A Randomized Controlled Trial of End-Tidal Carbon Dioxide Detection of Preterm Infants in the Delivery Room

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Objective To compare the ability of qualitative versus quantitative methods of end-tidal carbon dioxide ($EtCO_2$) detection to maintain normocarbia during face mask ventilation (FMV) of preterm infants (<32 weeks) in the delivery room.

Study design Preterm infants <32 weeks were randomly assigned to the use of a disposable PediCap $EtCO_2$ detector (Covidien, Dublin, Ireland) (qualitative) or a Microstream side stream capnography device (Covidien) (quantitative) for FMV in the delivery room, via a NeoPuff T-piece resuscitator (Fisher and Paykel, Auckland, New Zealand). The primary outcome was the presence of normocarbia, based on partial pressure of CO_2 ($PaCO_2$) readings obtained in the neonatal intensive care unit within an hour of birth. Normocarbia was defined as a $PaCO_2$ measure between 37.5 and 60 mm Hg (5-8 kPa).

Results Of the 59 infants included, 59% (35/59) were within the $PaCO_2$ target range within an hour of birth. There was no difference in the primary outcome; 64% (21/33) of infants in the quantitative group were within the $PaCO_2$ range compared with 54% (14/26) in the qualitative group ($P = .594$); and 93% of participants <28 weeks' gestation were within the $PaCO_2$ normocarbic range (90% [9/10] in quantitative group and 100% [5/5] in the qualitative group [$P = 1$]). There was no difference in the intubation rate, days of ventilation, or bronchopulmonary dysplasia rates between the 2 groups.

Conclusions Quantitative or qualitative $EtCO_2$ detection methods are both feasible for FMV in the delivery room. Although there was no difference in the incidence of normocarbia, the use of either form of $EtCO_2$ monitoring should be considered during newborn stabilization, especially in infants less than 28 weeks' gestation. *(J Pediatr 2017;182:74-8).*

Trial registration ISRCTN: ISRCTN10934870.

Excessive alterations in carbon dioxide (CO_2) may result in adverse outcomes for preterm infants. Hypocarbia may contribute to lung injury[1] and periventricular leukomalacia,[2,3] and hypercarbia may contribute to an increase in the risk of intraventricular hemorrhage (IVH).[4,5] Although CO_2 monitoring is an important component of routine preterm care in the neonatal intensive care unit (NICU) setting, its use during noninvasive ventilation in the delivery room is not well studied.[6-9] End-tidal CO_2 ($EtCO_2$) monitoring may provide early evidence of lung expansion and gas exchange and help guide successful respiratory support in the delivery room.[9,10]

Methods of $EtCO_2$ detection during manual positive pressure ventilation (PPV) include qualitative methods via disposable $EtCO_2$ detectors and quantitative methods via capnography and capnometry. The use of $EtCO_2$ detection reduces the time to confirmation of endotracheal tube placement and has been endorsed in newborn resuscitation guidelines.[11,12] The use of $EtCO_2$ detectors during face mask ventilation (FMV) helps determine airway patency and can aid resuscitation teams in recognizing airway obstruction and leak during PPV.[7,9,13,14] We previously demonstrated the feasibility of using quantitative methods of $EtCO_2$ detection during noninvasive ventilation of preterm infants in the delivery room.[15] In a recent mannequin study, quantitative capnography was superior to CO_2 detectors in improving efficacy of FMV and was also the preferred method by end users.[16]

The aim of this trial was to determine whether quantitative $EtCO_2$ monitoring during FMV in the delivery room reduced the incidence of hypocarbia and hypercarbia within the first hour of life compared with qualitative $EtCO_2$ monitoring in preterm infants <32 weeks.

BPD	Bronchopulmonary dysplasia
CO_2	Carbon dioxide
$EtCO_2$	End-tidal CO_2
FMV	Face mask ventilation
IVH	Intraventricular hemorrhage
NICU	Neonatal intensive care unit
PPV	Positive pressure ventilation

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Methods

This was a prospective randomized controlled trial conducted in the delivery room of the Cork University Maternity Hospital, Ireland, over a 15-month period from June 2014 to September 2015. Preterm infants <32 weeks' gestational age were eligible for inclusion. Exclusion criteria included oligohydramnios (amniotic fluid index <5) and any known congenital anomalies such as congenital diaphragmatic hernia, congenital airway anomalies, chromosomal disorder, or congenital heart disease. No change in overall stabilization training or practice occurred during the timeline of this trial. Patients were randomized to 1 of 2 approaches; 1 arm using a qualitative method of $EtCO_2$ detection (control arm) and the other using a quantitative method (intervention arm). The qualitative arm used a colorimetric $EtCO_2$ detecting device (PediCap $EtCO_2$ detector; Covidien, Dublin, Ireland) during respiratory support. This device has a dead space of 3 mL, was attached between the facemask and T-Piece resuscitator (NeoPuff; Fisher and Paykel, Auckland, New Zealand), and the detector changed from purple to yellow upon detection of CO_2 with each breath. When it returns to purple, the measured CO_2 is indicated as falling below approximately <0.5% (<7.5 mm Hg), according to the manufacturer's data. The intervention arm used a side stream capnography device (Microstream CO_2 filterline; Covidien, Dublin, Ireland) during respiratory support. This device has a dead space of less than 0.5 mL, was attached between the facemask and T-Piece resuscitator, and provided the user with an $EtCO_2$ trace (capnography) as well as $EtCO_2$ values (capnometry); both were displayed on a Phillips MP70 monitor.

$EtCO_2$ detection during FMV has been used regularly in our delivery room during the stabilization of preterm infants over the last 2 years. As a result, it was considered that removing the option of having any form of $EtCO_2$ monitoring in the delivery room would be unethical, and there was no equipoise among clinicians to allow this. Therefore, a randomization group without an $EtCO_2$ detecting method was not included. All medical staff was trained in a simulation laboratory on the provision of facemask ventilation with these devices. During absence of a color change (during qualitative monitoring) or absence of a waveform and a numeric readout (during quantitative monitoring), physicians were instructed to ensure mask seal and head position were correct to prevent obstructed breaths. During these occurrences, the medical team was instructed to make all relevant interventions in accordance with Neonatal Resuscitation Program guidelines. Infants received mask PPV with a size 00 round silicone face mask (Laerdal; Stavanger, Norway) connected to the trial device and NeoPuff resuscitator. The default settings on the NeoPuff resuscitator, prior to delivery of the infant, were set at a gas flow of 8 L/min, a peak inspiratory pressure of 20 cm H_2O, and a positive end expiratory pressure of 5 cm H_2O. The maximum attainable peak inspiratory pressure was limited to 30 cm H_2O, as was routine practice for all preterm deliveries at our unit. Once an infant was placed on the resuscitation table, stabilization commenced with the assigned $EtCO_2$ detection system. $EtCO_2$ monitoring was discontinued at the time of transfer from the delivery room to the neonatal unit.

The Clinical Research Ethics Committee of the Cork Teaching Hospitals approved this trial. The trial was registered in February 2015, after 13 of the planned 60 patients had been enrolled (ISRCTN: ISRCTN10934870); no interim analysis was performed prior to registry. Informed written consent was obtained from parents during the antenatal period. When additional consent was provided, the stabilization process was also video recorded and stored on a secure server. This was completed to retrospectively analyze delivery room performance by the resuscitation team and to identify instances of intervention completed during the stabilization process.

Randomization was stratified by age (<28 and ≥28 weeks' gestation) with a 1:1 allocation to either the qualitative or quantitative group. Randomization was performed using a computer based randomization program and allocation concealment was achieved by using opaque, sequentially numbered, sealed envelopes. These envelopes were stratified to infants <28 and ≥28 weeks' gestation. Upon confirmation that an infant was to be delivered, a randomization envelope was opened, group assignment determined, and a member of the research team transported the required equipment to the delivery room. The research team members were not part of the medical team responsible for the care of any participant.

The primary outcome was defined as the incidence of normocarbia determined from a blood gas analysis completed within an hour of birth, which is routinely performed for all preterm infants entering our NICU. Normocarbia was defined as a $PaCO_2$ between 37.5 and 60 mm Hg (5-8 kPa). Secondary outcomes included the rate of intubation, days of mechanical ventilation, days of continuous positive airway pressure, the duration of oxygen therapy, and the incidence of bronchopulmonary dysplasia (BPD).

Sample Size Calculation and Statistical Analyses

At the time of trial design, an analysis of a historical cohort of preterm (<32 weeks) infants recruited in our unit over a 4-month period from March 2013 to July 2013 described a combined incidence of hypercarbia and hypocarbia at approximately 60% with the use of a qualitative $EtCO_2$ detection device. An a priori sample size calculation indicated that 27 babies would be required in each group (total n = 54) to detect a reduction to 20% (60% in the qualitative group [control arm] vs 20% in the quantitative group [intervention arm] outside the range). This was calculated using Fisher exact test with 80% power, a 5% level of significance, and a 2-tailed test.

However, as twins were eligible to be included in the trial and observations from siblings may be correlated, this would have reduced statistical power.[17] To compensate for this, the sample size was increased to n = 30 per group (total n = 60). This was based on a design effect of 1.0825 (assuming 25% of babies enrolled would be twins and intraclass correlation coefficient equal to 0.33). For comparisons between 2 groups, the Mann-Whitney test was used for continuous variables and Fisher exact test was used for categorical variables. All statistical analyses were performed using SPSS 22.0 (IBM, Armonk,