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Physiological measurements of the effect of cord clamping strategies

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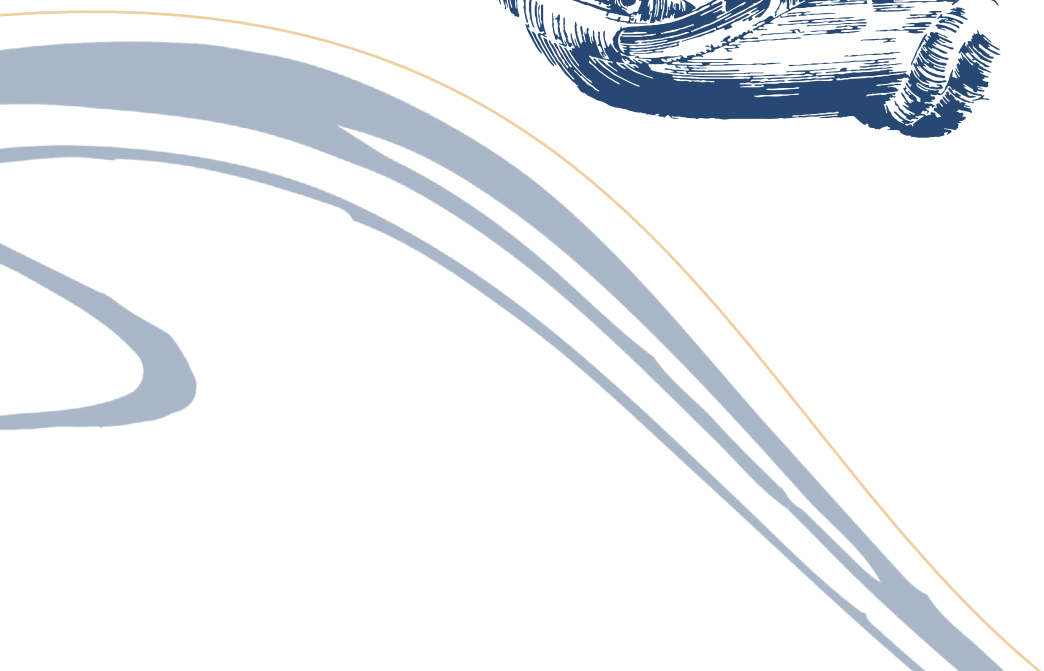
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CHAPTER 5

Physiological-based cord clamping in very preterm infants – randomised controlled trial on effectiveness of stabilisation

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ABSTRACT

AIM

To test whether stabilising very preterm infants while performing physiological-based cord clamping (PBCC) is at least as effective as the standard approach of time-based delayed cord clamping (DCC).

METHODS

A randomised controlled non-inferiority study was performed in two centres from May until November 2018, including preterm infants born below 32 weeks of gestational age. Infants were allocated to PBCC or standard DCC. Infants receiving PBCC were stabilised on a purpose-built resuscitation table with an intact umbilical cord. The cord was clamped when the infant had regular spontaneous breathing, heart rate ≥ 100 bpm and $\text{SpO}_2 > 90\%$ while using $\text{FiO}_2 < 0.40$. In infants receiving DCC, the cord was clamped at 30-60 seconds after birth before they were transferred to the standard resuscitation table for further treatment and stabilisation. Primary outcome was time to reach respiratory stability.

RESULTS

Thirty-seven infants (mean gestational age 29+0 weeks) were included. Mean cord clamping time was $5:49 \pm 2:37$ min in the PBCC ($n=20$) and $1:02 \pm 0:30$ min in the DCC group ($n=17$). Infants receiving PBCC needed less time to reach respiratory stability (PBCC $5:54 \pm 2:27$ min; DCC $7:07 \pm 2:54$ min; mean difference corrected for gestational age $-1:19$ min, 95% CI $(-3:04 - 0:27)$), showing non-inferiority with the pre-defined limit of 1:15 min. No significant differences between the groups were found for maternal blood loss, postpartum haemorrhage, infant temperature at admission or short-term neonatal outcomes.

CONCLUSION

Stabilisation of very preterm infants with physiological-based cord clamping is at least as effective as with standard DCC.

INTRODUCTION AND RATIONALE

Management of very preterm infants in the first minutes of life can have a major impact on neonatal morbidity and mortality.^(1, 2) During the transition to extra-uterine life, lung aeration is pivotal to initiate the major physiological changes in respiratory and cardiovascular function that are required for survival after birth.^(3, 4) Most preterm infants require respiratory support at birth, as they often fail to aerate their immature lungs.⁽⁵⁾ Respiratory support is commonly started only after umbilical cord clamping, which in experimental studies has been shown to compromise cardiovascular function.⁽⁶⁾

Preterm infants could benefit from placental transfusion (blood transfer from the placenta to the infant) when cord clamping is delayed. A recent meta-analysis comparing delayed cord clamping (DCC) with immediate cord clamping (ICC) in preterm infants, showed increased haematocrits, less blood transfusions, a decrease in neonatal mortality and a trend towards less intraventricular haemorrhages (IVH).⁽⁷⁾ However, in most studies DCC was performed using a fixed time-point of 30-60 s whereas placental transfusion may take up to 3 min to complete.⁽⁸⁾ In addition, preterm infants needing immediate interventions for stabilisation or resuscitation were generally clamped immediately and excluded from these series. These infants are however at the highest risk of complications and may receive the greatest benefit from DCC.

While the rationale of most DCC studies was based on increased placental transfusion, experiments in preterm lambs have shown that delaying cord clamping until after ventilation onset prevents a significant reduction in cardiac output.⁽⁶⁾ This approach of physiological-based cord clamping (PBCC) in lambs also prevented large fluctuations in systemic and cerebral blood pressures and flows.⁽⁹⁾ In preterm infants these detrimental effects may be avoided when infants are first stabilised whilst connected to the cord and only clamped when the infant has a stable breathing pattern, possibly resulting in decreased risk of mortality and (cerebral) morbidity.⁽¹⁰⁾

The aim of the PBCC approach in preterm infants is to establish lung aeration, adequate pulmonary blood flow and pulmonary gas exchange prior to cord clamping. To facilitate this approach, a new purpose-built resuscitation table (the Concord) has been developed at Leiden University Medical Centre (LUMC). This mobile resuscitation table is designed to provide full standard care in stabilisation of preterm infants at birth while the cord remains intact. All equipment that is needed for stabilisation and resuscitation is incorporated in the table allowing preterm infants needing immediate respiratory support to also receive the possible benefits of PBCC. This study is the second in our Aeration, Breathing, Clamping (ABC) research project determining the benefit of PBCC using the Concord. We

recently demonstrated feasibility of this approach with a median cord clamping time of almost four and half minutes (ABC1 study).⁽¹¹⁾

Aim of the study

The aim of the present study (ABC2 study) was to assess whether using the Concord to stabilise preterm infants with PBCC is at least as effective as using the standard approach of stabilising infants after a period of DCC (30-60s) using a standard resuscitation table.⁽¹²⁾ Our hypothesis was that stabilisation with PBCC was non-inferior to stabilisation after DCC.

METHODS

Trial design

The study was a randomised controlled non-inferiority trial in two tertiary centres (LUMC and Erasmus University Medical Centre) and performed in the labour room or operating theatre in case of caesarean section. Infants were randomised 1:1 to either stabilisation according to the PBCC approach using the Concord, or stabilisation according to the standard DCC approach using the standard resuscitation table. The study was approved by the LUMC Institutional Review Board (IRB, P18.025) and registered in the Netherlands Trial Register (NTR7194/NL7004). Infants were included in the study from May 9th until November 18th 2018. Details on study procedures, randomisation, investigational products and sample size are as previously described.⁽¹²⁾

Participants

Infants born vaginally or by caesarean section prior to 32 weeks and 0 days of gestational age (GA) were eligible. Exclusion criteria were significant congenital malformations influencing cardiopulmonary transition, placental abruption, placenta praevia and signs of severe fetal distress necessitating emergency caesarean section. Parental written informed consent was obtained prior to birth.

Investigational procedures

Prior to the start of the study, all health care providers involved in labour room care were trained in using the Concord for PBCC. A standard operating procedure was developed to optimise close collaboration between neonatologists and obstetricians. All neonatal caregivers involved were trained and accredited for neonatal resuscitation. Centres adhered to local resuscitation guidelines for stabilisation of preterm infants.

Preterm infants randomised to the intervention group were stabilised according to the PBCC approach (figure 1). This involved providing standard postnatal respiratory management and heat loss prevention while the infant was on the Concord close to its mother, with the cord still intact. Importantly, stabilisation started as soon as the infant was placed on the platform, with the cord still intact, which was clamped only after the infant was judged to be stable, as defined by the presence of regular spontaneous breathing, a heart rate (HR) > 100 bpm and oxygen saturation (SpO₂) above 90% while using supplemental oxygen (FiO₂) < 0.40. Uterotonic drugs were administered immediately after cord clamping.



Figure 1 | Physiological-based cord clamping approach using the Concord

In case of twins and vaginal birth, a similar stabilisation protocol and definition of the moment of cord clamping was used. Clamping in the first infant was performed sooner if the second infant was about to be born. The first infant was then transferred to the standard resuscitation table, so that the second twin could be stabilised on the Concord.

PBCC could be abandoned at any time during the procedure, which involved clamping the cord and transferring the infant to the standard resuscitation table. This could result (1) from a clinical emergency in the woman or the second twin requiring additional working space for the obstetrician, (2) when full resuscitation was needed, and (3) when maternal blood loss was excessive and the obstetrician decided to clamp the cord and administer uterotonic drugs without delay.

Preterm infants randomised to the standard DCC group were transferred to the standard resuscitation table following cord clamping to administer any treatments or interventions required to stabilise the infant, according to local resuscitation

guidelines. Clamping was time-based and occurred 30-60 s after birth, depending on the clinical condition of the infant; early cord clamping was deemed necessary if the infant needed assistance. Uterotonic drugs were administered immediately after cord clamping.

Randomisation, blinding and treatment allocation

Randomisation was stratified by gestational age (24-27+6 and 28-31+6 weeks) and by treatment centre using variable block (4-8) sizes. Concealment of allocation was ensured by using the randomisation process of Castor EDC, an electronic data capture system. Blinding of the study was not possible.

In case of twins born vaginally, both infants were randomised to the same group. In case of twins born by caesarean section, it was technically not possible to perform PBCC for both infants. After consent, both infants were included; the first infant always received DCC and the second infant was randomised to either PBCC or DCC.

Primary outcome

Primary outcome was the time to stabilisation of the infant, starting from birth. A stable infant was defined by the presence of regular spontaneous breathing, a HR \geq 100 bpm and SpO₂ above 90% while using FiO₂ < 0.40.

Secondary outcomes

In addition to patient and maternal demographics, multiple secondary outcomes were collected as described in the study protocol.⁽¹²⁾ These outcomes were related to the procedure itself and to the transition of the infant. Furthermore, short-term neonatal and maternal outcomes were collected. Important safety outcomes were infant temperature at admission at the neonatal intensive care unit (NICU) and maternal peripartum blood loss, postpartum haemorrhage and surgical site wound infection after caesarean section.

Statistical analysis

When designing this study, no data were available on the effectiveness of stabilising infants during PBCC and comparing PBCC with DCC to conduct a power analysis. Few studies have performed initial respiratory support before cord clamping, but all used predefined timing of cord clamping, varying from 30 to 120 s. Data from our feasibility study showed that the median [IQR] time to obtain respiratory stability was 4:23 min [3:00 – 5:11] during PBCC.

In our unit, the mean time (from birth) needed to stabilise an infant using DCC is 5 ± 2 minutes.⁽¹³⁾ If the time to stabilisation was not different between DCC and PBCC, we calculated that 64 infants (32 in each treatment arm) were required. This would give 80% power to assess whether the upper limit of a one-sided 97.5% confidence interval (equivalent to a 95% two-sided confidence interval) around the difference in mean time to stabilisation would be below the non-inferiority limit of 75 s. A non-inferiority margin of 75 s was chosen as current clinical guidelines for targeting of oxygen saturation indicate that this time difference is acceptable during stabilisation.⁽¹⁴⁾

Normally distributed data is presented as means \pm standard deviations, whereas data that is not normally distributed is presented as medians and interquartile ranges. Categorical data were analysed using the Chi-square test or Fisher's exact test. Continuous data were analysed using the Student's t test or Mann-Whitney test as appropriate. Intention-to-treat analysis was performed. For the primary outcome an additional as-treated analysis was performed, analysing results based on the received rather than allocated treatment. The effect of PBCC on the primary outcome was assessed by multivariable linear regression analysis including GA as additional covariate. An additional sensitivity analysis correcting for other possible confounders that were unbalanced between the groups was performed. The primary test of non-inferiority is reported with a one-sided p-value and compared to an alpha of 2.5%; all other (superiority) p-values are reported two sided and compared to an alpha of 5%.

RESULTS

Following a discussion between the investigators and three independent experts (an ethicist, a statistician and an epidemiologist), it was decided to stop this trial before reaching the target sample size due to a slower than anticipated recruitment. The recruitment period for this trial was predetermined and limited by the funding conditions of the next-stage, and larger, ABC3 trial. Ceasing the trial at this time allowed an analysis of trial outcomes in recruited infants and review by the research ethics committee so that ABC3 trial could be approved by the required date, as long as the results of ABC2 trial were satisfactory. The analysis occurred at 50% recruitment and found that the predefined non-inferiority limit was already met.

A total of 191 women were assessed for eligibility (figure 2). Of these women 158 were deemed eligible and 120 approached for study participation. A total of 74 parent couples consented for study participation and 39 infants (35 pregnancies) were randomised, allocating 22 infants to PBCC and 17 infants to DCC. Two

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infants were excluded either because of lung hypoplasia or due to an emergency caesarean section. Another two infants in the PBCC group received standard treatment, due to technical failure of the radiant heater of the Concord and birth prior to timely preparation of the Concord. Baseline characteristics of the study patients are presented according to their allocation (table 1).

Table 1 | Baseline characteristics

	PBCC group (n=20)	DCC group (n=17)
Gestational age, weeks	28 ⁺⁴ [27 ⁺⁶ – 30 ⁺³]	30 ⁺² [27 ⁺⁵ – 31 ⁺⁰]
Birthweight, grams	1155 [1043 – 1349]	1200 [895 – 1620]
Female	16 (80.0)	8 (47.1)
Twins	5 (25.0)	3 (17.6)
Antenatal steroids		
Yes	20 (100)	17 (100)
Complete (≥ 48h)	16 (80.0)	9 (52.9)
Caesarean Section	9 (45.0)	9 (52.9)
PE/HELLP	3 (15.0)	2 (11.8)
Premature contractions	15 (75.0)	12 (70.6)
Chorioamnionitis	7 (35.0)	6 (35.3)

Data presented as median [IQR] or n (%). PBCC, physiological-based cord clamping; DCC, delayed cord clamping; PE, preeclampsia; HELLP, Haemolysis Elevated Liver-enzymes Low Platelets syndrome.

Physiological-based cord clamping in very preterm infants

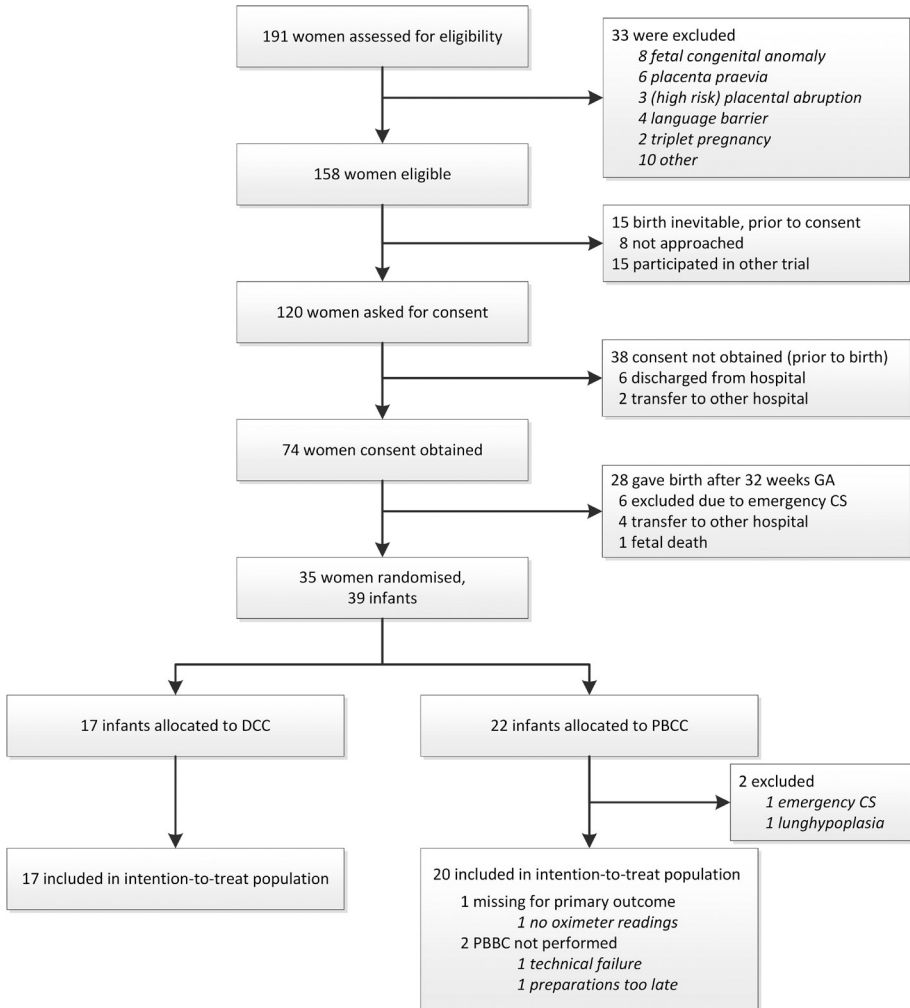


Figure 2 | CONSORT diagram

CONSORT, Consolidated Standards of Reporting Trials; GA, gestational age; CS, caesarean section; DCC, delayed cord clamping; PBCC, physiological-based cord clamping.

Primary outcome

Primary outcome was recorded for 36 infants, as pulse-oximeter measurements were not obtained for one infant and primary outcome could therefore not be determined. Intention-to-treat analysis showed that the mean time to stabilisation was 5:54 ± 2:27 min for infants in the PBCC group and 7:07 ± 2:54 min for infants in the DCC group. Mean difference, corrected for GA, was -1:19 min with a 95% confidence interval of -3:04 to 0:27 min. The pre-defined non-inferiority limit of 75 s fell outside of the confidence interval (p<0.01; one sided non-inferiority test, figure 3). A total of three infants did not achieve the primary outcome within 10 min. Two of these infants were allocated to DCC and one to PBCC.

The baseline characteristics revealed a higher proportion of females in the PBCC group. Additionally, correcting for gender showed a mean difference of -0:45 min with a 95% confidence interval of -2:32 to 1:02 min (p=0.01; one-sided non-inferiority test).

As-treated analysis showed the mean time to stabilisation was 5:25 ± 1:35 min for infants in the PBCC group and 7:25 ± 3:10 min for infants in the DCC group. Mean difference, corrected for GA, was -2:02 min with a 95% confidence interval of -3:42 to -0:22 minutes (p<0.01, one sided non-inferiority test; p=0.019, two-sided superiority test, figure 3).

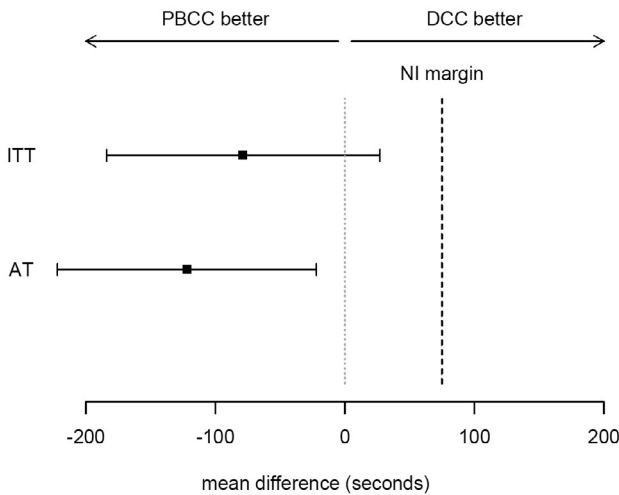


Figure 3 | Forest plot for time to stabilisation

Mean differences and 95% confidence intervals for intention-to-treat (ITT) and as-treated (AT) analysis, and the predefined non-inferiority (NI) margin of 75 seconds.

DCC, delayed cord clamping; PBCC, physiological-based cord clamping.

Secondary outcomes

Infants in the PBCC group were more likely to receive respiratory support earlier, and cord clamping was performed later at a mean time of 5:49 ± 2:37 min (table 2). No statistically significant differences were shown between the two groups for labour room or short term neonatal secondary outcomes, except for umbilical cord pH (table 2 and 3).

No postoperative infections were reported after caesarean sections. Median maternal blood loss was 300 [200-700] ml and 450 [263-538] ml for the PBCC and DCC group, respectively (p=0.53, table 2).

Table 2 | Secondary outcomes, labour room

	PBCC group (n=20)	DCC group (n=17)	P value
Time until cord clamping, min	5:49 ± 2:37	1:02 ± 0:30	0.00
Time until start support, min	1:11 ± 1:18	2:00 ± 0:47	0.04
Respiratory support			
None	1 (5.0)	0 (0.0)	1.00
CPAP	18 (90.0)	17 (100)	0.18
PPV	14 (70.0)	10 (58.8)	0.48
Intubation	1 (5.0)	0 (0.0)	1.00
Maximum FiO ₂ used, %	70 [50 – 90]	50 [30 – 88]	0.24
Apgar 1 minute	6 [5 – 8]	7 [6 – 8]	0.58
Apgar 5 minutes	8 [7 – 9]	9 [8 – 9]	0.39
Apgar 10 minutes	9 [8 – 10]	9 [9 – 10]	0.49
Umbilical cord pH	7.21 ± 0.09	7.29 ± 0.09	0.01
Temperature at admission, °C	36.5 ± 0.8	36.7 ± 0.6	0.61
Temperature < 36.0 °C	4 (20.0)	1 (5.9)	0.21
Maternal blood loss, ml	300 [200-700]	450 [263-538]	0.53
Postpartum haemorrhage (>1000 ml)	2 (11.1)	2 (12.5)	0.90

Data reported as analysed per intention-to-treat. Data presented as mean ± SD, n (%) and median [IQR]. PBCC, physiological-based cord clamping; DCC, delayed cord clamping; min, minutes; CPAP, continuous positive airway pressure; PPV, positive pressure ventilation; FiO₂, fraction of inspired oxygen.

Table 3 | Secondary outcomes, short term neonatal

	PBCC group (n=20)	DCC group (n=17)	P value
Haemoglobin first 24 h, g/dL	16.3 ± 2.9	16.8 ± 3.4	0.76
Haematocrit first 24 h, l/l	0.49 ± 0.07	0.50 ± 0.09	0.80
First infant pH after admission	7.27 ± 0.09	7.31 ± 0.10	0.27
Intubated during NICU stay	5 (25.0)	5 (29.4)	0.76
Need for surfactant	8 (40.0)	6 (35.3)	0.77
Treatment for hypotension <72h	3 (15.0)	0	0.23
Patent ductus arteriosus	6 (30.0)	4 (23.5)	0.66
IVH (all grades)	3 (15.0)	2 (11.8)	0.77
IVH ≥ grade 3	0	1 (5.9)	0.46
Maximum bilirubin	169.2 ± 43.2	163.7 ± 43.5	0.70
Need for phototherapy	20 (100)	15 (88.2)	0.12
Need for RBC transfusion	4 (20.0)	6 (35.3)	0.30
Early onset infection <72h	1 (5.0)	2 (11.8)	0.45
Late onset infection >72h	7 (35.0)	6 (35.3)	0.99
NEC ≥ grade 2A	2 (10.0)	1 (5.9)	0.65
Death	0	2 (11.8)	0.20
ROP (all grades)	7 (35.0)	2 (14.3) (n=14)	0.18
BPD (all grades)	4 (20.0)	4 (26.7) (n=15)	0.64

Data reported as analysed per intention-to-treat. Data presented as mean ± SD and n (%). PBCC, physiological-based cord clamping; DCC, delayed cord clamping; NICU, neonatal intensive care unit; IVH, intraventricular haemorrhage; RBC, red blood cells; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia.

DISCUSSION

This is the first reported trial comparing physiological-based cord clamping to delayed cord clamping treatment in very preterm infants. The timing of cord clamping in the PBCC group was based on the infant's transitional status, which in contrast with the time-based approaches used previously, lead to a considerably longer cord clamping time of 5:49 min. Our results demonstrate that stabilisation of preterm infants when performing PBCC using the Concord, is at least as effective as stabilising infants using the current routine DCC approach and a standard resuscitation table.

Few studies have investigated the provision of respiratory support to very preterm infants before cord clamping. All previous studies have used a time-based approach, with cord clamping varying between 60 s and 3 min after birth.⁽¹⁵⁻¹⁹⁾ These studies either used a bedside trolley or performed resuscitation while the neonate was positioned on the mother's leg or abdomen, reporting feasibility of the approach between 59% and 100%. In the present study, in all but two infants allocated to the PBCC approach this was feasible resulting in a 90% success rate of the PBCC approach using the Concord, which is comparable to our first cohort.⁽¹¹⁾ The two most important predefined safety parameters were maternal blood loss and admission temperature of the infant at the NICU. Although cord clamping is performed considerably later in the PBCC group than in all previous reported studies performing DCC in very preterm infants, maternal blood loss was not increased. This observation is in concordance with earlier studies showing that maternal blood loss is not increased after DCC.^(20,21) Mean infant temperature at NICU admission was not different, although four infants had moderate hypothermia in the PBCC group as compared to one infant in the DCC group. Temperature management from birth to NICU admission during PBCC was performed conform standard care, but remains an important focus during training for the PBCC approach, which is also emphasised by others using slightly different approaches.^(17,18) No important safety concerns were observed for the PBCC approach using the Concord, as all other short term neonatal outcomes were not different between groups. Three infants in the PBCC group were treated for hypotension in the first 72 h after birth by the administration of one bolus of fluid. This occurred twice after the administration of propofol prior to intubation. No infant needed inotropes during the first 72 h after birth.

This study showed stabilisation using PBCC is at least as effective as stabilising infants according to the current DCC approach. Interestingly, the as-treated analysis, based on actual received treatment, showed infants were stabilised faster when the PBCC approach was performed with a statistically significant difference between the two groups ($p=0.019$). This may reflect the positive effect PBCC has on cardiorespiratory

stability and ultimately stabilisation of preterm infants. Umbilical cord pH was lower for the PBCC group, whereas Apgar scores and first neonatal pH values during NICU admission did not differ between the two groups. The delay in obtaining umbilical cord blood after the PBCC approach could have resulted in lower umbilical cord blood pH values, as described previously after delayed cord clamping.^(22,23) Since first neonatal pH values and Apgar scores were not different, clinical relevance of the difference in cord blood pH is most likely minimal.

This study has some important limitations. Infants were only included after having received antenatal consent from both parents. Women giving birth soon after admission, were not approached since this was deemed inappropriate. Using deferred consent for this type of interventional labour room studies may overcome this problem and increase generalisability.⁽²⁴⁾ Likewise, infants born by emergency caesarean section were also not eligible, as there would be insufficient time for equipment set-up. In contrast, these infants probably may benefit most from PBCC and including these infants in future studies may further increase generalisability. Lastly, respiratory support in infants in the PBCC group was initiated earlier compared to the control group, which is simply a hallmark and consequence of the overall PBCC approach. Thus, evaluation of the PBCC approach in this study includes earlier start of respiratory support, later umbilical cord clamping and the utilization of the Concord.

Previous animal models already showed increased respiratory and haemodynamic stability when using the physiological-based cord clamping approach.⁽⁶⁾ Increased stability during PBCC could explain for infants in this group to be stabilised faster. The aim of the PBCC approach in preterm infants is to establish lung aeration, adequate pulmonary blood flow and pulmonary gas exchange prior to cord clamping. No clear criteria are available to define when an infant is respiratory stable. In this study, stabilised was defined as the infant having established regular spontaneous breathing with SpO₂ above 90%, HR > 100 bpm while using FiO₂ < 0.40. Others used different criteria for cord clamping in a physiological approach, for example including exhaled carbon dioxide as a marker for pulmonary gas exchange.⁽²⁵⁾ Our definition of being stable was useful in our study as SpO₂ and HR are monitored for every preterm infant. However, the target of 90% may be set relatively high, as current international guidelines aim for SpO₂ of 85% at 5 min. We previously demonstrated the feasibility and now tested the effectiveness of the PBCC approach using the Concord.⁽¹¹⁾ The next step is to determine whether this approach results in beneficial effects on important clinical outcomes in very preterm infants. In 2019, a large multicentre randomised clinical trial (ABC3 trial) has been started in the Netherlands.

CONCLUSIONS

In conclusion, stabilisation of very preterm infants performing the PBCC approach results in considerably longer cord clamping times and is at least as effective as stabilisation according to the current routine DCC approach. Larger randomised clinical trials are needed to show potential beneficial clinical effects for preterm infants.

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