Enhancing endogenous stem cells in the newborn via delayed umbilical cord clamping

Christopher Lawton, Sandra Acosta, Nate Watson, Chiara Gonzales-Portillo, Theo Diamandis, Naoki Tajiri, Yuji Kaneko, Paul R. Sanberg, Cesar V. Borlongan

Center for Excellence for Aging and Brain Repair, Department of Neurosurgery and Brain Repair, University of South Florida College of Medicine, Tampa, FL, USA

Abstract

There is currently no consensus among clinicians and scientists over the appropriate or optimal timing for umbilical cord clamping. However, many clinical studies have suggested that delayed cord clamping is associated with various neonatal benefits including increased blood volume, reduced need for blood transfusion, increased cerebral oxygenation in pre-term infants, and decreased frequency of iron deficiency anemia in term infants. Human umbilical cord blood contains significant amounts of stem and progenitor cells and is currently used in the treatment of several life-threatening diseases. We propose that delayed cord clamping be encouraged as it enhances blood flow from the placenta to the neonate, which is accompanied by an increase supply of valuable stem and progenitor cells, as well as may improve blood oxygenation and increase blood volume, altogether reducing the infant’s susceptibility to both neonatal and age-related diseases.

Key Words: stem cells; umbilical cord blood; neonates; regenerative medicine

Therapeutic Manipulation of Umbilical Cord Clamping

The timing of umbilical cord clamping, which separates the newborn from the placenta, has been the subject of much debate for decades (Mercer et al., 2001). 'Early' or 'immediate' umbilical cord clamping (ICC) remains the most commonly employed method and is performed in the third stage of labor, during the period extending from complete delivery of the infant to complete delivery of the placenta (Alaifel et al., 2012; Sheldon et al., 2013). In a recent Cochrane review (McDonald et al., 2014), early cord clamping was defined as covering a wide range from immediately following birth to less than 1 minute post-birth, whereas delayed cord clamping occurs one or more minutes after birth or when cord pulsation ceases. The benefits of delayed umbilical cord clamping (DCC) have been well documented and include lower risks of intraventricular hemorrhage (all grades), lower risk for necrotizing enterocolitis, increased early hemoglobin concentration, increased iron stores, and increased cerebral oxygenation in preterm infants (Baenziger et al., 2007; Rabe et al., 2012; McDonald et al., 2013). This raises the question of why early or immediate cord clamping still predominates. While some contend that the prevalence of ICC is simply because of custom, other reasons include reduced risk of post-partum hemorrhage, easier identification of placental detachment, minimized risk of rhesus iso-immunization, and time constraints faced by physicians in the busy environment of the delivery room (Hutchon, 2010; Downey and Bewley, 2012). However, it is worth noting that recent studies have found no significant differences between early versus late cord clamping groups for the primary outcome of severe postpartum hemorrhage (McDonald et al., 2014).

The benefits of DCC are primarily attributed to an increase in neonatal blood volume, secondary to placenta-fetal transfusion (Niermeyer and Velaphi, 2013). This transfusion has been suggested to follow an exponential decay curve with 25% being transferred within the first 15 seconds, 50% by 60 seconds, and flow ceasing in most infants by 2–3 minutes (Yao et al., 1968, 1969; Yao and Lind, 1974). However, venous and arterial umbilical flow may occur for longer than previously described and placental transfusion appears to be complex and dependent on several factors (Boere et al., 2014). The transfer of umbilical cord blood is of particular interest in this review because of the various valuable stem cells contained such as hematopoietic stem cells, endothelial cell precursors, mesenchymal progenitors and multipotent/pluripotent lineage stem cells.

Stem Cells in Umbilical Cord Blood

Human umbilical cord blood (hUCB) plays a significant role...
Table 1 Early versus delayed cord clamping

| Timing of cord clamping (second) | Blood volume saved (mL) | Additional hematopoietic stem cells received by neonate |
|----------------------------------|-------------------------|-------------------------------------------------------|
| Early umbilical cord clamping    | 5                       | 0                                                     |
| Delayed umbilical cord clamping  | 180                     | 75                                                    | 1,100–45,000                                          |

A 180-second delay in cord clamping can transfer additional hematopoietic stem cells to the baby which may afford therapeutic benefits to the newborn. The infant may also benefit from an increase in his/her endogenous stem cell reservoir at a later age when confronted with adult onset diseases (Yao et al., 1969; Brocklebank and Sparrow, 2001).

Alternative Non-Stem Cell Mechanisms

Alternative non-stem cell mechanisms may account for some of the therapeutic effects of DCC. Of note, DCC has a significant impact on newborn hemodynamics, mainly because of increased blood volume and improved blood oxygenation (Yigit et al., 2015). These two mechanisms may contribute to the therapeutic benefits rendered by DCC. For example, germinal matrix hemorrhage is known to occur with hypoxia, and DCC may protect against this hemorrhage by way of enhanced blood oxygenation and larger blood volume delivered to the baby. As previously stated, DCC is associated with less necrotizing enterocolitis and reduced incidence of intraventricular hemorrhage (Mercer et al., 2006; Aziz et al., 2012), which may be due to the increase of stem cells transferred to the baby (Sanberg et al., 2010; Tolosa et al., 2010). Likewise, DCC may improve cerebral oxygenation (Baenziger et al., 2007) and may increase blood volume (Yigit et
al., 2015), altogether reducing the incidence of intraventricular hemorrhage and necrotizing enterocolitis.

**Neuroprotective Effects of Delayed Cord Clamping**

Clinical and research-based evidence suggests that DCC may benefit neurodevelopment and ameliorate early neurological disorders, especially in preterm neonates (McAdams, 2014). DCC’s reduction of intraventricular hemorrhage incidence (Rabe et al., 2012) is an implicated method of therapy. Abnormal neurodevelopment often spurs infant iron-deficient anemia (Yager and Hartfield, 2002), and DCC is a seemingly effective intervention. With iron deficiency affecting a substantial portion of the world’s population and approximately 25% of global births (de Benoist et al., 2008), DCC could prove a very low-cost and easy to implement treatment.

Current research also suggests that DCC provides therapeutic relief beyond the neonatal period (McDonald, 2008). Andersson et al. (2013) produced a multi-year study investigating the neurodevelopmental benefits of DCC at various age increments. Beginning two days after birth, infants were seen to have significantly higher hemoglobin levels as well as a decrease in neonatal anemia (Andersson et al., 2015). In conjunction, data suggested more long-term relief. DCC neonates were seen to have increased scores on a series of five different fine-motor tests at 4 years of age. Such a long-term relief suggests that DCC may have a substantial impact in development. However, on the time intervals prior to the four-year mark, the data was not as promising (Andersson et al., 2015). Interestingly enough at the 12-month checkup, DCC did not have large effect on the iron levels or neurodevelopment in the infant population. While these sporadic improvements have been documented, more research needs to be done to demonstrate the biological cause of this phenomenon (Andersson et al., 2014).

Another anemia therapy, immediate blood transfusion, has been shown to also produce neuroprotective effects. These transfusions significantly reduce early brain injury in preterm infants by altering the oxygen extraction demand within the body (Osborn, 2007). An elevated cerebral fractional tissue oxygen extraction (cFTOE) typically precedes intraventricular hemorrhage in very preterm infants (Verhagen, 2010; Balegar, 2014; Noori, 2014). The transfusion of red blood cells (RBC) balances the low blood flow and the high oxygen demand, eliminating the risk of hypoxia-ischaemia (Altman, 1993). Additionally, research also suggests an improvement in cardiac output and cerebral tissue in late anaemia prematurity (Andersson et al., 2015).

**Conclusion**

In summary, DCC can increase in neonatal blood volume, secondary to placenta-fetal transfusion. A larger blood volume may result in a higher stem cell supply to the neonate, which likely accompanies this hUCB-transfusion. Human umbilical cord blood is known to possess valuable stem and progenitor cells, which the newborn likely stands to benefit from. Human umbilical cord blood is currently being evaluated for its efficacy in mitigating the effects of various diseases and the artificial loss of stem cells imposed by early or immediate clamping of the umbilical cord may negatively affect a child’s endogenous ability to combat various diseases. In conjunction with improved oxygenation and increased blood volume, the additional stem cells delivered to the baby following DCC may afford therapeutic effects against neonatal- and adult-onset diseases.

**Author contributions:** CL, SA, NW, CGP, TD, NT, YK, PRS, CVB contributed to the conception of the study, review of the literature, interpretation of the studies, wrote the manuscript and provided critical revision of the manuscript for intellectual content. PRS and CVB obtained funding, and provided administrative, technical, and material support, and led the supervision of the study. All authors approved the final version of this paper.

**Conflicts of interest:** PRS and CVB are consultants and hold patents to a number of stem cell-based biotech companies.

**References**

Acosta SA, Tajiri N, Shinozuka K, Ishikawa H, Sanberg PR, Sanchez-Ramos J, Song S, Kaneko Y, Borlongan CV (2014) Combination therapy of human umbilical cord blood cells and granulocyte colony stimulating factor reduces histopathological and motor impairments in an experimental model of chronic traumatic brain injury. PLoS One 9:e98953.

Acosta SA, Franzese N, Staples M, Weinbren NL, Babilonia M, Patel J, Merchant N, Simancas AJ, Slakter A, Caputo M, Patel M, Franyutti G, Franzblau MH, Suarez L, Gonzales-Portillo C, Diamandis T, Shinozuka K, Tajiri N, Sanberg PR, Kaneko Y, Miller LW, Borlongan CV (2013) Human umbilical cord blood for transplantation therapy in myocardial infarction. J Stem Cell Res Ther (Suppl 4) pii:54-005.

Aflaife N, Weeks AD (2012) Active management of the third stage of labour. BMJ 345:e45-46.

Aflaife N, Jefferson MJ, Volpe JP, Powers WJ (1993) Cerebral oxygen metabolism in newborns. Pediatrics 92:99-104.

Andersson CC, Karayil SM, Hodyl NA, Stark MJ (2015) Early red cell transfusion favourably alters cerebral oxygen extraction in very preterm newborns. Arch Dis Child Fetal Neonatal Ed doi:10.1136/archdis-child-2014-307565.

Andersson O, Domellöf M, Andersson D, Hellström-Westas L (2013) Effects of delayed cord clamping on neurodevelopment and infection at four months of age: a randomised trial. Acta Paediatrica 102:525-531.

Andersson O, Domellöf M, Andersson D, Hellström-Westas D (2014) Effect of delayed vs early umbilical cord clamping on iron status and neurodevelopment at age 12 months: a randomized clinical trial. JAMA Pediatr 168:547-554.

Andersson O, Hellström-Westas L, Andersson D, Clausen J, Domellöf M (2013) Effects of delayed compared with early umbilical cord clamping on maternal postpartum hemorrhage and cord blood gas sampling: a randomized trial. Acta Obstet Gynecol Scand 92:567-574.

Andersson O, Lindquist B, Lindgren M, Stjernqvist K, Domellöf M, Hellström-Westas L (2015) Effect of Delayed Cord Clamping on Neurodevelopment at 4 Years of Age: A Randomized Clinical Trial. JAMA Pediatr 169:631-638.

Aziz K, Chinnery H, Lacaze-Masmonteil T (2012) A single-center experience of implementing delayed cord clamping in babies born at less than 33 weeks' gestational age. Adv Neonatal Care 12:371-376.

Baenziger O, Stolkin F, Keel M, von Siebenthal K, Fauchere JC, Das Kundu S, Dietz V, Bucher HU, Wolf M (2007) The influence of the timing of cord clamping on postnatal cerebral oxygenation in preterm neonates: a randomised, controlled trial. Pediatrics 119:454-459.

Balegar KK, Stark MJ, Briggs N, Andersson CC (2014) Early cerebral oxygen extraction and the risk of death or sonographic brain injury in very preterm infants. J Pediatr 164:475-480.

Ballen KK, Gluckman E, Brommeyer HE (2013) Umbilical cord blood transplantation: the first 25 years and beyond. Blood 122:491-498.

Bhatt S, Alison BJ, Wallace EM, Crossley KJ, Gill AW, Kluckow M, te Pas AB, Morley CJ, Polglase GR, Hooper SB (2013) Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. J Physiol 591:2113-2126.

Boeke I, Roest AA, Wallace E, Terwee AD, Haak MC, Morley CJ, Hooper SB, te Pas AB (2014) Umbilical blood flow patterns directly after before delayed cord clamping. Arch Dis Child Fetal Neonatal Ed 0:F1-5.
Borlongan CV, Hadman M, Sanberg CD, Sanberg PR (2004) Central nervous system entry of peripherally injected umbilical cord blood cells is not required for neuroprotection in stroke. Stroke 35:2385-2389.

Brocklebank AM, Sparrow RL (2001) Enumeration of CD34+ cells in cord blood: a variation on a single-platform flow cytometry method based on the ISHAGE gating strategy. Cytometry 46:254-261.

Bronzmeier HE, Douglas GW, Hanganu G, Cooper S, Bard J, English D, Arny M, Thomas L, Boyse EA (1989) Human umbilical cord blood as a potential source of transplatable hematopoietic stem/progenitor cells. Proc Natl Acad Sci U S A 86:3828-3832.

Chakraborty SK, Banu LA, Rahman MF, Paul S (2014) Cord blood stem cells—a dream for future medicine. Myymensingh Med J 23:614-620.

Chen N, Hudson JE, Walczak P, Misita J, Garbuszova-Davis S, Jiang L, Sanchez-Ramos J, Sanberg PR, Zigova T, Willing AE (2005) Human umbilical cord blood progenitors: the potential of these hematopoietic cells to become stem. Cells 25:1560-1570.

Committee on Obstetric Practice, American College of Obstetricians and Gynecologists (2012) Committee Opinion No.543: Timing of umbilical cord clamping after birth. Obstet Gynecol 120:1522-1526.

de Benoist B, McLean E, Egli I, Cogswell M (2008) Worldwide prevalence of anaemia 1993–2005: WHO Global Database on Anaemia. Geneva (Switzerland): World Health Organization.

De la Peña I, Sanberg PR, Acosta S, Lin SZ, Borlongan CV (2014). Umbilical cord blood cell and granulocyte-colony stimulating factor: combination therapy for traumatic brain injury. Regen Med 9:409-412.

De la Peña I, Sanberg PR, Acosta S, Taijiri N, Lin SZ, Borlongan CV (2014) Stem cells and G-CSF for treating neuroinflammation in traumatic brain injury: aging as a comorbidity factor. J Neurosurg Sci 58:145-149.

Diaz-Rossello JL (2006) Cord clamping for stem cell donation: medical facts and ethics. NeoReviews 7:e557-e563.

Downey CL, Belsey S (2012) Historical perspectives on umbilical cord clamping and neonatal transition. J R Soc Med 105:325-329.

Eckerson-Owens DA, Mercer JS, Oh W (2012) Umbilical cord milking in term infants delivered by caesarean section: a randomized controlled trial. J Perinatol 32:380-384.

Gluckman E, Broxmeyer HA, Auerbach AD, Friedman HS, Douglas GW, Erickson-Owens DA, Mercer JS, Oh W (2012) Umbilical cord milking in term infants delivered by cesarean section: a randomized controlled trial. Arch Dis Child Fetal Neonatal Ed 93:F14-F19.

Hutchison DJ (2010) Why do obstetricians and midwives still rush to clamp the cord? BMJ 341:c5447.

Liu R, Zhang Z, Lu Z, Borlongan C, Pan J, Chen J, Qian L, Liu Z, Zhu L, Zhang J, Xu Y (2013) Human umbilical cord stem cells ameliorate experimental autoimmune encephalomyelitis by regulating immunoinflammation and remyelination. Stem Cells Dev 22:1033-1052.

Noori S, McCoy M, Anderson MF, Ranjfi F, Seri I (2014) Changes in cardiac function and cerebral blood flow in relation to peri/intraventricular hemorrhage in extremely preterm infants. J Pediatr 164:264-270.e1-e3.

Osborn DA, Evans N, Kluckow M, Bowen JR, Rieger I (2007) Low superior ven a cava flow and effect of inotropes on neurodevelopment to 3 years in preterm infants. Pediatrics 120:372-380.

Ot X, Yu S, Kaneko Y, Taijiri N, Bae EC, Chheda SH, Stahl CE, Yang T, Fang L, Hu K, Borlongan CV, Yu G (2010) Intravenous infusion of GDNF gene-modified human umbilical cord blood CD34+ cells protects against cerebral ischemic injury in spontaneously hypertensive rats. Brain Res 1366:217-225.

Perlman JM, Wetlie J, Kattwinkel DL, Atkins DL, Goldsmith JP, Guinsburg R, Hammar MF, Morley C, Richmond S, Simon WM, Sghal N, Szyld E, Tamura M, Velaphi S (2010) Part 11: Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation 122:S516-S538.

Rabe H, Diaz-Rossello JL, Duley L, Dowswell T (2012) Effect of timing of umbilical cord clamping on outcomes of infants born at less than 29 weeks’ gestation: a randomised controlled trial. Arch Dis Child 97:1205-211.

Sanberg PR, Park DH, Borlongan CV (2010) Stem cell transplants at childbirth. Stem Cell Rev 6:273-307.

Sheridan WR, Durocher J, Winkoff B, Blum JM, Trussel J (2013) How effective are the components of active management of the third stage of labor? BMC Pregnancy Childbirth 13:46.

Sirchia G, Rebulla P (1999) Placental/umbilical cord blood transplantation. Haematologica 84:738-747.

Tolosa JN, Park DH, Eve DJ, Klasko SK, Borlongan CV, Sanberg PR (2010) Mankind’s first natural stem cell transplant. J Cell Mol Med 14:488-495.

Upadhyay A, Gohill S, Parikh R, Garg A, Gupta A, Chawla D, Gulati IK (2010) Milking compared with delayed cord clamping to increase placental transfusion in preterm neonates: a randomized controlled trial. Obstet Gynecol 117:205-211.

Lawton C, et al. / Neural Regeneration Research. 2015;10(9):1359-1362.