A Randomized Trial of Conditioned or Unconditioned Gases for Stabilizing Preterm Infants at Birth

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Objective To determine whether the use of heated-humidified gases for respiratory support during the stabilization of infants <30 weeks of gestational age (GA) in the delivery room reduces rates of hypothermia on admission to the neonatal intensive care unit (NICU).

Study design A multicenter, unblinded, randomized trial was conducted in Melbourne, Australia, between February 2013 and June 2015. Infants <30 weeks of GA were randomly assigned to receive either heated-humidified gases or unconditioned gases during stabilization in the delivery room and during transport to NICU. Infants born to mothers with pyrexia >38°C were excluded. Primary outcome was rate of hypothermia on NICU admission (rectal temperature <36.5°C).

Results A total of 273 infants were enrolled. Fewer infants in the heated-humidified group were hypothermic on admission to NICU (36/132 [27%]) compared with controls (61/141 [43%], $P < .01$). There was no difference in rates of hyperthermia (>37.5°C); 20% (27/132) in the heated-humidified group compared with 16% (22/141) in the controls ($P = .30$). There were no differences in mortality or respiratory outcomes.

Conclusions The use of heated-humidified gases in the delivery room significantly reduces hypothermia on admission to NICU in preterm infants, without increased risk of hyperthermia. *(J Pediatr 2017;■■:■■-■■).*

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See editorial, p •••

Newborn infants are at risk of hypothermia because of heat loss through evaporation, conduction, convection, and radiation. Preterm infants are at greater risk because of their large surface area to body mass ratio, thin skin, and lack of brown adipose tissue.[1]

Admission hypothermia is an independent risk factor for mortality in preterm infants and is associated with morbidities such as coagulopathy, infection, acidosis, respiratory distress syndrome, and delayed transition from fetal circulation.[2,3] For each 1 degree Celsius (1°C) decrease in admission temperature below the normal range (36.5°C -37.5°C), there is an associated 28% increase of mortality in infants <1500 g.[4] However, hypothermia rates remain high in this population; 40%-50% of extremely preterm and very low birth weight infants have a core temperature below <36.0°C at admission to the neonatal intensive care unit (NICU).[4-7]

Interventions in the delivery room have previously been shown to reduce the incidence of hypothermia in preterm infants, including polyethylene occlusive wraps,[8] increasing ambient temperature,[9,10] and exothermic mattresses.[11] Current international guidelines on the care of newborn preterm infants recommend thermal management using radiant heaters, heated mattresses, increased ambient temperature, and polyethylene bags or wraps,[12,13] to target a core temperature >36.5°C.[14]

Standard delivery room practice includes providing respiratory support using unconditioned gases. The use of heated-humidified ventilator gases are not currently recommended in international resuscitation guidelines.[12,13] Unconditioned gases are "cold and dry"; typically room temperature (23°C), with very low

GA	Gestational age
IVH	Intraventricular hemorrhage
MCH	Monash Children's Hospital
NICU	Neonatal intensive care unit
RWH	The Royal Women's Hospital

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relative humidity 2%-5%,[15] ambient relative humidity is usually 30%-40%. This differs from standard practice in the NICU where medical gases are heated and humidified to international standards, 37°C and 100% relative humidity,[16] during the provision of respiratory support.

We hypothesized that the use of heated-humidified gases for respiratory support during stabilization of preterm infants <30 weeks of gestation, in addition to standard measures, would reduce the rate of hypothermia at NICU admission.

Methods

This randomized controlled trial was conducted at 2 centers in Melbourne, Australia, The Royal Women's Hospital (RWH) and Monash Children's Hospital (MCH), between February 1, 2013, and June 25, 2015. Infants were eligible if they were born before 30 weeks of gestational age (GA). Infants were excluded if there was maternal pyrexia >38°C within 4 hours of delivery, if delivery occurred in an area of the hospital where gas conditioning equipment was not available (eg, emergency department), if there was a known major congenital anomaly, or if infants were to receive palliative care in the delivery room. Infants were recruited at all times of day and night. The study was approved by the Human and Ethics Research Committee at both sites and prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12613000093785).

Both prospective antenatal and retrospective postnatal consent procedures were allowed; eligible infants could be randomized and retrospective consent sought from the parents as soon as possible afterward, to use the data already collected, and to continue collecting secondary outcome data until hospital discharge.

A computer-generated block randomization sequence with variable block sizes was used. Multiple births were randomized as individuals. Stratification was by gestation (23-25^{+6} and 26-29^{+6} weeks of gestation), location of birth (operating theater or birth suite), and by recruiting center. A sequentially numbered, sealed, opaque envelope containing the allocation was opened just before the birth of a potentially eligible infant. The allocated mode of gas delivery, either heated-humidified or unconditioned, was applied both during stabilization in the delivery room, and during transfer to NICU. Because of the different circuits used to deliver the gases, blinding of the intervention was not possible.

Infants randomized to the control group were supported using an RD110 Neopuff circuit and T-piece resuscitator (Fisher and Paykel Healthcare, Auckland, New Zealand). Infants randomized to receive heated-humidified gases, were supported using a humidification unit consisting of an MR850 humidifier unit, MR225 manual refillable humidification chamber, and an RD110 Neopuff circuit and T-piece resuscitator plus temperature probes (Fisher and Paykel Healthcare). The chamber and circuit were single patient use. Humidification units were connected to power, set to the "invasive" mode (this targets 37°C at the point of delivery), filled with 50 mL of sterile water using single use ampoules just before the birth of the infant, and switched on for immediate use. No warming up period was required.[17] A gas flow rate of 8-10 L/minute was used in both groups. All staff involved in the study were trained to set up and use the humidification units before managing infants participating in the study. Care was provided under the direction of the clinical team. For both arms of the trial, standard resuscitation equipment and thermal control procedures were used according to national resuscitation guidelines[18]; thermal control was maintained using radiant warmers set to 100% for all infants, plus polyethylene bags and woolen hats applied to infants <28 weeks of gestation, in accordance with the Australian Resuscitation Guidelines.[18] A heated stabilization room was available for surgical births at the lead study site; other birthing rooms were heated to maternal comfort. Exothermic mattresses were not used. The allocated treatment was continued during transport to NICU if the infant required on going respiratory support. At the RWH, infants were transported using a transport incubator (Airshield Isolette TI500; Draeger, Lubeck, Germany) with a fixed pre-set temperature. Respiratory support, if required, was provided by the transport ventilator (F180-Mobil; Fritz Stephan GmbH, Gackenbach, Germany), with or without heated-humidification activated. At MCH, infants were transported on the resuscitation trolley (Resuscitaire warmer; Draeger, Lubeck, Germany). Respiratory support was provided with the inbuilt T-piece resuscitator if required during transfer to NICU. Heated-humidification was maintained during transport using the humidification unit powered by a portable power supply. Servo control was not used during stabilization in delivery room or transport to NICU.

The primary outcome was the rate of hypothermia at NICU admission, defined as rectal temperature <36.5°C. Rectal temperature was measured on arrival in NICU before moving the infant from the transport device (incubator or resuscitation trolley) to the NICU cot, using a calibrated Nexcare (3M; Saint Paul, MN) (RWH) or Livingstone (Roseberry, New South Wales, Australia) digital thermometer (MCH). Prespecified secondary outcomes included admission temperature (°C) for each infant, early respiratory outcomes, days of respiratory support, common neonatal morbidities, and length of hospital stay. Admission temperature was further classified as normothermia (36.5°C-37.5°C), mild hypothermia (36.0°C-36.4°C), moderate hypothermia (32.1°C-35.9°C) and severe hypothermia (<32.0°C) in keeping with the World Health Organization's definitions.[19]

Statistical Analyses

Data collected from 2009 to 2011 at the lead center (RWH) indicated that 50% of infants <30 weeks of gestation were hypothermic (<36.5°C) at NICU admission. We hypothesized that the use of the intervention would reduce this by 20%. This reduction was based on a conservative interpretation of a previous observational study that reported a >30% reduction in hypothermia after the introduction of heated-humidified medical gases in the delivery room.[20] To detect

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