Randomized Comparative Clinical Assessment of the Umbilical Cord Clamping Timing in Preterm Infants Delivered by Cesarean Section

Amit Kumar[1], Bankey Bihari Singh[2], Ravindra Kumar[3]

[1]Senior Resident, Department of Pediatrics, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India.
[2]Associate Professor, Department of Pediatrics, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India.
[3]Associate Professor, Department of Pediatrics, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India.

Abstract

Aim: To compare three different cord clamping timing (immediate cord clamping(ICC) delayed cord clamping(DCC) and umbilical cord milking(UCM) in preterm infants delivered by cesarean section (CS).

Material & Methods: The randomized clinical trial was conducted at Department of Pediatrics, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India, over a period of one year. A total of 60 pregnant women at less than 32 week's gestation admitted for cesarean section were enrolled in the study and randomly allocated to three group.

Results: The mean gestation age of studied infants was 30.38±1.20 weeks and their birth weight was 1220 ± 43 grams. Duration of O_2 therapy in UCM group was 15.00±9.2, in DCC group was 12.50±3.96 and in UCM group was11.50±7.68(p = >0.05 statistically not significant).

Conclusion: UCM may be as effective as DCC to increase hemoglobin in preterm infants delivered by CS. Although the hemoglobin of infants with DCC and UCM was significantly higher than infants with ICC, the rate of blood transfusion was not significantly decreased during hospital stay.

Keywords: Blood transfusion, Cesarean section, Preterm infants, Umbilical cord clamping.

Introduction

Severe postpartum hemorrhage (PPH) is one of the most important contributors to maternal mortality, particularly in low resource countries [1, 2]. To reduce maternal blood loss, active management of the third stage of labor has been recommended by the World Health Organization (WHO) since 2007, although it was already performed since the 1960s [2–4].

Active management involves three components: (i) prophylactic administration of uterotonic drugs (oxytocin), (ii) controlled cord traction to

support placental delivery, and (iii) massage of uterine fundus after placental delivery [2, 5]. However, a critical review of this guideline showed that the benefit of this approach was completely attributed to the administration of oxytocin [1, 5–7]. On the other hand, to minimize potential neonatal exposure to oxytocin, immediate cord clamping was incorporated into routine clinical practice [3]. In term infants, the placenta holds up to one-third of the total blood volume and immediate cord clamping would thus withhold this from the neonatal circulation [8].

The American College of Obstetrics and Gynaecologists' recommends delayed cord clamping (DCC) for preterm and full- term newborns [9]. There is increasing evidence which suggests delayed umbilical cord clamping may be beneficial. Delayed cord clamping may be beneficial because of the increased amount of placental blood received by neonate and improved transit from fetal to neonatal life [10-12]. Improved blood pressure, reduced need for blood transfusion, intra-ventricular hemorrhage, necrotizing enterocolitis and infection are shown by delayed umbilical cord clamping in infants born before 37 weeks of gestation [13].

Umbilical cord milking is an alternative to delayed cord clamping in which unclamped umbilical cord is grasped and blood is pushed toward the infant within 20 seconds before it is clamped. Some studies demonstrated that infants delivered at less than 33 weeks who undergo umbilical cord milking have higher hemoglobin and are at lower risk for Broncho pulmonary dysplasia and intraventricular hemorrhage in comparison with immediate cord clamping [14].

Thus, we aim to compare three different cord clamping timing (immediate cord clamping, delayed cord clamping and umbilical cord milking) in preterm infants delivered by cesarean section (CS).

Material & Methods:

The randomized controlled clinical trial was conducted at Department of Pediatrics, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India. over a period of one year. A total of 60 pregnant women at less than 32 week's gestation admitted for cesarean section were enrolled in the study.

Exclusion criteria:

Patients with placental abruption, placenta previa, known Rh sensitization, hydrops fetalis, mono chorionic multiples, nuchal cords and infants with major anomalies or who need immediate resuscitation were excluded from the study.

Methods:

Computer generated random numbers in opaque sealed envelopes just before delivery randomly assigned the patients to three groups (immediate cord clamping, delayed cord clamping and umbilical cord milking). A clock in the operation room was used for timing. The primary outcome was anemia of prematurity and need of blood transfusion; and the secondary outcome was the bronchopulmonary dysplasia (BPD), and duration of hospital stay. A total of 60 patients with gestation age 32 weeks or less delivered by cesarean section that met inclusion criteria were enrolled in this study.

Intervention:

In delayed cord clamping (DCC) group, 60 seconds elapsed from when the infant was delivered until the obstetrician assistant clamped the time the umbilical cord. The infant was held at the same level as the placenta in umbilical cord milking (UCM) group. By holding the placental end of umbilical cord, gently milked blood within umbilical vessels was directed toward the neonate over 2 seconds duration three times with a brief pause between each milking motion. Cord clamping was performed within 10 seconds after infant delivery in immediate cord clamping (ICC) group.

Laboratory measurements:

The hemoglobin and hematocrit level was measured by venipuncture at 6 hours after birth, one month of age and at discharge in all neonates. We considered hematocrit above 65% as polycythemia (15). Cranial ultrasound examination was performed on days 5 to 7 of birth for the diagnosis of intraventricular hemorrhage (IVH) by an experienced pediatric radiologist. BPD was defined as the need for supplemental oxygen for at least 28 days and its severity was determined at 36 weeks of gestation age based on the fraction of inspired oxygen (16). Patent ductus arteriosus (PDA) was diagnosed based on clinical signs and confirmed by echocardiography performed by an expert pediatric cardiologist. Infants with moderate to severe cardiac or respiratory diseases received blood transfusion to maintain hematocrit 30-40%. An experienced nurse who was not aware about the studies' objective and patient's groups recorded all data.

Ethical consideration:

Ethic clearance was taken prior to the study and written informed consent was obtained from parents.

Data Analyses:

A person who was not involved in the diagnosis and treatment of infants using SPSS software version 25performed the analyses. Quantitative data were presented as mean ± standard deviation (SD) and qualitative data as frequency and percentage. Categorical data were analyzed by Chi-square test or Fisher's exact test. One way ANOVA was used for continuous outcomes. A p-value of less than 0.05 was considered statistically significant.

Results:

A total of 60 patients with gestation age 32 weeks or less delivered by cesarean section that met inclusion criteria were enrolled in this study. Each group (immediate cord clamping, delayed cord clamping and umbilical cord milking) consisted of 20 neonates. The mean gestation age of studied infants was 30.38 ± 1.20 weeks and their birth weight was 1220 ± 43 grams. [Table.1]

Table1: Baseline characteristics of patients in three groups (n=60).

Variables	ICC group n=20	DCC group n=20	UCM group n=20	P- value
Gestation age, week	30.38 ± 1.20	30.49 ± 1.16	30.67 ± 1.72	0.391
Birth weight, gr	1220 ± 43	1139 ± 140	1177 ± 189	0.102
Male, n (%)	15 (75%)	10(50%)	14 (70%)	0.299
Apgar score				
1min	7.62 ± 1.4	6.44 ± 1.8	7.72 ± 1.1	0.001
5 min	9.38 ± 1.1	8.63 ± 0.6	8.83 ± 0.9	0.071
Antenatal corticosteroids				
No	4	2	2	0.724
1 dose	7	6	11	
2 doses	19	22	17	

(ICC=immediate cord clamping, DCC= delayed cord clamping, UCM=umbilical cord milking)

The hemoglobin and hematocrit concentrations at different ages are shown in Table.2. It was statistically significant with all the three groups (p=0.001). Duration of O_2 therapy in ICC group was 15.83 ± 12.8, in DCC group was 13.27 ± 8.4 and in UCM group was12.7 ± 14.2. [Table 2]

Table 2: Laboratory and clinical measurements in studied patients (n=60).

Variables	ICC group n=20	DCC group n=20	UCM group n=20	P- value
Hb at admission, g/dl	19.62 ± 2.0	18.53 ± 1.4	20.52 ± 2.4	0.001
Hb at 1 month, g/dl	15.88 ± 2.8	13.77 ± 3.6	15.82 ± 3.10	0.001
Hb at discharge, g/dl	11.48 ± 1.9	11.21 ± 2.8	14.65 ± 3.1	0.583
TSB at day 7, mg/dl	8.0 ± 1.4	9.06 ± 2.2	9.49 ± 1.7	0.001
Need for mechanical ventilation, n (%)	9 (45%)	4(20%)	1(5%)	0.447
Duration of O_2 therapy, day	15.83 ± 12.8	13.27 ± 8.4	12.7 ± 14.2	0.280
Surfactant therapy, n (%)	11 (55%)	14(70%)	15(75%)	0.492
PDA, n (%)	1 (5%)	2(10%)	4(20%)	0.391

(ICC= immediate cord clamping, DCC= delayed cord clamping, UCM= umbilical cord milking, Hb= hemoglobin, TSB= total serum bilirubin, PDA= patent ductus arteriosus.)

Discussion:

The question of early versus late umbilical cord clamping is still a controversial issue, especially due to the greater emphasis on the problems of excessive The question of early versus late umbilical cord clamping is still a controversial issue, especially due to the greater emphasis on the problems of excessive placental transfusion (hyper-bilirubinemia, polycythemia, and hypervolemia).

Saigal et al. compared the placental transfusion in preterm and term infants, and found that the complete transfusion was of similar size (47% and 50% increase in blood volume in preterm and term infants, respectively).A larger proportion of the 5-minute transfusion occurred by 1 minute in full-term (76%) than in premature infants (56%).(17) Over half the full transfusion occurred by 1 min in the preterm infants. Infants who were held 15 cm above the introitus for 1 min received a transfusion which was 60% of that received by infants held dependent for the same time. There was a direct correlation between venous haematocrit and blood volume at age 4 h among infants of similar size.

Based on these data we thought it was likely that a modest transfusion would occur by 30 s, even without lowering the infant below the introitus. In addition, syntocinon was administered in all cases after delivery. The onset of action of syntocinon is within 45 s of intravenous injection (18). This might result in an excessive placental transfusion which we wished to avoid.

Placental blood during UCM is directed toward the lungs during a time when there is a rapid fall in pulmonary resistance unlike any other period when volume is given. Concerns about rapid changes in venous pressure during cord milking were addressed in an early trial that demonstrated no greater increase in venous pressures with UCM compared with uterine contractions or a newborn cry during intact placental circulation. (19) Although there are limited data on neurodevelopmental outcomes in premature infants, (20) UCM has been studied in 7 randomized controlled trials and 9 controlled trials over the past 60 years in term and preterm infants (n = 1904), documenting its safety and efficacy. (21-22)

The impact of uterine contractions and breathing is not well-established (23). This is particularly important given that the potential side-effect of the additional blood volume is neonatal hyperbilirubinemia and the need for phototherapy, due to breakdown of red blood cells. The need for phototherapy in our study was higher in neonates after delayed cord clamping, as

was also demonstrated in earlier trials [24]. Neonatal temperature management in the delivery room is of high importance, since hypothermia is associated with a higher risk of hypoglycemia and respiratory distress [25].

Although the mean Apgar score was lower in DCC group in our study, the median Apgar score was not less than five. The meta-analyses carried out so far have shown no differences between delayed cord clamping and early cord clamping groups in terms of Apgar scores and body temperatures taken on admission to the newborn unit [26].

Delayed cord clamping at cesarean section resulted in a mixed respiratory and metabolic acidosis with increased pCO_2 and lactate, in combination with a reduction in base excess [27-30].

Conclusion:

UCM may be as effective as DCC to increase hemoglobin in preterm infants delivered by CS. Although the hemoglobin of infants with DCC and UCM was significantly higher than infants with ICC, the rate of blood transfusion was not significantly decreased during hospital stay.

References:

1. McDonald SJ, Middleton P, Dowswell T, Morris PS. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane Database Syst Rev. 2013; 2013:CD004074.
2. Winter C, Macfarlane A, Deneux-Tharaux C, Zhang WH, Alexander S, Brocklehurst P, et al. Variations in policies for management of the third stage of labour and the immediate management of postpartum haemorrhage in Europe. BJOG. 2007; 114:845–54.
3. Begley CM, Gyte GM, Devane D, McGuire W, Weeks A, Biesty LM. Active versus expectant management for women in the third stage of labour. Cochrane Database Syst Rev. 2019; 2:CD007412.
4. De Paco C, Herrera J,Garcia C, Corbalan S, Arteaga A, PertegalM, et al. Effects of delayed cord clamping on the third stage of labour, maternal haematological parameters and acid-base status in fetuses at term. Eur J Obstet Gynecol Reprod Biol. 2016; 207:153–6.
5. Rabe H, Gyte GM, Diaz-Rossello JL, Duley L. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database Syst Rev. 2019; 9:CD003248.
6. Salati JA, Leathersich SJ, Williams MJ, Cuthbert A, Tolosa JE. Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. Cochrane Database Syst Rev. 2019; 4:CD001808.
7. Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database Syst Rev. 2018; 12: CD011689.
8. Katheria AC, Lakshminrusimha S, Rabe H, McAdams R, Mercer JS. Placental transfusion: a review. J Perinatol. (2017) 37:105–11.
9. Committee on Obstetric practice committee opinion No. 684: delayed umbilical cord clamping after birth. Obstet Gynecol 2017; 129: e5-10.
10. Moradi WT, Morris J, Kiby A, Robledo K, Askie L, Brown R, et al. delayed cord clamping in preterm infants. The New Engl J Med. 2012; 377:2445-55.
11. Rabe H, Reynolds G, Diaz-Rossello JL. A systematic review and meta-analysis of a brief delay in clamping of umbilical cord of preterm infants. Neonatology 2008; 93:138-44.

12. Manley BJ, Owen LS, Hooper SB, Jacobs SE, Cheong JLY, Doyle LW, et al. Towards evidence based resuscitation of newborn infants. Lancet 2017; 389: 1639-48.

13. Robe H, Reynolds G, Draz- Rossello J. A systematic review and meta-analysis of a brief delay in clamping the umbilical cord of preterm infants. Neonatology 2008;93: 138-44.

14. Al-Wassian H, Shah PS. Efficacy and safety of cord milking at birth: a systematic review and meta- analysis. JAMA Pediatr 2015; 169 (1):18-25.

15. Alsafadi TRM, Hashmi SM, Youssef HA, SulimanAK, Mansour Abbas H, Albaloushi MH. J Clin Neonatol. 2014; 3 (2): 93–8.

16. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Resp Crit Care. 2001. 163: 1723-29.

17. Saigal S, O'Neill A, Surainder Y, Chua L, Usher R. Placental transfusion and hyperbilirubinaemia in the premature. Pediatrics 1972 Mar;49(3):406-19.

18. Gibbens D, Boyd NRH, Crocker S, Baumber S, Chard T. The circulating levels of oxytocin following administration of syntometrine. J. Obstet. Gynaecoi. Brit. Common. 1973; 79 644-6.

19. McCausland AM, Holmes F, Schumann WR. Management of cord and placental blood and its effect upon the newborn. Calif Med. 1949;71 (3): 190–196

20. Ghavam S, Batra D, Mercer J, et al. Effects of placental transfusion in extremely low birthweight infants: metaanalysis of long- and short-term outcomes. Transfusion. 2014;54(4): 11 92–1198

21. Colozzi AE. Clamping of the umbilical cord; its effect on the placental transfusion. N Engl J Med. 1954;250 (15): 629–632

22. Erickson-Owens DA, Mercer JS, Oh W. Umbilical cord milking in term infants delivered by cesarean section: a randomized controlled trial. J Perinatol. 2012;32(8):580–584

23. Boere I, Roest AA, Wallace E, Ten Harkel AD, Haak MC, Morley CJ, et al. Umbilical blood flow patterns directly after birth before delayed cord clamping. Arch Dis Child Fetal Neonatal Ed. 2015; 100: F121– 5.

24. Emhamed MO, van Rheenen P, Brabin BJ. The early effects of delayed cord clamping in term infants born to Libyan mothers. Trop Doct. 2004; 34: 218–22.

25. Laptook AR, Watkinson M. Temperature management in the delivery room. Semin Fetal Neonatal Med. 2008; 13:383–91.

26. Gokalp AS, Gunlemez A, Oguz D.Umbilical Cord .Clamping Time in Premature Infants. J Neonatal Biol 2017; 6:1.

27. Giovannini N, Crippa BL, Denaro E, Raffaeli G, Cortesi V, Consonni D, et al. The effect of delayed umbilical cord clamping on cord blood gas analysis in vaginal and caesarean-delivered term newborns without fetal distress: a prospective observational study. BJOG. 2020; 127:405– 13.

28. Valero J, Desantes D, Perales-Puchalt A, Rubio J, Diago Almela VJ, Perales A. Effect of delayed umbilical cord clamping on blood gas analysis. Eur J Obstet Gynecol Reprod Biol. 2012; 162:21–3.

29. Wiberg N, Källén K, Olofsson P. Delayed umbilical cord clamping at birth has effects on arterial and venous blood gases and lactate concentrations. BJOG. (2008) 115:697–703.

30. Wijegunasekara, H. Reproductive Health Management Information System in Sri Lanka: Reflective writing. Journal of Medical Research and Health Sciences, 2021; 4(9): 1456–1460.