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ORIGINAL ARTICLE

Effects and safety of delayed versus early umbilical cord clamping in newborns of HIV-infected mothers

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ABSTRACT

Objective: To investigate the effect of a 2 minutes-delayed cord clamp (DCC) versus early cord clamp (ECC) on neonate haemoglobin concentration 24 hours and 1 month after birth, and assess the safety of DCC concerning the risk of HIV infection.

Design: Sixty-four mother-infant peers were enrolled. All mothers were on stable ARV therapy. Viral load, $CD4^+$ count and blood haemoglobin (Hb) concentrations 24 hours before delivery were collected from all mothers and their infants.

Methods: All patients were enrolled at the Department of Paediatrics, AO FBF Sacco Hospital in Milan, and were followed until 18 months after birth. Women with haematological diseases and obstetrical complications were excluded. All of 64 mother and infants couples (32 ECC group and 32 DCC group) completed the study. ECC and DCC are defined as application of umbilical clamp within 30 seconds and 120 seconds after birth, respectively.

Results: Mean birth weight was significantly higher in the DCC compared with ECC group. Mean Hb levels at birth were significantly higher in DCC than in ECC group ($p = .05$): this difference persisted at 1 month of life. All newborns showed negative viral load.

Conclusions: DCC 2 minutes after birth is proven to be a safe procedure, particularly beneficial in newborns from HIV mothers. The risk of anemia is significantly decreased at 24 hours after birth and persists at age of 1 month without any increased risk of neonatal jaundice or polycitemia.

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Introduction

Perinatal transmission of HIV-infection from HIV-infected mothers to newborns can be prevented by antiretroviral (ARV) therapy during pregnancy, intrapartum and postnatal prophylaxis [1]. The use of Highly Active Antiretroviral Therapy (HAART) in pregnancy has decreased the prevalence of HIV vertical transmission to less than 1% in developed countries, although relevant side effects [2]. One of the antiretroviral drugs, 3′-azido-3′-thymidine, AZT (zidovudine), is commonly used as a component of treatment for pregnant HIV-infected mothers and also as postnatal prophylaxis in newborns. Common adverse effects are dose- and time-dependent anaemia (34% of treated patients), often accompanied by macrocytosis, while bone marrow failure is observed more rarely [3,4].

Infants born to anaemic mothers during pregnancy are twice more likely to be anaemic (8.6 versus 3.8%) at birth than ones born to nonanaemic mothers [5,6]. Delayed cord clamping (DCC) is one of the action used for preventing postpartum haemorrhage of mothers, increasing haemoglobin levels and body iron stores in infant and reducing blood transfusion in preterm [7]. Currently, the World Health Organization (WHO) and the European Resuscitation Council, recommend DCC to improve maternal and infant health and nutritional outcomes [8–11].

Prenatal iron deficiency affects the normal development of brain structures, neurotransmitter systems and myelination [12]; therefore, anaemia and iron deficiency are largely demonstrated to be associated with impaired psychomotor development, impaired performance in language tests, and in motor and coordination skills [13–15]. DCC performed in the first minutes after birth, allows newborn, either to anaemic and nonanaemic mothers, to receive a substantial blood transfusion from placenta and increase blood volume of an average 32%, leading to obtain higher birthweight and haemoglobin concentration [8]. Few adverse effects such as hyperbilirubinemia, polycythaemia and respiratory symptoms have been reported [16,17]. However, a recent Cochrane review, based on term infants, reports no significant differences

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regarding neonatal morbidities (low Apgar score, admission to the neonatal intensive care unit, jaundice, polycythaemia) between the use of early cord clamping (ECC) and DCC [18].

The aims of our study were primarily to investigate the effect of a 2 minutes-DCC versus ECC on neonate haemoglobin status 24 hours and 1 month after birth, secondarily to assess the safety of DCC concerning the risk of HIV infection by vertical transmission.

Materials and methods

The study was conducted between January 2012 and March 2016 in the Paediatric Department of Luigi Sacco Hospital, University of Milan, one of the referral centres for infectious diseases in Italy. Informed consent was collected from all participants, as appropriate. The study has been conducted according to the principles expressed in the Declaration of Helsinki. HIV-infected pregnant women were considered eligible for the enrolment if on stable ARV therapy, without evidence of any medical or obstetrical complications. The following data were collected from mothers: age, ethnicity, antiretroviral therapy, viral load, $CD4^+$ count and blood haemoglobin (Hb) concentration 24 hours before delivery. Women with haematological diseases were excluded from this study. Mothers' anaemia was defined by haemoglobin concentration below 11 g/dL, according WHO definition [19]. The following data were collected from infants: gestational age, type of delivery, anthropometric parameters (weight, length, head circumference), Apgar score, Hb concentrations 24 hours and 1 month after birth, HIV-RNA and $CD4^+$ count. Anaemia in newborns was defined as a Hb concentration below 13.5 g/dL [20].

Mothers and infants were divided in two groups: who received ECC (group 1) and DCC (group 2). ECC was defined as application of a clamp to the umbilical cord within 30 seconds after birth and it was the standard method in our hospital in the period between January 2012 and January 2014. Delayed cord clamping was defined as application of a clamp to the umbilical cord 120 seconds after birth, using a chronometer, and it was performed in our hospital, between February 2014 and March 2016: the neonate was placed between supine mother's thighs and the cord was clamped while placenta remaining *in utero*. The umbilical cord was cut in the operating room by the obstetrician after counting the time by a midwife.

A total of 32 newborns who received ECC (group 1) and 32 newborns who received DCC (group 2) were evaluated during the study period. All infants were born by caesarian section.

Newborns' physical examination was assessed within 1 hour after delivery and again 24, 48, 72 hours later by paediatric staff. The evaluation included neurological and dermatological assessment (in particular the presence of jaundice), gastrointestinal and respiratory functions. All neonates, regardless the timing of umbilical cord clamping, were managed equally including laboratory testing, nutritional management with formula and antiretroviral prophylaxis, which was performed with zidovudine 2 mg/kg/dose QID for 4–6 weeks, started 6 hours after birth [21]. Serum bilirubin assessments were performed 72 hours after birth, or before if required and evaluated according to Bhutani Nomogram [22]. Symptomatic polycythaemia was defined as haematocrit over 65% with evidence of newborn distress as assessed by the paediatric staff [23,24].

HIV-vertically transmission was excluded at birth, and at 1, 3, 6 and 12 months of age by HIV-DNA (RT-PCR) or HIV-RNA (RT – PCR) assessment, depending on maternal ethnicity. HIV-Ab (Elisa/EIA) was performed at 18 months of age for definitive exclusion of HIV transmission. Blood samples were collected for Hb level 24 hours and 1 month after birth.

Data analysis was performed with STATA®14. Baseline characteristics and measurements were compared across groups with chi-square statistic for categorical variables and Student's t-test for continuous

Table 1. Mothers' and newborns' characteristics.

	ECC (<30 sec) Group 1	DCC (120 sec) Group 2
Mothers' Characteristics		
Age yrs mean (range)	33.9 (21.6–43)	34.7 (23.8–44.1)
Ethnia (Caucasian/Other)	21/11	16/16
Antiretroviral Therapy (PI based regimen)	28/32	25/32
HIV-RNA <37 cp/mL	30/32	29/32
Hb g/dL mean (range)	10.9 (7.3–13.4)	11.0 (7.4–13.3)
Newborns' Characteristics		
Gestational Age wks mean (range)	38 (33^{+4} – 40^{+4})	38^{+2} (37–39^{+5})
Weight g mean (range)	2880 (1360–3485)	3159 (2695–3910)
Male/Female	19/13	17/15
Apgar <7/10	4/32	0/32
24 h Hb g/dL mean value (range)	15.1 (12.6–21.2)	17.4 (13.1–20.9)
Phototherapy	0/32	0/32

variables. Group means were compared by using the t student significant difference test. All results were based on two-tailed tests and a p value of .05 was used as the criterion for significance.

Results

Sixty-four mother–infant peers participated at the study, recruited for 4 years from January 2012 to November 2015. Regarding maternal characteristics and neonatal baseline data, there were no significant differences between the DCC and ECC groups (Table 1).

Maternal haemoglobin values 24 hours before delivery were not significantly different between ECC and DCC group. No significant differences were found in Apgar score between the two groups, no infant required neonatal intensive care, nor phototherapy for jaundice.

Mean birth weight was significantly higher in the DCC compared with ECC group (+ 282 g). Hb values were obtained at 24 hours of life: 9 infants resulted to be anaemic, respectively 3% in DCC and 25% in ECC group. Only anaemic infants were treated with bisglycine chelated iron supplementation (Tecnofer®, Lab. Baldacci Spa) at the dose of 0.75 mg/kg/day up to a maximum of 7.5 mg/day.

Mean Hb levels were significantly higher in DCC (17.36 g/dL, range 13.1–21.1 g/dL) than in ECC (15.1 g/dL, range 10.9–21.2 g/dL) group ($p = .05$). The difference in Hb concentration persisted at 1 month of life, despite iron supplementation in anaemic newborns tested at 24 hours from birth: in the DCC group the mean haemoglobin level was 10.9 g/dL while in ECC was 9.7 g/dL ($p < .05$). No more difference in Hb concentration was detected after 12 months. All newborns showed HIV-PCR negative at birth, at 1, 6, 12 and 18 months of life.

Discussion

Perinatal antiretroviral therapy has dramatically reduced the risk of HIV vertically transmission. Evaluation of infant toxicity from exposure to maternal HAART in pregnancy regards principally haematologic toxicity. Several antiretroviral drugs, especially zidovudine and others nucleoside reverse transcriptase inhibitors (NRTIs), are known to cause anaemia both in adults and in children. Currently, WHO recommends DCC in HIV positive pregnant women: it is a quick and inexpensive method of enhancing haematologic status, preventing neonatal anaemia by enriching iron stores and ferritin levels and improving neurodevelopmental outcome. Moreover, a longer duration of placental transfusion allows an increase supply of valuable stem and progenitor cells, allows a better a fetal-to-neonatal transition and a greater red cell mass for oxygenation and iron content essential for the maturation of the preoligodendrocytes and myelin production [18,25,26].

DCC may be one of the procedures that offer infants many advantages both in the short and long-term. Several studies support the benefits of DCC and demonstrate the absence of association with increased risk of hyperbilirubinemia or symptomatic polycythaemia. Consistently with literature data, mean birthweight in DCC group is significantly higher than ECC group [27,28].

DCC 2 minutes after birth is particularly beneficial in newborns from HIV mothers due to high prevalence of anaemia in this population. Compared with ECC, the risk of anaemia is significantly decreased at 24 hours after birth and persists at age of 1 month. We didn't found any increased risk of neonatal jaundice or polycythaemia associated to DCC. WHO guidelines suggest DCC in HIV women to improve maternal and infant health and nutrition outcomes because benefits outweigh "the theoretical, and unproven, harm" of virus transmission. In our knowledge, till now no data are available regarding the correlation between DCC and vertically HIV-infection [9].

This study has several limitations: first of all, the limited number of patients, secondly the biased evaluation of anaemia at 1 month after birth, affected by iron supplementation and the limited follow up time after birth. Nevertheless, the difference in Hb concentration persisted at 1 month of life. A future aim of this study will be the evaluation of neurocognitive and linguistic performance in newborns from DCC group versus ECC.

Conclusions

Despite the advances in the past decades in caring HIV-infected mothers, DCC remains a common procedure both in high and low-income countries and our results confirm the efficacy of DCC in term of increased haemoglobin level in newborns and the safety of this procedure regarding the vertical transmission of HIV virus.

Given its cost-effectiveness and simplicity, the DCC practice in HIV population could be crucial in improving child health especially in developed countries, where maternal high viral load, or a not completely-negative viral load at the moment of delivery are still common.

Disclosure statement

No potential conflict of interest was reported by the authors.

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