Initial Respiratory Support with Cold, Dry Gas versus Heated Humidified Gas and Admission Temperature of Preterm Infants

Michael P. Meyer, FRACP, MD[1,2], David Hou, FRACP[1,2], Nazmul N. Ishrar, RN[1], Ingrid Dito, RN[3], and Arjan B. te Pas, PhD[3]

Objective To assess whether the addition of heated humidified gas (HHG) at delivery and until neonatal unit arrival improved admission temperatures of preterm infants.

Study design This multicenter, randomized controlled trial was performed in New Zealand and The Netherlands. Infants <32 weeks' gestation who required respiratory support after delivery were randomized to either cold, dry gas or HHG from birth. Standard measures to prevent hypothermia included heated delivery rooms, the use of radiant warmers, body wrap, and head covering. The primary outcome was axillary temperature in the normothermic (36.5-37.5°C) range on admission to a neonatal intensive care unit. Secondary outcomes were measures of respiratory support and neonatal morbidities. The effect of humidification was analyzed by the use of logistic regression.

Results Of 203 randomized infants, 100 received HHG (humidifier set to 37°C) and 103 received cold, dry gas. In the HHG group, 69 (69%) were normothermic compared with 57 (55%) in the cold, dry gas group (unadjusted OR 1.8, 95% CI 1.01-3.19). A greater number of infants <28 weeks were normothermic on admission in the HHG group (24/35; ie, 69%) compared with the cold, dry gas group (16/38; ie, 42%; $P = .03$). In addition, 2 (2%) infants in the HHG group had admission temperatures <35.5°C compared with 12 (12%) in the cold, dry gas group ($P = .007$). Respiratory and short-term outcomes were not different.

Conclusion Adding HHG during respiratory support in preterm infants from birth increased the incidence of normothermia at admission. *(J Pediatr 2015;166:245-50)*.

Low admission temperatures in preterm infants have been associated with increased rates of morbidity and mortality. In the SNAPPE II (Score for Neonatal Acute Physiology and SNAP Perinatal Extension) study,[1] a temperature <35.5°C was associated with an increase in mortality. Likewise, 61% of infants at 27 and 28 weeks' gestation in the United Kingdom had admission temperatures <36°C and an increased rate of death (OR 1.7, 95% CI 1.2-2.4).[2] Other large cohort studies have reported similar associations between hypothermia and mortality.[3,4]

Even with careful attention to the use of known preventive strategies, such as warming the delivery room and use of powerful radiant warmers and plastic wrap during stabilization, 25%-30% of preterm infants had admission hypothermia.[5,6]

Respiratory support with cold, dry gas at 6-10 L/min is commonly used at birth and during transport to the neonatal unit. Although the cooling effect of this gas flow has not been studied, an observational study showed that supplying heated humidified gas (HHG) during respiratory support from birth to admission reduced admission hypothermia.[7] Although not studied during the birth transition, exposure of the respiratory tract to cold, dry gas for short periods, decreased lung compliance, increased work of breathing in preterm infants, and released proinflammatory cytokines.[8,9] As little as 60 seconds' exposure to cold, dry gas damaged the mucociliary layer in experimental animals.[10] Our aim was to investigate the effects of HHG on admission temperature. Measures of respiratory support and common neonatal morbidities were secondary outcomes.

Methods

A nonblinded, randomized controlled trial was performed in 2 centers: Middlemore Hospital, Auckland, New Zealand (NZ), and Leiden University Medical Center, Leiden, The Netherlands (NL). Preterm infants <32 weeks' gestation that were deemed by the clinical team to require respiratory support at delivery were eligible

BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
DCC	Delayed cord clamping
HHG	Heated humidified gas
NL	The Netherlands
NZ	New Zealand

From the [1]KidzFirst Neonatal Unit, Middlemore Hospital; [2]Department of Pediatrics: Child and Youth Health, University of Auckland, Auckland, New Zealand; and [3]Division of Neonatology, Department of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands

Fisher & Paykel Healthcare (Auckland, New Zealand) provided partial funding for a research nurse and humidifier circuits for the study. A.teP. is supported by The Netherlands Organisation for Health Research and Development, part of the Innovational Research Incentives Scheme Veni-Vidi-Vici (91612027). The authors declare no conflicts of interest.

Registered with the ANZCTR (Australia New Zealand Clinical Trials Registry): 12609000694213.

http://dx.doi.org/10.1016/j.jpeds.2014.09.049

for the study. Infants were randomized to either unconditioned, cold, dry gas, or HHG during respiratory support at birth and during transport. Initial respiratory support was instituted with a T-piece resuscitator (Fisher & Paykel, Auckland, New Zealand), and this was used to provide continuous positive airway pressure (CPAP) or positive pressure ventilation. Infants receiving mechanical ventilation for transport were excluded. Other reasons for exclusion were maternal pyrexia (>38°C in labor) and major congenital abnormality. The study was conducted from March 2011 to June 2013.

Randomization was stratified by center (NZ and NL) and gestation (<28 weeks' and ≥28 weeks'). Random numbers were computer generated. Opaque, sealed sequentially numbered envelopes were used and were opened when delivery was expected within about 10 minutes or when a decision was taken to proceed to operative delivery.

Delivery room temperatures were set to 25-26°C. Radiant warmer surfaces were preheated. Occlusive body wrap was applied, and for this the infant was not dried. At one hospital, all infants were wrapped; at the other, infants <30 weeks' were wrapped, in accordance with local protocols. After wrapping (or drying if not wrapped), a hat was placed. Full heater output was initially provided from the radiant warmer; after placing a thermistor, servo control was used in NZ (abdominal set temperature 37°C), but servo was not used in the NL and the warmer remained at full output. Heating and humidification was achieved using a humidifier (MR225 or MR850) and a heated resuscitation circuit (900RD110) supplied by Fisher & Paykel Healthcare, New Zealand. Sterile water (20-50 mL) was added to the chamber and the device turned on approximately 5 minutes before delivery. The gas flow rate was set at 8 L/min; the gas was derived from either the hospital piped supply or gas bottles. The humidifier temperature was noted just before delivery and recorded in NZ and the circuit checked for leaks at both centers. Saturations and heart rate were monitored using pulse oximetry and oxygen concentrations were noted.

Stabilization during transition was performed according to local guidelines. Delayed cord clamping (DCC) (for 40 seconds) was performed in NZ. For this, the infant was wrapped and placed on the mother's bed at the level of the introitus after vaginal delivery. After operative delivery, the infant was wrapped and placed on the mother's thighs. No ventilatory assistance, and therefore no humidification, was provided during the DCC. In NL, DCC was not standard procedure for preterm deliveries.

The infant was transported with the wrap left in place. Transport to the neonatal unit was with either a radiant warmer (NZ)[6] or preheated incubator set at 35°C (NL).[7] The radiant warmer (and humidifier if appropriate) were powered by an uninterrupted power supply. The incubator (NL) did not provide power for the humidifier, but the neonatal intensive care unit is located adjacent to the delivery room (10 m), and the operating theater is on a different floor (approximate travel time 5 minutes).

Nursing staff measured the axillary temperature just as the infant was taken from the transport device. Temperature was measured with a digital electronic thermometer (Welch Allyn, Skaneateles Falls, New York, or Thermoval, Hartmann, Heidenheim, Germany). The primary outcome measure was an axillary admission temperature within the desired range of 36.5 to 37.5°C (defined as normothermia). Other outcome measures included the receipt of respiratory support during transition and in the neonatal unit. In addition, in NZ, fraction of inspired oxygen was recorded at 30 minutes and 60 minutes, as was the total number of minutes of oxygen exposure in the first hour. Measures of neonatal morbidity, such as bronchopulmonary dysplasia (BPD), defined as respiratory support or oxygen requirement at 36 weeks' gestation, grade 3 or 4 intraventricular hemorrhage, necrotizing enterocolitis, and retinopathy of prematurity treated with laser therapy were noted.

Previous studies indicated the expected incidence of admission temperature outside the normothermic range was 62% at the 2 sites combined.[6,7] To demonstrate a 30% reduction in the incidence, ie, from 62 to 41%, a sample size of 200 (100 from each site) would be required (80% power at a significance level of .05).

Approval for the study was from local ethics boards. At both centers, antenatal consent was requested before birth if the mother was not in established labor and there was sufficient time to make an informed choice. In situations in which a more rapid delivery was anticipated, a waiver of consent was obtained, and parents approached for retrospective consent for data use as soon as possible after delivery.

Statistical Analyses

All analyses were performed on an intention-to-treat principle. For proportions, the χ^2 test was used. Nonparametric continuous variables were analyzed with the Mann-Whitney *U* test. Binary logistic regression was used to explore the relationship between admission temperature in the desired range and humidity. *P* values <.05 were considered to indicate statistical significance. Analysis was performed with SPSS for Windows (SPSS Inc, version 13.0, Chicago, Illinois).

Results

Analysis was performed on 103 infants who received cold, dry gas and 100 who received HHG during respiratory support; 105 infants were entered in NZ and 98 in NL (**Figure 1**). There were no differences in baseline characteristics (**Table I**). The median humidifier temperature as recorded in NZ was 36.7°C (IQR 36.2-37.0°C) before birth, and there were no instances in which the humidifier ran dry, nor was there loss of gas flow/pressure through the circuit. Two infants who were randomized did not receive the intervention because equipment was not available, and in one the radiant warmer power supply failed. Overall, 82% of the HHG group and 76% of the cold, dry gas group had 40 seconds DCC, and 3 infants had cord milking. DCC did not significantly alter admission temperature in either univariate or multivariate logistic regression (results not shown).

Sixty-nine (69%) infants in the HHG group had normothermia compared with 57 (55%) in the cold, dry gas group