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Transitional hemodynamics in preterm infants with a respiratory management strategy directed at avoidance of mechanical ventilation☆,☆☆,★

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ABSTRACT

Background: Early respiratory management of very low birth weight infants has changed over recent years to a practice of early use of CPAP with early selective surfactant administration, and decreased use of mechanical ventilation. One strategy is to use the combination of surfactant and prompt extubation to nasal continuous positive airway pressure (INtubate, SURfactant, Extubate, or INSURE). The aim of this study is to describe blood flow and ductal flow in a prospective cohort during the transitional period when this respiratory management strategy is used.

Methods: Inborn infants <29 week gestation underwent INSURE within 30 min of birth using 200 mg/kg Curosurf. Blood pressure and blood flow parameters (RVO, LVO, SVC flow, ductus arteriosus) were measured at 6, 24 and 72 h of age and information on morbidity was collected.

Results: Sixty-eight infants with a median (range) weight of 940 (450–1380) g were studied. 13 (19%) patients needed mechanical ventilation within 72 h of life (INSURE failure). Blood flows and blood pressure were within reported ranges. Eleven (16%) patients had a blood pressure <gestational age and 9 (13%) patients had low blood flow.

Conclusion: These data show a low prevalence of low blood pressure and low blood flow in the first 3 days after INSURE as compared to cohorts where mechanical ventilation was preferred during transition. We speculate that altered ventilation strategies have helped decrease the incidence of low blood flow and low blood pressure.

1. Introduction

Transitional hemodynamics in preterm infants has been extensively studied in the last two decades. Studies on blood pressure and blood flow have shown a distinct pattern of cardiovascular adaptation to extra uterine life in very low birth weight (VLBW) infants [1,2]. Many infants in the neonatal intensive care show a hypoperfusion reperfusion cycle in the first 24 h of life, with up to 30% showing low blood flow and/or low blood pressure during this cycle.

Most preterm infants in the cohort studies studying transitional blood flow received mechanical ventilation in the first days of life [3–7]. The early respiratory management of VLBW infants has changed over recent years to a practice of early use of nCPAP (nasal continuous positive airway pressure) with early selective surfactant administration and decreased use of mechanical ventilation. The combination of surfactant and prompt extubation to nCPAP, the INtubation-SURfactant-Extubation or INSURE method, has been described and subjected to randomized trials in VLBW infants [8–10]. Despite short term pulmonary benefits of this approach, little information is available about the hemodynamic effects of early respiratory management strategies where mechanical ventilation is avoided. A historical cohort study investigating the clinical impact of early management practice changes, including INSURE, showed a 19% reduction in vasopressor use in the first 24 h of life [11]. It is likely that decreased intrathoracic pressures with nCPAP compared to mechanical ventilation will alter pulmonary, systemic and ductal blood flows and might affect the incidence of low blood

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flow. The aim of this study is to describe central blood flow and ductal flow during the transitional period in a cohort of preterm infants with a respiratory management strategy directed at avoidance of mechanical ventilation.

2. Methods

2.1. General

This was a prospective observational cohort study from 2007 till 2009 in the neonatal intensive care unit, John Hunter Children's Hospital, Newcastle, Australia. All inborn infants less than 29 weeks of gestation were eligible, as at the time of this study our unit was practicing prophylactic surfactant administration for this gestational age group. Infants where mechanical ventilation was the intended mode of respiratory support from birth (e.g. lung hypoplasia) and infants with severe congenital abnormalities were excluded. The study was approved by the local ethics committee and written informed consent was obtained from the parents of eligible infants, often before birth.

2.2. Respiratory management

Standard delivery room resuscitation and management took place using a Neopuff device (Fisher and Paykel, New Zealand) at delivery with a PEEP of 5–8 cm H_2O. Intubation and surfactant administration was performed immediately after transport to the neonatal unit. Surfactant (Curosurf, Chiesi, Italy) 200 mg/kg was administered as a single bolus via a neonatal endotracheal tube. No premedication was used. Manual ventilation after surfactant instillation was administered for just a couple of breaths, if required for desaturation, until the saturation improved, followed by prompt extubation. Infants were placed on nCPAP with 6–8 cm H_2O generated by a bubble system using Hudson nasal prongs. The FiO_2 was adjusted to target oxygen saturations between 90 and 94%. If the FiO_2 increased above 0.4 after 6 h of life, a repeat INSURE procedure was performed. Criteria for the use of mechanical ventilation were frequent apnea, not responding to caffeine, persistent hypercarbia with acidosis ($pCO_2 > 70$ mm Hg and/or pH < 7.20) or $FiO_2 > 0.6$. INSURE failure was defined as the need for mechanical ventilation for any reason in the first 72 h of life.

2.3. Hemodynamic management

Total fluid administration was started at 60 to 80 ml/kg per day and advanced by 20 ml/kg/day. Blood pressure was recorded by an indwelling arterial line or a non-invasive oscillometric device and recorded from a Philips monitor (Philips, The Netherlands). For the purpose of this study, hypotension in the first 72 h of life was defined as mean blood pressure (MBP) less than the infant's gestational age in weeks. Treatment of hypotension was initiated if there were clinical signs of poor perfusion. Management consisted of a standardized protocol of 0.9% sodium chloride solution boluses, followed by dopamine and/or dobutamine treatment and, if needed, hydrocortisone treatment. The blood flow measurements in this study were not used to guide treatment. A ductus arteriosus was considered hemodynamically significant if its diameter was larger than 1.5 mm and there were significant clinical signs of pulmonary volume overload. No prophylactic or early targeted ductal treatment was offered.

2.4. Ultrasound measurements

Ultrasound measurements of right ventricular output (RVO), left ventricular output (LVO), superior vena cava flow (SVC flow) and evaluation of the ductus arteriosus (DA) were performed at 6 h of age, and as close as possible to 24 and 72 h of age. Doppler echocardiographic measurements were performed by 2 investigators (KW and AL) using an iE33 ultrasound system (Philips Medical, The Netherlands) with a 12 MHz vector array transducer. All Doppler measurements were performed according to previously published methodology [3,4]. Low blood flow was defined as a SVC flow less than 45 ml/kg/min or a RVO or LVO less than 150 ml/kg/min [3,7].

2.5. Statistics

General linear models with repeated measurements were performed for normally distributed outcomes to test the within subjects effects at the three measurement time points. A Friedman test was used for non-parametric outcomes. One-way analysis of variance was used to identify risk factors for low blood flow, low blood pressure or INSURE failure. The association between INSURE failure and low blood flow or low blood pressure was evaluated with linear regression analysis. p-Values smaller than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 12 (SPSS Chicago, IL).

3. Results

During the 26 month study period there were 116 inborn infants less then 29 week gestation admitted to the neonatal intensive care. Fourteen infants met the exclusion criteria and from 10 infants no consent was obtained. Twenty-four eligible infants were not included because the investigators were not available for at least 2 measurements, leaving 68 infants for analysis.

The infant characteristics are presented in Table 1. Ten infants died, 3 within the 72 h study period, with severe respiratory distress syndrome (1), pulmonary hemorrhage (3), severe intraventricular hemorrhage (1), periventricular leucomalacia (1) and late sepsis/necrotizing enterocolitis (4).

The transitional hemodynamics are presented in Table 2 and Fig. 1. An increase in mean blood pressure and blood flow was seen during the first days of life (RVO within subjects effect $F = 40.3$, $p < 0.001$, LVO $F = 33.4$, $p < 0.001$, SVC flow $F = 21.0$, $p < 0.001$, MBP $F = 32.6$, $p < 0.001$). Heart rate did not change ($F = 1.6$, $p = 0.213$).

The clinical hemodynamic outcomes are presented in Table 3. Eleven infants (16%) had a mean blood pressure lower than gestational age, all within 24 h of life. Nine infants (13%) showed low blood flow at the 6 hour measurement, with 1 infant showing a low RVO at 24 h while on mechanical ventilation for a pulmonary hemorrhage.

The clinical respiratory outcomes are presented in Table 4. Thirteen infants (19%) needed mechanical ventilation within 72 h after birth (INSURE failure). Eight needed mechanical ventilation in the first 6 h of life due to apnea or high oxygen need, with 3 infants still ventilated at 6 h. Six infants started mechanical ventilation between 6 and 72 h of life due to pulmonary or cerebral hemorrhage (4) or apnea (2).

Analysis of risk factors for low blood flow, low blood pressure and INSURE failure using gestational age, birth weight, mean airway pressure (or PEEP pressure), FiO_2, blood pressure and blood flow showed that an early higher respiratory support pressure or a low RVO or LVO was a risk factor for INSURE failure (one way ANOVA $F = 14.6$, $p < 0.001$ and $F = 10.6$, $p = 0.002$). Lower birth weight was a risk factor for low SVC flow and treated hypotension (one way ANOVA $F = 5.2$, $p = 0.025$ and $F =$

Table 1
Characteristics of the 68 included patients, presented as total number (%) or median (range) where appropriate. SGA, small for gestational age.

Gestational age (weeks)	26	(23–28)
Birth weight (g)	940	(450–1380)
Antenatal steroids		
Full course	58	(85%)
Any	67	(99%)
SGA (<10th percentile)	7	(10%)
Mortality	10	(15%)