Initiating resuscitation before umbilical cord clamping in infants with congenital diaphragmatic hernia: a pilot feasibility trial

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ABSTRACT

Background Infants with congenital diaphragmatic hernia (CDH) often experience hypoxaemia with acidosis immediately after birth. The traditional approach in the delivery room is immediate cord clamping followed by intubation. Initiating resuscitation prior to umbilical cord clamping (UCC) may support this transition.

Objectives To establish the safety and feasibility of intubation and ventilation prior to UCC for infants with CDH. To compare short-term outcomes between trial participants and matched controls treated with immediate cord clamping before intubation and ventilation.

Design Single-arm, single-site trial of infants with CDH and gestational age ≥36 weeks. Infants were placed on a trolley immediately after birth and underwent intubation and ventilation, with UCC performed after qualitative CO2 detection. The primary feasibility endpoint was successful intubation prior to UCC. Prespecified safety and physiological outcomes were compared with historical controls matched for prognostic variables using standard bivariate tests.

Results Of 20 enrolled infants, all were placed on the trolley, and 17 (85%) infants were intubated before UCC. The first haemoglobin and mean blood pressure values at 1 hour of life were significantly higher in trial participants than controls. There were no significant differences between groups for subsequent blood pressure values, vasoactive medications, inhaled nitric oxide or extracorporeal membrane oxygenation. Blood gas and oxygenation index values did not differ between groups at any point.

Conclusions Intubation and ventilation prior to UCC is safe and feasible among infants with CDH. The impact of this approach on clinically relevant outcomes deserves investigation in a randomised trial.

INTRODUCTION

Physiological adaptation after birth is a critical transition for infants with congenital diaphragmatic hernia (CDH). In utero, the fetus has fluid-filled lungs, and gas exchange occurs at the placenta. Immediately after birth, the infant must aerate the lungs, which triggers a physiological transition of reduced pulmonary vascular resistance, increased pulmonary blood flow and gas exchange in the lung.1 2 Infants with CDH struggle to independently achieve lung aeration due to pulmonary hypoplasia and space-occupying effects of herniated abdominal organs. Furthermore, they are at risk for decreased pulmonary blood flow due to pulmonary hypertension. In a preclinical model of CDH, physiological challenges during transition include lower lung compliance, more respiratory acidosis and poor cerebral oxygenation.3 Clinically, this manifests as hypoxaemia, hypercarbia and acidosis after birth, often reflected in low Apgar scores.4-6 Limited data inform the delivery room management for infants with CDH.7 The standard approach is immediate umbilical cord clamping (UCC) followed by intubation and ventilation.6-8 An alternative strategy is to establish lung aeration prior to UCC, which has been called ‘physiologically based cord clamping’.8,9 Physiologically based cord clamping may stabilise gas exchange during neonatal transition among infants with CDH by supporting aeration of the hypoplastic lung and increasing pulmonary blood flow through the thickened pulmonary vasculature before UCC. In
The objectives of this pilot trial were to: (1) establish the safety and feasibility of intubation and ventilation prior to UCC for infants with CDH, but most infants in that study had mild CDH prognostic parameters.19

The primary feasibility endpoint was successful intubation prior to UCC within the 3 min timeframe. Prespecified neonatal safety outcomes included cord avulsion, cardiopulmonary resuscitation and first measured temperature. Maternal safety outcomes included estimated blood loss, therapeutic uterotonic

An attending neonatologist, respiratory therapist and neonatal nurse attended each delivery (figure 1). A mobile LifeStart Trolley (Inditherm Medical, Rotherham, UK) was adjusted to the level of the introitus for vaginal deliveries and just above the level of the incision for caesarean deliveries. An activated chemical warmer mattress was placed on the trolley mattress for thermoregulation. For caesarean deliveries, the trolley and neonatal providers were steriley draped.

Initially, the study used a purpose-built respiratory pole with air and oxygen tanks and a Neopuff Infant T-piece resuscitator (Fisher and Paykel, Auckland, New Zealand). Suction tubing was connected to canisters in the labour room or obstetrical suite. Midway through the trial, this equipment was replaced by a portable T-piece resuscitator that included suction (Giraffe Stand Alone Resuscitation System, GE Healthcare, USA). Airway equipment and respiratory tubing were not sterile and were handled to avoid contact with the sterile operative field for caesarean deliveries.

Immediately after delivery, the obstetrical provider placed the infant on the trolley. The neonatologist intubated the infant, and ventilation was commenced using settings per hospital protocol (initial pressures 20–25/5 cm H₂O, fractional inspired oxygen 0.5). UCC was performed after consistent qualitative colorimetric CO₂ detection, with guidelines for maternal uterotonic administration after UCC. After UCC, the neonatal team moved the trolley and respiratory equipment away from the mother, taped the endotracheal tube, covered the infant with warm towels and transported the infant with ongoing ventilation to the resuscitation warmer bed. All remaining care was per clinical guidelines. The protocol stipulated for UCC to be performed prior to intubation for any of the following: the infant could not be placed on the trolley, intubation was not successful within 3 min from birth, cord avulsion or bleeding or any obstetrical or neonatal provider concerns.

The study team developed training videos and conducted equipment and simulation training for staff. A study team member was present for all resuscitations to ensure protocol adherence. When time allowed, the intervention was video recorded.
obstetrical concern for contamination of the sterile surgical field and wound infection (for caesarean deliveries). Feasibility outcomes and timing of procedural interventions were recorded by a dedicated staff member and abstracted from video recordings when available.

Physiological outcomes included first haemoglobin measurement, mean blood pressure values and blood gas parameters in the first 48 hours after birth, the first clinically obtained echocardiogram and mortality in the first week after birth. Echocardiogram images were independently reviewed by an unblinded single assessor (MVF) for signs of pulmonary hypertension. If present, the severity of pulmonary hypertension was graded based on the most severe assessment of the following criteria: direction of shunting at the ductus arteriosus (bidirectional: moderate; all right to left: severe), estimated systolic right ventricular pressures through continuous wave interrogation of the tricuspid regurgitant jet and calculation of a systolic right ventricle-to-right atrium pressure gradient by using the modified Bernoulli equation \[\text{pressure gradient} = 4 \times \text{jet velocity}^2\] \((<\frac{1}{2} \text{ systemic: normal/mild; } \geq \frac{1}{2} \text{ and } < \text{ systemic: moderate; } \geq \text{ systemic: severe})\) and qualitative evaluation of interventricular septal position at the end of systole (rounded: normal/mild; flattened: moderate and bowing: severe).

Interventions assessed included respiratory support and inhaled nitric oxide in the first 48 hours of life and extracorporeal membrane oxygenation (ECMO) in the first week after birth. Historical controls were identified from an ongoing pulmonary hypertension programme registry and matched with trial participants on the basis of gestational age, mode of delivery, side of CDH, liver position (intrathoracic vs intra-abdominal) and observed to expected lung-to-head ratio (O/E LHR) obtained, and these images were not assessed. All infants had evidence of pulmonary hypertension (online supplementary table). One trial participant not matched due to postnatal diagnosis of major anomaly. O/E LHR %, observed to expected lung-to-head ratio from anterior-posterior diameter method by the TOTAL trial calculator for infants with left-sided congenital diaphragmatic hernia.

### RESULTS

Between January and October 2018, 20 eligible infants were allocated to receive the intervention (figure 2). Demographic characteristics of enrolled infants and matched controls are shown in table 1. One enrolled infant was diagnosed with a second major anomaly postnatally. This infant was included in the assessment of safety and feasibility but not physiological outcomes; no control was matched to this participant.

All 20 infants were placed on the trolley and 17 (85%) infants were successfully intubated prior to UCC (online supplementary video). The median interval between birth and UCC was 2 min (IQR 1:15–2:32). Among the 17 successful cases, the median duration between birth and intubation was 1:02 (IQR 0:55–2:00), with 14 infants intubated on the first attempt and 3 intubated on the second attempt within this timeframe. The median duration between onset of ventilation and colorimetric CO2 detection was 14 (IQR 11–19) s. In three cases, the infant was not successfully intubated by 3 min after birth, and the umbilical cord was therefore clamped and cut prior to intubation. Two of these infants were born via vaginal delivery and one via caesarean delivery. Neonatal providers in those cases identified that infant positioning was the major impediment to procedural success, and all three of these infants were intubated after UCC once placed on the warmer bed.

Safety outcomes were similar between trial participants and historical controls (table 2). The first measured haemoglobin was higher among trial participants than historical controls (table 3). Mean blood pressure values were higher in trial participants at 1 hour of life. Subsequent mean blood pressure values assessed at 6 hours of life and beyond were similar between groups (data not shown). Blood gas parameters and oxygenation indices did not differ between trial participants or controls on the first blood gas or at any point in the first 48 hours after birth. There were no differences between groups in the use of vasoactive medications, inhaled nitric oxide or ECMO. No trial participants and one historical control died in the first week after birth.

Echocardiograms were obtained at a mean of 13 hours after birth. One trial participant and one historical control were supported with ECMO when the echocardiograms were obtained, and these images were not assessed. All infants had evidence of pulmonary hypertension (online supplementary table).

### Table 1 Baseline characteristics of trial participants

| Characteristic                        | Trial participants (n=20) | Historical controls (n=19)* |
|---------------------------------------|--------------------------|-----------------------------|
| Gestational age, weeks; mean (SD)     | 38.7 (0.5)               | 38.5 (0.8)                  |
| Birth weight, grams; mean (SD)        | 3374 (499)               | 3409 (577)                  |
| Male sex, n (%)                       | 15 (75)                  | 12 (63)                     |
| Vaginal delivery, n (%)               | 8 (40)                   | 8 (42)                      |
| Left sided defect, n (%)              | 15 (75)                  | 15 (79)                     |
| Any portion of liver in chest, n (%)  | 14 (70)                  | 13 (68)                     |
| O/E LHR %; median (IQR)              | 30.1 (25.6–35.9)         | 34.2 (27.4–36.7)            |

*One trial participant not matched due to postnatal diagnosis of major anomaly.

### Table 2 First measured haemoglobin

| Characteristic                        | Trial participants (n=20) | Historical controls (n=19)* |
|---------------------------------------|--------------------------|-----------------------------|
| Mean haemoglobin (g/dL)               | 6.8 (1.6)                | 6.1 (1.5)                   |
| Birth to first measured haemoglobin   | 1 hour; mean (SD)        |                             |
|                                      | 6.0 (1.5)                |                             |

*One trial participant not matched due to postnatal diagnosis of major anomaly.
**DISCUSSION**

We conducted this pilot trial to assess the safety and feasibility of initiating resuscitation prior to UCC for infants with CDH. It was possible to position all enrolled infants on a trolley adjacent to their mothers after birth. In most cases, it was possible to perform immediate intubation and ventilation with an intact umbilical cord. We did not find any evidence that this approach to resuscitation poses increased risk to infants or their mothers. Enrolled infants had higher haemoglobin levels and transiently higher systemic blood pressures compared with matched historical controls.

This study contributes to a growing body of literature demonstrating the feasibility and safety of initiating resuscitation prior to UCC. In contrast to our study population, few infants in previous trials required invasive respiratory support. In the trial by Duley et al., more invasive interventions were performed, including intubation and cardiac resuscitation of enrolled newborns. However, the protocol completion rate was lower among infants in the intervention group in that study (59%) compared with other trials of preterm infants (89%–100%).

Intubation is a standard approach to the delivery room management for all infants with CDH in our hospital. Thus, establishing lung aeration prior to UCC among infants with CDH requires intubation with an intact cord. In this trial, 17/20 infants were intubated within the specified 3 min timeframe before UCC. The threshold of allowing 3 min for intubation prior to UCC was considered to represent a reasonable balance between providing sufficient time for the neonatologist to intubate the infant without introducing an excessive delay in intubation and onset of ventilation if intubation before UCC was not possible. Neonatologists involved in unsuccessful cases expressed that positioning on the trolley was the major impediment to intubation, suggesting that additional time beyond 3 min may not have resulted in procedural success.

UCC was performed after colorimetric CO2 detection. It is possible that a longer duration of ventilation after intubation would allow for more adequate lung aeration before UCC. Physiologically based cord clamping has been variably defined. Lefebvre et al. specified for UCC to occur after ‘stabilisation’, indicated by measures of heart rate and oxygen saturation. Brouwer et al. targeted vital sign parameters as well as exhaled tidal volume >4 mL/kg as a indicator of lung aeration among preterm infants. This may not be a reasonable target for infants with CDH and related pulmonary hypoplasia, in whom tidal volumes after birth are often <4 mL/kg for both spontaneous breaths and manual inflations. In addition, tidal volume monitoring is not standard of care in most delivery rooms, and we sought to avoid introducing additional equipment into a crowded physical space for the study intervention.

Colorimetric CO2 detectors are small, portable and standardly used to confirm intubation success. Expired CO2 is correlated with tidal volume, and colorimetric CO2 precedes rise in heart rate among bradycardic infants. Blank et al. targeted UCC to occur ≥60 s after colorimetric CO2 detection for infants who required respiratory support in a recent feasibility trial. In future studies of infants with CDH, it may be reasonable to provide ventilation for a similar duration after CO2 detection before UCC.

This single-arm pilot trial was not designed to detect the impact of the study intervention on cardiopulmonary outcomes for infants with CDH. A randomised study powered for relevant outcomes is needed to address this question. There were transient differences in physiological outcomes such as haemoglobin and blood pressure between trial participants and historical controls. We assessed for echocardiographic evidence of pulmonary hypertension, but these studies—obtained for clinical indications—were performed on average 13 hours after birth and may not have reflected infants’ haemodynamic status immediately after birth. Lefebvre et al. reported that infants treated with intact cord resuscitation experienced transiently higher systemic blood pressures and blood gas pH values. In the present study, blood gas parameters were similar between participants and historical controls at all assessed time points, and initial pH values were low in both groups. One potential explanation for this is that infants enrolled by Lefebvre et al. had less severe antenatal parameters, with mean O/E LHR of 55%.

We acknowledge study limitations. Neonatal intubations were performed by attending neonatologists. Feasibility outcomes may not generalise to less experienced providers, who typically have lower intubation success rates.

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**Table 2** Maternal and infant safety outcomes

| Neonatal outcomes                  | Trial participants (n=20) | Historical controls* (n=19) | P value |
|------------------------------------|--------------------------|-----------------------------|---------|
| Cord avulsion                       | 0                        | 0                           | N/A     |
| Chest compressions                 | 0                        | 0                           | N/A     |
| Hypothermia on first temperature (<36°C), n (%) | 3 (15)                  | 2 (11)                      | >0.99   |
| First temperature (°C), mean (SD)  | 36.7 (0.9)               | 36.8 (0.6)                  | 0.56    |

**Table 3** Physiological outcomes

|                  | Trial participants (n=19) | Historical controls (n=19) | P value |
|------------------|--------------------------|---------------------------|---------|
| Apgar score at 1 min, median (IQR) | 5 (3–7)                  | 7 (3–8)                    | 0.51    |
| Apgar score at 5 min, median (IQR) | 8 (5–8)                  | 8 (5–9)                    | 0.72    |
| First Haemoglobin, g/dl; mean (SD) | 17.6 (1.3)               | 16.3 (1.9)                 | 0.02    |
| Mean blood pressure 1 hour after birth; mean (SD)* | 51.1 (8.5)              | 44.3 (6.3)                 | 0.008   |
| First blood gas after birth* | pH, mean (SD)          | 7.02 (0.15)                | 7.03 (0.13) | 0.74 |
|                      | CO2, mean (SD)          | 90.26 (26)                 | 88.25 (26) | 0.82 |
|                      | Base deficit, mean (SD) | 8.3 (3.3)                  | 9.8 (3.8) | 0.51 |
| Oxygenation index with first blood gas, median (IQR) | 17.5 (12.8–25.5)         | 16.3 (12.2–22.8)           | 0.74    |
| Vasopressors (first 48 hours), n (%) | 13 (68)                 | 16 (84)                    | 0.45    |
| INO (first 48 hours), n (%)        | 9 (47)                   | 11 (58)                    | 0.52    |
| ECMO (first 7 days), n (%)         | 7 (37)                   | 4 (21)                     | 0.48    |
| Mortality (first 7 days), n (%)    | 0                        | 1 (5)                      | >0.99   |

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We acknowledge study limitations. Neonatal intubations were performed by attending neonatologists. Feasibility outcomes may not generalise to less experienced providers, who typically have lower intubation success rates. In addition, we did not...
capture granular data on physiological parameters such as heart rate and oxygen saturation during the initial resuscitation, and non-invasive measures of pulmonary blood flow are not readily available. Study strengths include a prospective trial design with extensive training and oversight by the study team. We used a physiology-based, rather than time-based, approach to UCC. Finally, the trial included infants with a wide spectrum of prognostic CDH parameters, including severely affected infants.

In conclusion, performing intubation and initiating ventilation prior to UCC is safe and feasible among infants with CDH. The impact of this approach on clinically relevant outcomes deserves investigation in a randomized trial.

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REFERENCES
1 Te Pas AB, Davis PG, Hooper SB, et al. From liquid to air: breathing after birth. J Pediatr 2008;152:607–11.
2 Hooper SB, Te Pas AB, Lang J, et al. Cardiovascular transition at birth: a physiological sequence. Pediatr Res 2015;77:608–14.
3 Kashyap AJ, Crossley KJ, DeKoninck PL, et al. Neonatal cardiopulmonary transition in an ovine model of congenital diaphragmatic hernia. Arch Dis Child Fetal Neonatal Ed 2015;31:1005–13.
4 Abbas PI, Cars DJ, Okoye GO, et al. Persistent hypercarbia after resuscitation is associated with increased mortality in congenital diaphragmatic hernia patients. J Pediatr Surg 2015;50:739–43.
5 Grover TR, Murthy K, Brozanski B, et al. Short-Term outcomes and medical and surgical interventions in infants with congenital diaphragmatic hernia. Am J Perinatol 2015;32:1038–44.
6 Patel MJ, Bell CS, Lally KP, et al. Lowest PaCO2 on the first day of life predicts mortality and morbidity among infants with congenital diaphragmatic hernia. J Perinatol 2019;39:229–36.
7 Snoek KG, Reiss IKM, Greenough A, et al. Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH EURO consortium consensus - 2015 update. Neonatology 2016;110:66–74.
8 McHenry M. Congenital diaphragmatic hernia, management in the newborn. Pediatr Surg Int 2015;31:1005–13.
9 Badillo A, Gingalewski C. Congenital diaphragmatic hernia: treatment and outcomes. Semin Perinatol 2014;38:92–6.
10 Finer N, Tierney A, Ethies PC, et al. Congenital diaphragmatic hernia: developing a protocolized approach. J Pediatr Surg 1998;33:1331–7.
11 Hooper SB, Polglase GR, te Pas AB. A physiological approach to the timing of umbilical cord clamping at birth. Arch Dis Child Fetal Neonatal Ed 2015;100:F355–F360.
12 Kashyap AJ, Hodges RJ, Thio M, et al. Physiologically based cord clamping improves cardiopulmonary haemodynamics in lambs with a diaphragmatic hernia. Arch Dis Child Fetal Neonatal Ed 2019;fetalneonatal-2019-316906.
13 Winter J, Kattwinkel J, Chisholm C, et al. Ventilation of preterm infants during delayed cord clamping (VentFirst): a pilot study of feasibility and safety. Am J Perinatol 2016;34:111–6.
14 Katheria A, Poeltler D, Durham J, et al. Neonatal resuscitation with an intact cord: a randomized clinical trial. J Pediatr 2016;176:75–80.
15 Duley L, Dorling J, Pushpa-Rajah A, et al. Randomised trial of cord clamping and initial stabilisation at very preterm birth. Arch Dis Child Fetal Neonatal Ed 2016;103:F6–F14.
16 Brouwer E, Knel R, Vernooij ASN, et al. Physiologically-based cord clamping in preterm infants using a new purpose-built resuscitation table: a feasibility study. Arch Dis Child Fetal Neonatal Ed 2019;104:F396–402.
17 Katheria AC, Brown MK, Faksh A, et al. Delayed cord clamping in newborn born at term at risk for resuscitation: a feasibility randomized clinical trial. J Pediatr 2017;187:313–7.
18 Blank DA, Badureden S, Omar F, Kamlin C, et al. Baby-directed umbilical cord clamping: a feasibility study. Resuscitation 2018;131:1–7.
19 Lefebvre C, Raizada T, Weilinck N, et al. Feasibility and safety of intact cord resuscitation in newborn infants with congenital diaphragmatic hernia (CDH). Resuscitation 2017;120:20–5.
20 Calculator- TOTAL trial. Available: https://totaltrial.eu [Accessed 9 April 2019].
21 Riley JS, Antiel RM, Rintoul NE, et al. Reduced oxygen concentration for the resuscitation of infants with congenital diaphragmatic hernia. J Perinatol 2018;38:834–43.
22 O’Rourke-Potocki A, Ali K, Murthy V, et al. Resuscitation of infants with congenital diaphragmatic hernia. Arch Dis Child Fetal Neonatal Ed 2017;102:F320–F323.
23 Mank A, Carrasco Carrasco C, Thio M, et al. Tidal volumes at birth as predictor for adverse outcome in congenital diaphragmatic hernia. Arch Dis Child Fetal Neonatal Ed 2019. doi:10.1136/archdischild-2018-316504. [Epub ahead of print: 29 Jun 2019].
24 Hooper SB, Forgus A, Siew M, et al. Expired CO2 levels indicate degree of lung aeration at birth. PLoS One 2013;8:e70895.
25 Blank D, Rich W, Leone T, et al. Pedi-cap color change precedes a significant increase in heart rate during neonatal resuscitation. Resuscitation 2014;85:1568–72.
26 Foglia EE, Ades A, Sawyer T, et al. Neonatal intubation practice and outcomes: an international registry study. Pediatrics 2019;143:e20180902.
27 Hooper SB, Binder-Heschl C, Polglase GR, et al. The timing of umbilical cord clamping at birth: physiological considerations. Matern Health Neonatal Perinatol 2016;2.