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Correlation between Late Cord Clamping and Phototherapy and Other Neonatal Unfavorable Outcomes: A Randomized Clinical Trial

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Abstract

Background: Recently, late umbilical cord clamping is generally recommended, which decreases neonatal anemia; however, it may also increase neonatal jaundice and some other poor outcomes. **Objectives:** We here attempted to determine whether late clamping actually increases the incidence of phototherapy for jaundice and other poor outcomes of the term "low-risk newborns". **Methods:** With the approval of the Brazilian Registry of Clinical Trials (REBEC), a total of 357 low-risk newborns (singleton, uncomplicated pregnancy/delivery, in a Brazilian public institution) were randomized into two groups: group I (n = 114): cord clamping < 1 minute (early clamping) or group II (n = 243): cord clamping between 1 - 3 minutes (late clamping). Statistics were used appropriately (*i.e.*, measures of central tendency, dispersion for continuous variables, Shapiro-Wilk, Mann-Whitney test, or Chi-square test). **Results:** Phototherapy was performed in 5.3% in both groups. Also, there were no statistical differences in the occurrence of secondary outcomes, such as sepsis, neonatal ICU admission, and transient tachypnea of the newborns: *i.e.*, 0.9%, 15.8%, and 3.5%, respectively for group I versus 1.2%, 15.6%, and 5.8%, respectively for group II. **Conclusion:** Late umbilical cord clamping does not increase the need for phototherapy in low-risk neonates. This result corroborates the current recommendation of late cord clamping, whenever appropriate.

Keywords

Phototherapy, Neonatal Anemia, Neonatal Jaundice, Late Cord Clamping

1. Introduction

Currently, the World Health Organization (WHO) recommends late clamping of the umbilical cord, immediate skin-to-skin contact and initiation of exclusive breastfeeding [1]. Late cord clamping should be instituted whenever there is no contraindication to the mother and newborn [2]. Several studies have demonstrated fetal benefits for late cord clamping, such as a significant increase in hemoglobin and ferritin in the first 6 months of life [3] [4]. However, there may be a greater need for phototherapy in infants in which this measure was instituted [5]. Because there is an increase in hematocrit and hemoglobin of the newborn, there may be hyperbilirubinemia with clinical jaundice and the need for phototherapy, therefore, late clamping is suggested only if it is not contraindicated [2] [6]. This study aims to verify the rate of phototherapy in newborns undergoing late cord clamping in low-risk parturients, as well as neonatal Intensive Care Unit (ICU) admission, transient tachypnea in the newborn and neonatal sepsis between groups.

2. Methods

2.1. Trial Design

A unicentric, interventional, randomized and non-blind controlled clinical trial, based in the CONSORT guidelines. Neonates of parturients at usual risk who were admitted to the obstetric center of the Hospital de Clínicas de Porto Alegre (HCPA) were randomized.

2.2. Participants, Study Settings and Interventions

Participants were recruited from the HCPA maternity between January and December 2012. Were included women with habitual risk prenatal. Participants with gestational age below 37 weeks, HIV infection, Rh isoimmunization, severe maternal anemia (hemoglobin < 9 g/dL), gestational diabetes, placenta previa, placenta abruption, HELLP syndrome, maternal coagulopathy, or mothers of newborns who presented cord-round-the-neck, hypotonia and meconium amniotic fluid were excluded.

The participants were allocated to receive immediate or delayed umbilical cord clamping by a statistician. The researchers were responsible for the clamping of the umbilical cord according to the list generated by randomization. There was no blinding during randomization.

The early clamping (group I) was defined by a cord clamping 1 minute after birth and the late cord clamping (group II) by clamping between 1 and 3 minutes after birth.

2.3. Data Organization and Analyses

Regarding the data processing, the database double entry and review were performed using the SPSS, version 18.0. (SPSS Inc., Released 2009, PASW Statistics for Windows, Version 18.0. Chicago). Symmetric quantitative data was expressed as mean and standard deviation (±SD), or standard error of mean (±SEM), or by

median and interquartile range (percentiles 25th-75th, (P25-P75)). Categorical variables were described as absolute (n) and relative (n%) frequencies. To compare means between groups, Student's t test for independent samples was applied. In asymmetry cases, the Mann-Whitney test was used to perform comparisons. Associations between categorical variables were conducted by chi-square test with adjusted residual analysis. Spearman's correlations were applied between variables of interest. Significance was set at 5% for all analysis.

3. Results

Of all 3815 births in 2012, 3459 were not included in the study considering the exclusion criteria (meconium n = 180, hypotonic newborn n = 180, circular umbilical cord n = 726, indication by Pediatrician n = 311, prematurity n = 294, maternal diseases (anemia, diabetes mellitus, human immunodeficiency virus, arterial hypertension and coagulopathies) n = 557, placental change n = 76, non-elective cesarian section n = 692) or declined to participate/other reasons, for example, in the night shift there was no researcher for data collection (n = 443), and a total of 356 women were randomly allocated to immediate (n = 176) or delayed (n = 180) umbilical cord clamping groups. Considering the umbilical cord clamping performed, 114 (32.0%) women were submitted to immediate and 242 (68.0%) were submitted to delayed clamping. The schematic diagram of sample selection and randomization is shown in Figure 1.

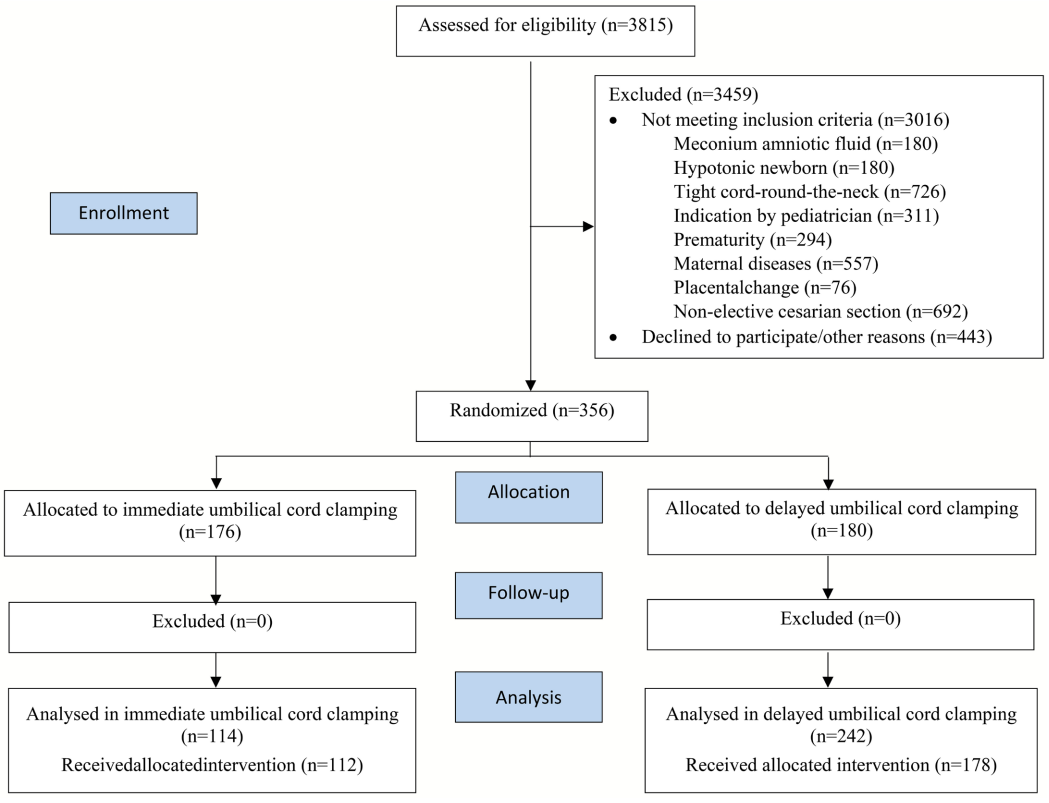

Figure 1. Screening, enrollment, randomization, and follow-up of participants flow chart. Legend: n—absolute frequency.

Regarding the characteristics of the newborns (Table 1), there was a difference in relation to APGAR, which presented higher values in the 1st and 5th minutes in the patients of the early clamping group. There was an inversely proportional correlation evaluating APGAR and late umbilical cord clamping, with 18% and 15% reduction in APGAR in the first and fifth minutes, respectively, in patients with late cord clamping (Table 2).

Concerning unfavorable outcomes in newborns, there was no statistically significant increase in phototherapy, neonatal sepsis, transient newborn tachypnea, or ICU admission between the late and early cord clamping groups. Birth weight was similar between groups.

There were no significant correlations in other parameters such as gestational age, type of delivery, maternal BMI, or neonatal ICU stay (Table 3).

4. Discussion

It is known that one minute of late cord clamping after birth to equate to 80 ml more blood in the newborn's circulation and 3 minutes leads to a 100 ml increase.

Table 1. Characteristics of newborns.

Variables	Total (N = 357)	Early clamping (n = 114)	Late Clamping (n = 243)	*p-value
Birth weight (grams)—mean ± SD [minimum-maximum]	3305.76 ± 23.18 [1610.00 - 4650.00]	3302.72 ± 38.91 [2420.00 - 4440.00]	3307.19 ± 28.81 [1610.00 - 4650.00]	**0.928**
APGAR 1st minute—median [95% CI] [minimum-maximum]	9.00 [8.14 - 8.44] [1.00 - 10.00]	9.00 [8.63 - 8.85] [5.00 - 10.00]	9.00 [7.87 - 8.29] [1.00 - 10.00]	**0.001**
APGAR 5th minute—median [95% CI] [minimum-maximum]	10.00 [9.36 - 9.51] [4.00 - 10.00]	10.00 [9.50 - 9.70] [8.00 - 10.00]	9.00 [9.25 - 9.45] [4.00 - 10.00]	**0.006**

Caption: md—median. 95% CI—95% confidence interval. SD—standard deviation. n—absolute frequency. n%—relative frequency. APGAR—Fetal vitality assessment method. p—Statistical significance index. * Student t-test for independent samples or Mann-Whitney test for independent samples. Significance set at 5% for all analyzes.

Table 2. Neonatal outcomes.

Variables	Total (N = 357)	Early clamping (n = 114)	Late Clamping (n = 243)	*p-value
Phototherapy—n (n%)				
No	338 (94.7)	108 (94.7)	230 (94.7)	1.000
Yes	19 (5.3)	6 (5.3)	13 (5.3)	
Sepsis—n (n%)				
No	353 (98.9)	113 (99.1)	240 (98.8)	1.000
Yes	4 (1.1)	1 (0.9)	3 (1.2)	
Transient Tachypineia—n (n%)				
No	339 (95.0)	110 (96.5)	229 (94.2)	0.517
Yes	18 (5.0)	4 (3.5)	14 (5.8)	
Neonatal ICU stay—n (n%)				
No	301 (84.3)	96 (84.2)	205 (84.4)	1.000
Yes	56 (15.7)	18 (15.8)	38 (15.6)	

Caption: n—absolute frequency. n%—relative frequency. ICU—Intensive Care Unit. p—Statistical significance index. * Chi-square test with adjusted residual analysis. Significance set at 5% for all analyzes.

Table 3. Correlations of late cord clamping with maternal and fetal characteristics.

Variables	Late clamping	
	r_s	*p-value
Maternal age (in years)	−0.093	0.080
Gestational age (in days)	0.085	0.108
Caesarean section	0.077	0.148
Episiotomy	0.303	≤0.0001
Forceps	0.162	0.002
Etnia não-branca	0.002	0.975
BMI (in kg/m2)	0.080	0.135
RN weight	0.011	0.833
APGAR 1	**−0.181**	**0.001**
APGAR 5	**−0.145**	**0.006**
Phototherapy	0.002	0.973
Sepsis	0.016	0.766
Transient tachypnea	0.048	0.366
Neonatal ICU stay	−0.002	0.971

Caption: r_s—Spearman correlation index. p—statistical significance index. APGAR—Fetal vitality assessment method. Kg—kilograms. m—meters. RN—newborn. * Spearman correlations. Significance set at 5% for all analyzes.

This extra amount of circulating blood in the newborn equals 40 - 50 mg/kg of serum iron, which leads to a decrease in neonatal anemia by the sixth month of life [7] [8].

The major benefits of late cord clamping are the reduction of neonatal anemia, the need for blood transfusions and the incidence of intraventricular hemorrhage. In addition, a significant improvement in early childhood cognition is seen, inherent in a better iron level and a decrease in anemia in this age group [9] [10]. Some studies have associated late cord clamping with unfavorable outcomes in the newborn as increased need for phototherapy [11] [12]. A review by McDonald *et al.*, which compared data from 15 randomized controlled trials, noted increased rates of jaundice requiring phototherapy, suggesting that late clamping should be performed only in units where phototherapy treatment is available, as untreated jaundice can cause severe damage to newborns [2]. This, however, is not an official WHO recommendation. In the present study, there was no increase in phototherapy rates in the late cord clamping group, and even the same phototherapy rates were found between the two groups analyzed (5.3%).

Corroborating to what was found in this study, Chen *et al.* shows that there is an increase in hematocrit in neonates with late cord clamping without increased incidence of negative outcomes for both newborns and mothers [13]. Yang *et al.* also demonstrated increased transcutaneous bilirubin levels, increased blood cell

counts and increased diagnosis of jaundice, with no higher incidence of phototherapy in patients undergoing late cord clamping. This corroborates to the hypothesis that increased hematocrit level does not have clinically significant consequences for patients [14].

Regarding APGAR in the 5th minute, there was a decrease in the late clamping group compared to the early clamping, however this reduction was not clinically significant, since the patients only kept in their 1st minute APGAR score, whereas in the clamping group early they increased their grade after 5 minutes. In addition, performance always remained good in both groups, between 9 - 10. Some studies in the literature, such as McDonald *et al.* evaluated APGAR as a secondary outcome and established a cutoff score (APGAR less than 7) and yet found no differences between groups [15].

We found no increase in any other unfavorable outcomes such as neonatal ICU admission, incidence of sepsis or transient tachypnea of the newborn in the late clamping group compared to the early clamping group. The study by Kc *et al.* demonstrated that patients undergoing late cord clamping had 18% higher blood oxygenation in the first minute, first breath time, and regular breathing established earlier than patients with early cord clamping [16].

One point to be analyzed and that was studied by Ciubotariu *et al.* was the impact of late clamping on umbilical cord blood donations, which concluded that clamping from 60 seconds significantly decreased cell and blood volume, dramatically reducing the clinical use of this blood for recipients [17]. In this study, we did not evaluate this outcome.

One of the most recent studies by Carvalho OMC *et al.*, published this year, showed no association between late clamping and increased bilirubin, jaundice, or need for phototherapy. In addition, it showed that the practice is more common in vaginal births [18]. Our data corroborate the same result.

5. Conclusion

These data show a trend that the benefits of late cord clamping outweigh its possible risks, showing that the increase in hematocrit is unlikely to cause any clinical manifestation requiring intervention. However, the opposite is true, and the benefits of increased hematocrit and decreased childhood anemia levels are already established in the literature. This corroborates the guidance already made by WHO to perform this neonatal care in newborns without contraindication. As there are some discrepancies regarding results such as increased phototherapy, we believe further studies are needed to evaluate these data.

Ethics and Registration

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The project was approved by the Group of Research

and Postgraduation of the Hospital de Clínicas de Porto Alegre (CEP-HCPA 3.026.202) and Presentation Certificate for Ethical Appreciation—CAAE (02662918.1.0000.5327). The trial was registered with Brazilian Registry of Clinical Trials (ReBec-U1111-1233-9573).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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