

● INVITED REVIEW

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

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doi: 10.4103/1673-5374.165218  
<http://www.nrronline.org/>

Accepted: 2015-06-02

## 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

**Funding:** CVB is funded by NIH NINDS RO1 1R01NS071956-01, NIH NINDS 1R21NS089851-01, Department of Defense TATRC W811XWH-11-1-0634, Veterans Affairs BX001407-01A2, James and Esther King Biomedical Research Program 09KB-01-23123, and 1KG01-33966.

Lawton C, Acosta S, Watson N, Gonzales-Portillo C, Diamandis T, Tajiri N, Kaneko Y, Sanberg PR, Borlongan CV (2015) Enhancing endogenous stem cells in the newborn *via* delayed umbilical cord clamping. *Neural Regen Res* 10(9):1359-1362.

## 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 (Aflaifel 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 iden-

tification 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	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).

as a reservoir of stem and progenitor cells (Chen et al., 2005; Watson et al., 2015). These stem cells, which have infinite medical potential, are currently used in the treatment of several life-threatening diseases and are viewed by many as the stem cells source of choice for clinical and non-clinical research applications (Chakraborty et al., 2014). The hematopoietic progenitor cells (HPC) of umbilical cord blood have an extensive proliferative capacity that exceeds that of bone marrow HPC (Broxmeyer et al., 1989; Ballen et al., 2013), and even a single hUCB sample can provide enough hematopoietic stem cells for both short- and long-term engraftment (Sirchia and Rebutta, 1999). While the first umbilical cord blood transplant occurred 26 years ago in France in a child with Fanconi Anemia (Gluckman et al., 1989; Ballen et al., 2013), one might argue that nature's first stem cell transplant occurs at birth as the placenta and umbilical cord contract and pump blood toward the newborn (Sanberg et al., 2010; Tolosa et al., 2010). Once the blood equilibrates in both compartments, the cord becomes pulseless and blood flow ceases. This is the natural course in most placental mammals, yet in humans this cord blood transfusion is curtailed by early clamping of the umbilical cord, thus depriving infants of additional stem cells.

The existence of stem cells in fetal circulation indicates that a delay in cord clamping should increase stem cell supply to newborns. Alternatively, the artificial loss of stem cells at birth could potentially impact later development. The effects of DCC on diseases such as neonatal and adult diseases, is unknown but warrants further investigation. Of note, transplantation of exogenous hUCB has been shown to be therapeutic in animal models of cerebral palsy (Yasuhara et al., 2010), autoimmune diseases (Liu et al., 2013), acute injuries like traumatic brain injury (Acosta et al., 2014; Dela Pena et al., 2014a,b) and myocardial infarction (Acosta et al., 2013), and adult-onset disorders, such as stroke (Borlongan et al., 2004; Yu et al., 2009, 2010; Ou et al., 2010), altogether implicating that prophylactic stem cell transplantation, as may be achieved with DCC, can afford benefits against diseases in neonates and adults.

The postnatal transfer of hUCB may be particularly important in preterm infants born between 24 to 31 weeks gestation because of the higher concentration of primitive HPC and long-term culture-initiating cells when compared with cord blood of infants born closer to term (Haneline et al., 1996). Consequently, the timing of umbilical cord clamping may be especially

important in preterm neonates. DCC may prove to be a safe and inexpensive practice that could potentially decrease morbidity and mortality associated with many newborn conditions, especially when there is no plan to harvest such important cells through cord blood banking.

### Ideal Timing for Delayed Cord Clamping

In 2010, the International Liaison Committee on Resuscitation (ILCOR) recommended that cord clamping be delayed for at least 1 minute in healthy term infants, but stated that evidence was insufficient to recommend a time for clamping in those who require resuscitation (Perlman et al., 2010). Ironically, it could be argued that these infants stand to receive the greatest benefit from DCC.

Several systematic reviews have suggested that DCC decreased incidence of intracranial hemorrhage in preterm infants (Committee on Obstetric Practice, 2012). Delaying cord clamping (for at least 30–60 seconds), with the infant maintained at or below the level of the placenta was associated with increased blood volume, reduced need for transfusion, and decreased frequency of iron deficiency anemia in term infants (Committee on Obstetric Practice, 2012). The existence of stem cells in fetal circulation suggests that a delay in cord clamping should increase stem cell supply to the neonate, providing immediate benefits if neonatal disease is indicated (**Table 1**). In fact, if cord clamping was delayed by 180 seconds, the newborn may receive an additional 75 mL of blood volume (Yao et al., 1969; Diaz-Rossello, 2006) that could contain approximately 1,100–45,000 hematopoietic stem cells.

Some studies have even suggested that physicians delay cord clamping until ventilation (Bhatt et al., 2013), relying on the infant's physiology rather than proceeding in a simple time-dependent fashion. Umbilical cord milking or stripping has also been put forth as a viable means of placental transfusion and been suggested to have beneficial effects for newborns (Hosono et al., 2008; Rabe et al., 2011; Erickson et al., 2012; Upadhyay et al., 2013). Such milking likely increases stem cell supply to the neonate. In forming a consensus on the optimal timing for cord clamping, further investigation of the effects of DCC on concentrations of stem and/or progenitor cells in the newborn is essential. While DCC is likely to increase the supply of these valuable cells to the infant, it is unknown for what period of time cord clamping should be delayed for optimal benefit to the infant.

### 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 haemorrhage 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 (Andersen 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.

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