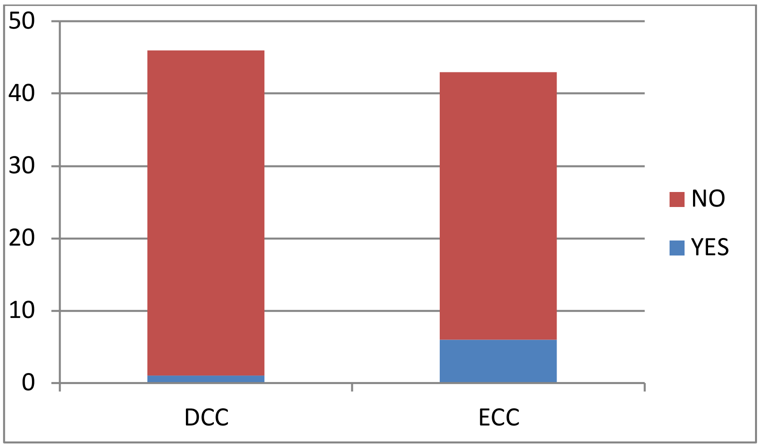

Figure 3: Comparison of frequency of anemia in DCC and ECC groups.

There is statistically no significant difference (p=0.10) in the incidence of anemia at 1 month of age in both DCC and ECC groups (chi square test).

Table 6: Frequency of anemia at 4 month in DCC and ECC groups

	Frequency of Anemia at 4 Month		
	Yes	No	Total
DCC	2	43	45
ECC	10	31	41
X2 Value 5.54 P Value 0.01			

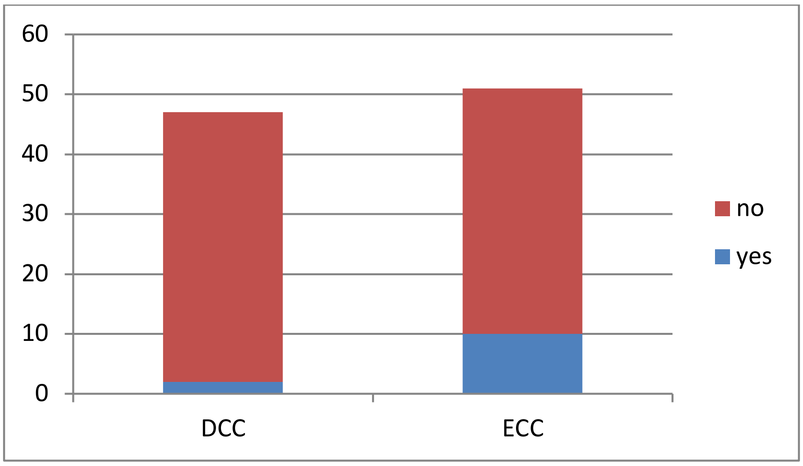

Figure 4: Comparison in incidence of anemia at 4 months of age in DCC and ECC groups

There is statistically significant difference (p=0.01) in the incidence of anemia at 4 months of age in both DCC and ECC groups (chi square test).

Table 7: Blood transfusion requirement in DCC and ECC groups

	Blood Transfusion Requirement		
	Yes	No	Total
DCC	2	43	45
ECC	9	32	41
X2 Value 4.63 P Value 0.031			

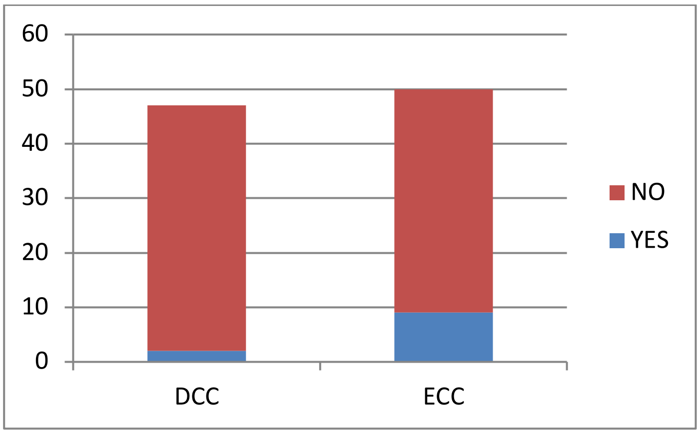

Figure 5: Comparison of blood transfusion requirement in DCC and ECC groups

There is statistically significant difference (p=0.03) in requirement of blood transfusion in both DCC and ECC groups(chi square test).Total requirement of blood transfusion reduced significantly by delayed clamping in DCC groups.

Table 8: Comparison of mean hemoglobin in DCC and ECC groups

	DCC	ECC	P VALUE
AT BIRTH(Hb)	14.59	13.52	0.0035
AT 1 MONTH(Hb)	12.80	11.95	0.0044
AT 4 MONTH(Hb)	13.23	11.75	0.0001
MCV(4 MONTH)	81.21	73.58	0.0001

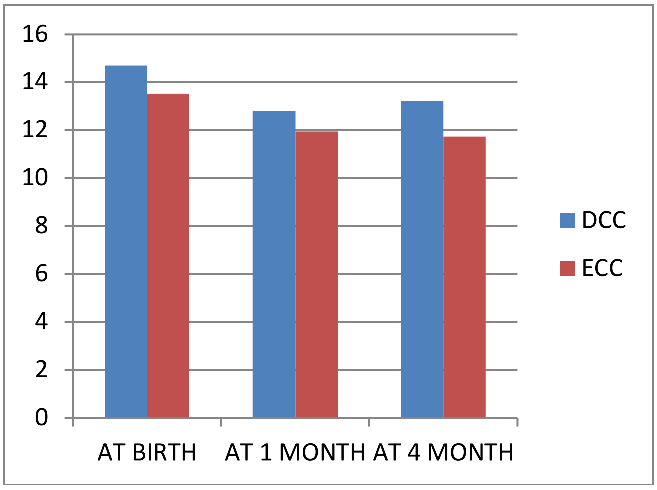

Figure 6: Comparison of mean hemoglobin in DCC and ECC groups

There is significant difference in mean hemoglobin between two groups DCC and ECC. DCC group is having significant higher hemoglobin level as compared to ECC.

CNS Outcome

Table 9: Comparison of IVH in DCC and ECC groups

	Frequency of IVH		
	Yes	No	Total
DCC	1	50	50
ECC	0	50	50
X2 value 1.01 P value 0.31			

There is statistically no significant difference (p=0.31) in the incidence of IVH in DCC and ECC groups (chi square test).

GIT Outcome

Table 10: Comparison of frequency of NEC in DCC and ECC groups

	Frequency of NEC		
	Yes	No	Total
DCC	0	50	50
ECC	1	49	50
X2 Value 1.01 P Value 0.31			

There is statistically no significant difference (p=0.31) in the incidence of NEC in DCC and ECC groups (chi square test).

Morbidity Outcome

Table 11: Comparison of mean duration of stay in days in DCC and ECC

	DCC(Mean)	ECC(Mean)	P Value
Duration of Stay(Days)	5.3	6.3	0.22

There is statistically no significant difference (p=0.22) in duration of stay in both DCC and ECC groups (chi square test).

Mortality Outcome

Table 12: Comparison of mortality in DCC and ECC groups

	Mortality		
	Yes	No	Total
DCC	1	49	50
ECC	3	47	50
X2 Value 0.26 P Value 0.6			

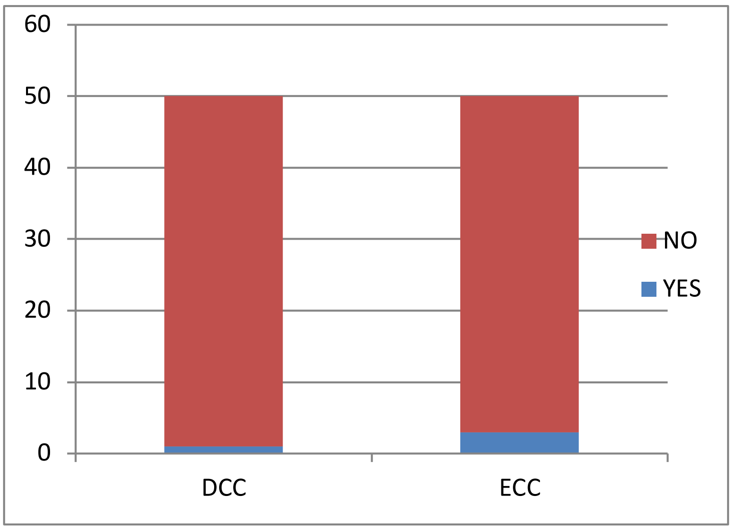

Figure 7: Comparison of mortality in both DCC and ECC groups

There is statistically no significant difference (p=0.60) in mortality rate in DCC and ECC groups (chi square test).

Discussion

The time to umbilical cord clamping may have important impact on a population's health, as shown by the results in this thesis and previous data. Even small effects on each individual may have great impact when multiplied in a large population. To demonstrate the size of effects cord clamping might have, the result showing that iron deficiency was reduced from 17 to 4.4 % at four months of age can be extrapolated [8].

This study was set out to make a broad approach to the subject, and tried to evaluate a wide array of proposed effects of delayed versus early cord clamping, both those considered beneficial and those considered disadvantageous. Furthermore, we wanted to have longer outcomes than previous studies, and included measures of MCV [9,10].

Several issues regarding effects of DCC as compared to ECC have shown contradictory results, such as risks for maternal PPH, and infants' risk for polycythaemia and jaundice. Possible benefits of improved iron status in a high income country are not known. As our main outcome for the study, and also the base for the sample size estimation, hb level at 4 months was chosen [11]

As a theoretical framework we chose the 'placental transfusion model' for the possible advantages of DCC. The increased placental transfusion associated with DCC will result in elevated neonatal haemoglobin, and probably persisting higher haemoglobin during the first two months of age. Through the normal turnover of red blood cells, haemoglobin is metabolized and transferred to iron stores. Increased haemoglobin would then result in increased iron stores, and could thus prevent iron deficiency, and as a consequence also protect infants from iron deficiency anaemia and iron deficiency-associated neurodevelopment and behavioral deficits [12].

The main proposed disadvantages of DCC in newborn infants are associated with events occurring close to birth, such as polycythaemia, respiratory distress and hyperbilirubinaemia and need for phototherapy. Reasons for ECC in obstetric practice are decreased maternal post-partum hemorrhage and to facilitate umbilical artery blood gas sampling [13,14].

As for polycythaemia, usually defined as venous haematocrit above 65%, and increased blood viscosity, Hutton and Hassan did find significantly higher rates of polycythaemia 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 to 1.27) [15].

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 haematocrit such as maternal diabetes and intrauterine growth restriction [16].

There are conflicting results, also in meta-analysis, regarding the risks for hyperbilirubinaemia after DCC. In a meta-analysis from 2007, Hutton and Hassan concluded that DCC was not associated with a higher mean of bilirubin, or a higher risk for, clinical jaundice (8 studies) or use of photo-therapy (3 studies), in contrast to results published in another meta-analysis, by van Rheenen *et al* three years earlier, demonstrating a higher risk of hyperbilirubinaemia after DCC (4 studies). Also the Cochrane analysis from 2008 suggested that DCC was associated with increased risk for jaundice requiring phototherapy but not for clinical jaundice. In this Cochrane analysis also unpublished data were included, contributing with over 50% of the data forming the basis for the conclusions [17]. In the present study, we did not find any indications of neither higher bilirubin, nor of proportion of infants having hyperbilirubinaemia or use of phototherapy in the DCC group significantly (p=0.73). However, our population is a selected population of preterm infants, and very few infants actually needed phototherapy [18,19]. A transiently higher respiratory rate after DCC was shown by Yao & al in 1971, but neither Hutton & Hassan or 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 differences in RDS between the two groups significantly (p=0.45) [20,21].

Conclusions

In the population studied in this thesis, 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 is reduced with delayed cord clamping up to 4 month of age significantly. Infant morbidity was not affected of delayed as compared to early cord clamping, neither when regarding the neonatal period (hyperbilirubinaemia/ jaundice, respiratory symptoms, polycythemia), nor the first 4 months of life (infection symptoms, gastro intestinal problems, contact with doctors).

We conclude that delaying umbilical cord clamping for 120 sec is a safe and feasible alternative when handling preterm birth. Iron status inferred from MCV is significantly reduced at 4 months of age, and the effects on neurodevelopment are to be seen at 12 months, therefore it cannot be studied as the effects on neurodevelopment are discovered at an older age.

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