Archives of Gynecology and Obstetrics (2019) 299:719–724
https://doi.org/10.1007/s00404-019-05048-5

MATERNAL-FETAL MEDICINE

Delayed cord clamping does not affect umbilical cord blood gas analysis

Jiachen Tang[1,2] · Rachel Fullarton[1] · Sheri-Lee Samson[3,4] · Yu Chen[1,5]

Received: 4 October 2018 / Accepted: 5 January 2019 / Published online: 17 January 2019

Abstract

Background Although delayed umbilical cord clamping has been shown to have significant benefits for both term and preterm infants, currently, data on its impact on blood gas analysis have been scant and conflicting.

Methods In a retrospective review, we compared the demographic characteristics and blood gas parameters of 114 delayed cord clamping (DCC—births between 45 and 90 s in length; 109 being for 60 s) versus 407 early cord clamping births (ECC—immediately after delivery) collected over a 1-year period. Intrapartum care and timing of cord clamping for individual cases were performed at the discretion of obstetricians. The differences were assessed for statistical and clinical significance.

Results The DCC group was found to have significantly higher mean Apgar scores at both 1 and 5 min ($p < 0.05$), as well as lower percentages of nulliparous births, cesarean-section deliveries, epidural anesthesia usage, and major pregnancy-related complications. No significant differences in maternal age, gestational age, neonate birthweight, sex, or in the presence of meconium at birth were observed. A higher umbilical artery pO_2 in the DCC group [21 (9) vs. 19 (10) mmHg, $p < 0.05$] was the only statistically significant difference found out of all the blood gas parameters analyzed.

Conclusions In this study, infants selected for the DCC procedure were found to be overall lower risk than those delivered as per the standard ECC procedure. No clinically significant difference in any blood gas parameter was observed, and therefore, no adjustment to clinical reference intervals is needed for DCC blood gas samples taken after a 1-min delay period.

Keywords Delayed cord clamping · Early cord clamping · Blood gas · Neonate · Pregnancy

Introduction

Early umbilical cord clamping (ECC) has been the standard of care for many decades, but recent accumulating evidence favoring delayed cord clamping (DCC) in terms and preterm infants has led to many professional organizations like the World Health Organization, American Academy of Pediatrics, Royal College of Obstetricians and Gynecologists, and American College of Nurse-Midwives, accrediting DCC as the recommended procedure for labor and delivery [1]. Many benefits can be conveyed to the newborn by a brief delay in cord clamping, as the placenta can supply up to an additional 100 mL of blood to the infant, 80 mL of which is delivered within the first minute [2].

DCC has been shown to be beneficial to term and preterm infants. Term infants experienced increased hemoglobin levels at birth and improved iron stores for the first several months of life [3]. A 2007 meta-analysis by Hutton and Hassan [4] found that a delay period of 2 min or more

✉ Yu Chen
yu.chen@horizonNB.ca

1 Department of Laboratory Medicine, Dr. Everett Chalmers Regional Hospital, Horizon Health Network, Fredericton, NB E3B 5N5, Canada

2 Faculty of Science, University of New Brunswick, Fredericton, NB, Canada

3 Department of Obstetrics and Gynecology, Dr. Everett Chalmers Regional Hospital, Horizon Health Network, Fredericton, NB, Canada

4 Department of Obstetrics and Gynecology, Dalhousie University, Halifax, NS, Canada

5 Department of Pathology, Dalhousie University, Halifax, NS, Canada

decreased the risk of anemia by 47% and the risk of iron store deficiencies by 33% at ages 2–3 months. It has also been proposed that DCC increases the supply of stem and progenitor cells, and could be an effective and non-invasive way of transplanting these cells to the infant to combat neonatal and age-related diseases [5, 6]. Studies have shown that DCC in preterm infants results in less need for blood transfusions, and lower incidences of necrotizing enterocolitis and intraventricular hemorrhage [3, 7]. The latter two benefits have been linked to improved transitional circulation as cord clamping before the onset of effective infant ventilation can result in large swings in cardiovascular function that may be harmful to the infant, particularly for the pressure passive neonatal brain [8].

Potential issues for DCC infants include an increase in polycythemia and neonatal jaundice requiring phototherapy. The increased polycythemia has been shown to be asymptomatic however, and the condition is considered benign [4, 9]. DCC does seem to slightly increase the risk of getting more severe neonatal jaundice that requires phototherapy treatment, but does not impact the overall risk of clinical jaundice as a condition itself [3]. A recent randomized trial involving 1634 preterm infants suggested that DCC does not result in a lower incidence of combined outcome death or major morbidity at 36-week gestational age compared to ECC infants [10]. Furthermore, there was no increased risk for the mother with respect to postpartum hemorrhage, increased blood loss at delivery, lower hemoglobin levels, or need for blood transfusions have been reported, and no significant difference in the use of uterotonic drugs [3].

Cord blood gas (BG) analysis is an important test used for assessing the status of the baby and the potential effects of labor, delivery, and intrapartum care on the newborn. Arterial umbilical cord BG is an essential criterion in defining neonatal encephalopathy and cerebral palsy due to an intrapartum cause, and cord blood acid–base measurements are used in diagnosing metabolic acidosis [11, 12]. Physiological changes at birth could impact BG parameters in DCC infants, which would call for new reference intervals. Evidence on the impacts of DCC on BG is currently scant and conflicting [13–15]. In this retrospective report, umbilical BG parameters in ECC and DCC samples taken after a 45–90 s delay (with over 95% of cases delayed for 60 s) were analyzed for statistical and clinical significance.

Materials and methods

The Department of Obstetrics and Gynecology at the Dr. Everett Chalmers Regional Hospital, Horizon Health Network (Fredericton, New Brunswick, Canada) gradually started 60 s DCC for uncomplicated cases in February 2017. For cases involving complicated births, such as twin pregnancies, births to diabetic mothers, placental abruption, and neonates requiring resuscitation, ECC procedures were preferentially carried out—intrapartum care and timing of cord clamping were left to the discretion of obstetricians. Timing of cord clamping was clearly indicated by staff in the Labor and Delivery Unit on the cord blood gas requisition form and transcribed to the laboratory information system (Meditech, Westwood, Massachusetts, United States).

All DCC and ECC cases of vigorous term and preterm infants between February 2017 and February 2018 were retrospectively reviewed with a study protocol approved by the institute's Research Ethics Board (File #: 2018–2614). Maternal and neonatal demographic variables including maternal and gestational age, parity, mode of delivery, epidural anesthesia usage, neonate birthweight, Apgar scores at 1 and 5 min, sex, presence of meconium at birth, and major pregnancy-related complications (including diabetes mellitus, chorioamnionitis, and cholestasis), were pulled from medical records and compared.

Routine arterial and venous samples were taken from doubly clamped cords, either immediately after delivery (ECC, $n = 407$) or after a 45–90 s delay (DCC, $n = 114$). To better compare with the all-singleton births in the DCC group, 27 non-singleton births in the ECC were excluded from the BG analysis. One DCC sample was also excluded from analysis due to it lacking almost all its demographic information. Blood gas measurements were made directly by GEM4000 (Instrumentation Laboratory, Bedford, MA, USA) for pH, pO_2, pCO_2, lactate, and total hemoglobin (Hb), with HCO_3^- and base excess (BE) being calculated afterwards. Samples with partially incomplete BG results due to instrumental error or blood clotting were still kept, maximizing sample sizes. Specimens were placed on ice-water slurry, and the turnaround time between sampling and receiving BG results was kept under 30 min to minimize the effects of blood cell metabolism on BG parameters.

Statistics

R Studio (version 3.3.2) and Excel 2016 were used for data analyses and manipulations. The Shapiro–Wilk and Levene's tests were used to test for normality and equal variance, respectively. The Mann–Whitney U test was used to compare numerical parameters and the Chi-square test was used to compare nominal parameters. A p value < 0.05 was considered statistically significant. Data used in the U test were summarized as medians with 95% confidence intervals, interquartile ranges (IQR), and 2.5th and 97.5th percentiles. No correction to the p value for multiple testing was applied for multiple reasons. First, in the current study, we are conducting a relatively small number of comparisons with preplanned hypotheses [16]. Second, we were concerned with the results of individual tests rather than testing for

a universal null hypothesis stating that all tests are not significant [16]. Finally, we wanted to avoid type II error more than type I error when looking at BG parameters as failing to detect a significant difference between DCC and ECC treatment groups would be more costly than a false positive for significant difference; this factor was exacerbated by the fact that we have unequal sample sizes which serves to decrease the statistical power of any test [17].

Clinical significance was judged by comparing DCC averages with values from the ECC group, using common clinical acceptance limits as a guideline (CAL, e.g., 0.04 for pH, 9 mmHg or 10% for pO_2, 5 mmHg or 8% for pCO_2, 0.4 mmol/L or 15% for lactate, and 7% for total hemoglobin) [18–20].

Results

As the patients were not randomized nor matched, and the timing of cord clamping was left to the discretion of obstetricians, demographic parameters were found to differ between DCC and ECC groups. The DCC group was found to have significantly higher mean Apgar scores at both 1 and 5 min ($p < 0.05$), as well as lower percentages of nulliparous births, C-section deliveries, epidural anesthesia usage, and major pregnancy-related complications. No significant differences in maternal age, gestational age, neonate birthweight, sex, or presence of meconium at birth were observed (see Table 1).

Over 95% of DCC samples were taken after a 60s delay period (109/114 DCC samples). ECC and DCC BG parameters varied in terms of sample size (n) from 355 to 378 and 95 to 112, respectively, due to clotting, small sample volume, instrumental error, etc. (see Tables 2, 3). A higher umbilical artery pO_2 in the DCC group [median (IQR): 21 (9) vs. 19 (10) mmHg, $p < 0.05$] was the only statistically significant difference found out of all the BG parameters analyzed.

Discussion

Umbilical cord blood gas analysis helps to assess a newborn's metabolic status and to determine the presence of hypoxic ischemic encephalopathy and birth injuries. Accurate cord blood gas analyses are used to guide neonatal care and as evidence in birth trauma lawsuits. Current clinical reference intervals for neonatal umbilical blood gas parameters have been set for early umbilical cord clamping cases. However, it is unclear whether these same standards can be applied to infants after delayed cord clamping. So far, studies comparing ECC and DCC BG parameters have reported contradicting results. Significant differences in BG parameters have been found in studies with different experimental designs. Wiberg et al. [13] conducted a longitudinal study

Table 1 Maternal and neonatal demographics

Characteristics	ECC ($n = 380$)	DCC ($n = 114$)	p value
Maternal age, median (IQR), years	29.7 (8.1)	30.1 (6.8)	0.2771
Gestational age, median (IQR), days	275 (10)	275 (10.7)	0.6516
Parity, *n* (%)			
Nulliparous	146 (38.4)	28 (24.6)	< 0.01**
Parous	234 (61.6)	86 (75.4)	
Mode of delivery, *n* (%)			
Vaginal	222 (58.4)	83 (72.8)	< 0.01**
Cesarean section	158 (41.6)	31 (27.2)	
Epidural anesthesia, *n* (%)	165 (43.7)	36 (31.6)	0.02855*
Neonatal sex, *n* (%)			
Male	192 (50.5)	68 (59.7)	0.1087
Female	188 (49.5)	46 (40.3)	
Birth weight, median (IQR), g	3451 (600)	3475 (717)	0.5766
Meconium-stained amniotic fluid, *n* (%)	85 (22.4)	19 (16.7)	0.2385
Apgar score at 1 min, median (IQR)	9 (2)	9 (1)	< 0.01**
Apgar score at 5 min, median (IQR)	9 (0)	9 (0)	0.02081*
Major pregnancy-related complications, *n* (%)	59 (15.5)	2 (1.8)	< 0.01**

Major pregnancy-related complications included gestational diabetes mellitus, chorioamnionitis, cholestasis, etc.

ECC early cord clamping, *DCC* delayed cord clamping, *IQR* interquartile (25–75th percentile) range

*$p < 0.05$; **$p < 0.01$

Table 2 Blood gas analysis in the umbilical vein

Parameters	ECC					DCC					*p* value
	n	Median (95% CI)	IQR	2.5th percentile	97.5th percentile	*n*	Median (95% CI)	IQR	2.5th percentile	97.5th percentile	
pH	378	7.31 (7.3–7.31)	0.09	7.09	7.4	112	7.31 (7.28–7.32)	0.09	7.16	7.42	0.4746
pO_2 (mmHg)	378	26 (25–27)	10.7	13	42	111	27 (25–28)	10.5	14.7	41.3	0.2716
pCO_2 (mmHg)	378	45 (44–46)	10	32	72.1	112	44 (43–46)	9.3	31.8	59.2	0.06615
HCO_3^- (mmol/L)	378	22.2 (22.0–22.6)	3	17	27.2	112	21.9 (21.5–22.3)	3.3	16.7	26.7	0.09856
BE (mmol/L)	378	− 4.1 (− 4.5 to − 3.9)	4	− 11.4	− 0.5	112	− 4.6 (− 5.0 to − 3.8)	3.3	− 10.9	− 0.5	0.6224
Lactate (mmol/L)	375	3.3 (3.1–3.5)	2.4	1.5	8.3	112	3.4 (3.1–3.7)	1.9	1.7	7.5	0.5153
Hb (g/L)	378	162 (160–164)	20	127	190	112	164 (160–165)	19.5	130	188.5	0.5485

ECC early cord clamping, *DCC* delayed cord clamping, IQR interquartile (25–75th percentile) range, *CI* confidence interval, *BE* base excess, *Hb* hemoglobin

Table 3 Blood gas analysis in the umbilical artery

Parameters	ECC					DCC					*p* value
	n	Median (95% CI)	IQR	2.5th percentile	97.5th percentile	*n*	Median (95% CI)	IQR	2.5th percentile	97.5th percentile	
pH	363	7.21 (7.20–7.22)	0.11	7.00	7.34	98	7.21 (7.17–7.22)	0.1	7.02	7.35	0.374
pO_2 (mmHg)	363	19 (18–19)	10	8.1	36.9	97	21 (19–22)	9	11	36.2	0.01641*
pCO_2 (mmHg)	363	61 (60–63)	15	41	87	98	61 (58–65)	13	41	80	0.9377
HCO_3^- (mmol/L)	363	24.1 (23.9 – 24.4)	3.6	18.4	29.1	98	23.5 (22.7–24.3)	4	18	28.3	0.1401
BE (mmol/L)	359	− 5.2 (− 5.6 to − 4.7)	4.4	− 13.2	− 0.3	97	− 5.2 (− 6.5 to − 4.7)	5	− 13.2	− 0.3	0.2551
Lactate (mmol/L)	355	4.3 (3.8–4.5)	2.8	1.8	9.4	95	4.6 (3.8 – 5.1)	2.9	2.1	9.3	0.2349
Hb (g/L)	358	164 (162–166)	22	135	191	95	165 (163–170)	19.5	139	190	0.3916

ECC early cord clamping, *DCC* delayed cord clamping, IQR interquartile (25–75th percentile) range, *CI* confidence interval, *BE* base excess, *Hb* haemoglobin

*$p < 0.05$

where 70 paired ECC and DCC samples were taken from unclamped cords after 45 and 90 s, whereas Valero et al. [15] conducted a paired study where samples were taken both immediately upon delivery from an unclamped cord and from doubly clamped cords at the time of spontaneous cessation of cord pulsations in 60 vaginally-delivered, healthy, term newborns. Both studies found significant decreases in arterial and venous pH, HCO_3^-, and BE along with increases in lactate and pCO_2 in DCC. Wiberg et al. [13] notably also found higher arterial pO_2 at 45 s that was not observed by Valero et al. [15]. These two studies suggest that the DCC protocol shifts the fetus umbilical blood towards respiratory and metabolic acidosis as a function of time of delay. Variations in delay time, multiple sampling, and different methods of sampling could explain reported differences that we did not observe in the present study.

Our design and results were most similar to the study by De Paco et al. [14] which only looked at 116 (51 DCC and 65 ECC) healthy birthweight, high Apgar scoring, vaginally-delivered, full-term singletons, with neither significant pregnancy complications nor maternal diseases. Their unpaired study also found only arterial pO_2 to differ in blood samples taken from doubly clamped cords after a 2-min delay in the DCC group—a difference which may be attributed to the onset of breathing by the neonate. The longer delay could explain the larger observed difference in arterial pO_2 compared to what we observed. Our delay was 60 s in over 95% of DCC samples, so any differences due to variation in delay would be minimal. In our opinion, this 1-min DCC is optimal as it obtains the most advantage (80 mL of possible total 100 mL perfuse from placenta) [2], while avoiding the potential risk of severe jaundice [3].

The major advantage of our study is the increased sample size, which increases our ability to detect any significant differences, but at the expense of not strictly controlling for demographic parameters. In the current study, demographic differences point to infants treated with the DCC protocol being slightly lower risk overall than their ECC counterparts. For example, patients delivered by cesarean section with abnormal fetal heart rate would not have undergone DCC, so there would be more cesarean section in the ECC group. We acknowledge the fact that the Mann–Whitney *U* test may have been subject to an increased type I error rate when comparing the Apgar scores at 1 and 5 min due to heteroscedasticity [21], but the distributions are similar enough between DCC and ECC—as seen through shared medians and close IQRs—the difference between the two groups is clinically irrelevant. Despite the demographic differences, no other BG parameters were found to be statistically significant different between these groups.

The only statistically significant difference that we observed was arterial pO_2 and it was within the clinical acceptance limit of 10% (i.e., not clinically significant). Therefore, we found no merit to adjusting BG reference intervals for DCC samples taken from doubly clamped cords after a 1-min delay period. In conclusion, delaying cord clamping for 1 min before taking a cord blood sample does not affect umbilical cord blood gas analysis.

Author contributions YC and S-LS contributed to the conception of the project. JT and RF collected data. JT and YC did data analysis and drafted the original manuscript. YC, S-LS, and RF critically revised the manuscript for intellectual content. All of the authors approved the final version to be published and agreed to act as guarantors of the work.

Compliance with ethical standards

Conflict of interest No potential conflict of interest relevant to this manuscript was reported.

Ethical standards All DCC and ECC cases of vigorous term and preterm infants between February 2017 and February 2018 were retrospectively reviewed with a study protocol approved by the Institute Research Ethics Board (File #: 2018-2614). Maternal and neonatal demographic variables including maternal and gestational age, parity, mode of delivery, epidural anesthesia usage, neonate birthweight, Apgar scores at 1 and 5 min, sex, presence of meconium at birth, and major pregnancy-related complications (including gestational diabetes mellitus, chorioamnionitis, and cholestasis, etc.), were pulled from medical records and compared.

Informed consent Informed consent was waived with the approval of the Research Ethics Board of Horizon Health Network.

Human and animal rights statement This article does not contain any studies with animals performed by any of the authors.

References

1. Nicolaides KH (2016) Committee opinion. Obstet 128(654):1–4. https://doi.org/10.1016/S0140-6736(16)31898-0
2. Linderkamp O, Nelle M, Kraus M, Zilow EP (1992) The effect of early and late cord-clamping on blood viscosity and other hemorheological parameters in full-term neonates. Acta Paediatr 81(10):745–750. https://www.ncbi.nlm.nih.gov/pubmed/1421876. Accessed 1 Aug 2018
3. McDonald SJ, Middleton P, Dowswell T, Morris PS (2013) Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane Database Syst Rev 7:CD004074. https://doi.org/10.1002/14651858.CD004074.pub3
4. Hutton EK, Hassan ES (2007) Late vs early clamping of the umbilical cord in full-term neonates: systematic review and meta-analysis of controlled trials. JAMA 297(11):1241–1252. https://doi.org/10.1001/jama.297.11.1241
5. Lawton C, Acosta S, Watson N et al (2015) Enhancing endogenous stem cells in the newborn via delayed umbilical cord clamping. Neural Regen Res. 10(9):1359. https://doi.org/10.4103/1673-5374.165218
6. Sanberg PR, Divers R, Mehindru A, Mehindru A, Borlongan CV (2014) Delayed umbilical cord blood clamping: first line of defense against neonatal and age-related disorders. Wulfenia 21(6):243–249. https://www.ncbi.nlm.nih.gov/pubmed/25400533. Accessed 1 Aug 2018

7. Rabe H, Diaz-Rossello JL, Duley L, Dowswell T (2012) 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 8:CD003248. https://doi.org/10.1002/14651858.CD003248.pub3
8. Bhatt S, Alison BJ, Wallace EM et al (2013) Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. J Physiol 591(8):2113–2126. https://doi.org/10.1113/jphysiol.2012.250084
9. Chopra A, Thakur A, Garg P, Kler N, Gujral K (2018) Early versus delayed cord clamping in small for gestational age infants and iron stores at 3 months of age - a randomized controlled trial. BMC Pediatr 18(1):234. https://doi.org/10.1186/s12887-018-1214-8
10. Tarnow-Mordi W, Morris J, Kirby A et al (2017) Delayed versus immediate cord clamping in preterm infants. N Engl J Med 377(25):2445–2455. https://doi.org/10.1056/NEJMoa1711281
11. MacLennan A (1999) A template for defining a causal relation between acute intrapartum events and cerebral palsy: international consensus statement. BMJ 319(7216):1054–1059. https://www.ncbi.nlm.nih.gov/pubmed/10521205. Accessed 28 June 2018
12. D'Alton ME, Hankins GDV, Berkowitz RL, Bienstock J, Ghidini A, Goldsmith J, Higgins R, Moore TR, Natale R, Nelson KB, Papile L-A, Peebles D, Romero RJ, Schendel D, Spong CY, Waldman RN, Yvonne W, Joseph GF Jr, Hawks D, Politzer A, Emig C, Thomas K (2014) Executive summary: neonatal encephalopathy and neurologic outcome, second edition. Report of the American college of obstetricians and gynecologists' task force on neonatal encephalopathy. Obstet Gynecol 123(4):896–901. https://doi.org/10.1097/01.AOG.0000445580.65983.d2
13. Wiberg N, Källén K, Olofsson P (2008) Delayed umbilical cord clamping at birth has effects on arterial and venous blood gases and lactate concentrations. BJOG An Int J Obstet Gynaecol 115(6):697–703. https://doi.org/10.1111/j.1471-0528.2008.01708.x
14. De Paco C, Florido J, Garrido MC, Prados S, Navarrete L (2011) Umbilical cord blood acid-base and gas analysis after early versus delayed cord clamping in neonates at term. Arch Gynecol Obstet 283(5):1011–1014. https://doi.org/10.1007/s00404-010-1516
15. Valero J, Desantes D, Perales-Puchalt A, Rubio J, Diago Almela VJ, Perales A (2012) Effect of delayed umbilical cord clamping on blood gas analysis. Eur J Obstet Gynecol Reprod Biol 162(1):21–23. https://doi.org/10.1016/j.ejogrb.2012.01.020
16. Armstrong RA (2014) When to use the Bonferroni correction. Ophthalm Physiol Opt 34(5):502–508. https://doi.org/10.1111/opo.12131
17. Alamolhoda M, Ayatollahi SMT, Bagheri Z (2017) A comparative study of the impacts of unbalanced sample sizes on the four synthesized methods of meta-analytic structural equation modeling. BMC Res Notes 10(1):446. https://doi.org/10.1186/s13104-017-2768-5
18. Yan R, Lou A, Watts G et al (2014) Comparison of Becton Dickinson Vacutainer rapid serum tube with the serum separator tube for routine chemistry and immunoassay tests. J Clin Pathol 67(7):599–604. https://doi.org/10.1136/jclinpath-2013-202130
19. Chen J, Gorman M, O'Reilly B, Chen Y (2016) Analytical evaluation of the epoc® point-of-care blood analysis system in cardiopulmonary bypass patients. Clin Biochem 49(9):708–712. https://doi.org/10.1016/j.clinbiochem.2015.12.015
20. Pupek A, Matthewson B, Whitman E, Fullarton R, Chen Y (2017) Comparison of pneumatic tube system with manual transport for routine chemistry, hematology, coagulation and blood gas tests. Clin Chem Lab Med 55(10):1537–1544. https://doi.org/10.1515/cclm-2016-1157
21. Skovlund E, Fenstad GU (2001) Should we always choose a nonparametric test when comparing two apparently nonnormal distributions? J Clin Epidemiol 54(1):86–92. https://www.ncbi.nlm.nih.gov/pubmed/11165471. Accessed 11 Sept 2018