# 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;■■:■■-■■).*

**Clinical Trial Registration** Australian and New Zealand Clinical Trials Register (www.anzctr.org.au) ACTRN12613000093785.

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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

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|---|---|
| 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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an absolute reduction from 50% to 30%, with 90% power and a 2-tailed alpha-error of 0.05, a sample size of 268 infants was required.

Data were checked and entered into a web-based electronic secure database (REDCap; Vanderbilt University, Nashville, Tennessee). Data were analyzed using the statistical software package STATA v 14 (Statacorp, College Station, Texas). Analysis of the primary and secondary outcomes was on an intention-to-treat basis. The primary outcome and dichotomous secondary outcomes were expressed as proportions and compared using Pearson $\chi^2$ test. Continuous outcome variables were presented as means (SD) if normally distributed, and as medians (IQR) if data were skewed. Student *t* test was used for parametric and Mann-Whitney *U* test for nonparametric comparisons. *P* values were 2 sided and considered statistically significant if <.05.

An independent data safety monitoring committee reviewed outcome data after 60 infants and 130 infants were recruited, and advised continued recruitment.

## Results

Of those eligible (n = 511 infants), 27% were not approached because the research team was not notified or was unavailable. This occurred more frequently at times of reduced staffing (nights and weekends). Seven percent of eligible infants delivered before randomization could occur, a reflection of the trial being carried out under emergency circumstances. In total, 320 infants were randomized; 47 infants were excluded as they either did not receive any respiratory support in the delivery room or because their parents did not provide consent (**Figure**). The remaining 273 infants were followed to hospital discharge

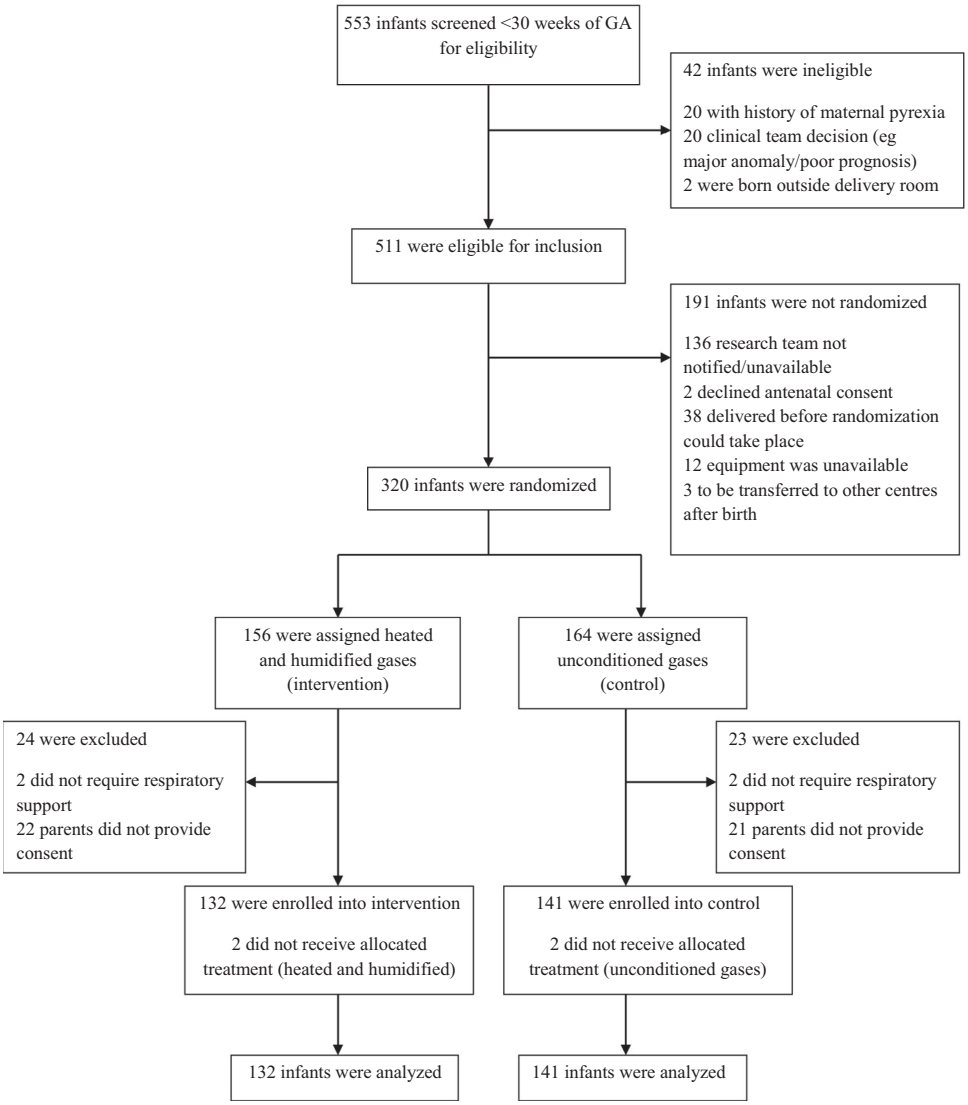


**Figure.** CONSORT flow diagram.



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**Table I. Demographics**

| | Heated-humidified (n = 132) | Unconditioned (n = 141) |
|---|---|---|
| GA (wk)* | 27 (1.8) | 27 (1.8) |
| Percentage of infants <26 wk of GA | 26 | 25 |
| Birth weight (g)* | 973 (288) | 930 (272) |
| White | 76 | 80 |
| Male sex | 48 | 42 |
| Birth by cesarean delivery | 69 | 74 |
| Multiple birth | 40 | 37 |
| Antenatal corticosteroids (any) | 96 | 99 |
| PPROM | 19 | 16 |
| Obstetric diagnosis of Chorioamnionitis | 17 | 13 |
| Apgar score at 1 min† | 5 (3-6) | 5 (3-7) |
| Apgar score at 5 min† | 8 (7-9) | 8 (7-9) |
| Intubation in delivery room | 36 | 37 |
| Min after birth infant arrived to NICU* | 27 (8.2) | 25 (9.0) |

*PPROM*, premature prolonged rupture of membranes >24 hours.
Data presented are percentages unless otherwise stated. No significant differences were observed between groups.
*Mean (SD).
†Median (IQR).

or death (132 in the heated-humidified group and 141 in the control group) and were included in the analysis. Four infants did not receive the allocated treatment but were analyzed within their assigned group. Two infants did not receive the intervention as there was a delay in setting up equipment, and 2 infants in the control group were given heated-humidified gases in error. Infants were well matched for baseline demographic characteristics, including duration of delivery room stabilization (**Table I**). Ambient delivery room temperature was not different between groups (median temperature 24.2°C in both groups, $P = .76$).

There was a significantly lower rate of hypothermia on admission in the heated-humidified group compared with the control group (27% vs 43% respectively, $P < .01$; **Table II**). Overall, 16 infants in the heated-humidified group and 27 infants in the control group had moderate hypothermia; admission temperature <36.0°C ($P = .11$). Subgroup analysis by GA showed a statistically significant difference in hypothermia rates in the more mature strata (≥26 weeks of GA; n = 204), 27% vs 45%, $P < .01$ (**Table II**) and no significant difference in infants <26 weeks (n = 69) (29% vs 37% unconditioned, $P = .50$).

The mean admission temperature in both groups was within the normothermic range (36.5°C-37.5°C). However, the mean admission temperature was higher in the heated-humidified group, 36.9°C (0.8) compared with control 36.6°C (0.8), $P = .02$ (**Table II**). There was no difference in the overall incidence of hyperthermia (>37.5°C) between groups (20% in the heated-humidified group vs 16% in the control group, $P = .30$). Twenty-nine percent of infants <26 weeks of GA in the heated-humidified group were hyperthermic compared with 11% in the control group, although this did not reach statistical significance ($P = .06$, **Table II**). Ten infants in the heated-humidified group and 7 infants in the control group had an admission temperature >38.0°C ($P = .37$).

**Table II. Primary outcome**

| All infants | Heated-humidified (n = 132) | Unconditioned (n = 141) | *P* value |
|---|---|---|---|
| All hypothermia (<36.5°C) | 36 (27) | 61 (43) | <.01 |
| Mild hypothermia (36.0°C -36.4°C) | 20 (15) | 34 (24) | .03 |
| Moderate hypothermia (32.0°C -35.9°C) | 16 (12) | 27 (19) | .11 |
| Severe hypothermia (<32.0°C) | 0 (0) | 0 (0) | |
| Normothermia (36.5°C -37.5°C) | 69 (52) | 58 (41) | .07 |
| Hyperthermia (>37.5°C) | 27 (20) | 22 (16) | .30 |
| Hyperthermia (>38.0°C) | 10 (8) | 7 (5) | .37 |
| Admission temperature (°C)* | 36.9 (0.8) | 36.6 (0.8) | .02 |
| **Primary outcome by GA subgroup** | | | |
| **<26 wk of GA** | **Heated-humidified (n = 34)** | **Unconditioned (n = 35)** | ***P* value** |
| All hypothermia (<36.5°C) | 10 (29) | 13 (37) | .50 |
| Mild hypothermia (36.0°C -36.4°C) | 2 (6) | 6 (17) | .12 |
| Moderate hypothermia (32.0°C -35.9°C) | 4 (11) | 11 (31) | .05 |
| Severe hypothermia (<32.0°C) | 0 (0) | 0 (0) | |
| Normothermia (36.5°C -37.5°C) | 14 (41) | 18 (51) | .39 |
| Hyperthermia (>37.5°C) | 10 (29) | 4 (11) | .06 |
| Hyperthermia (>38.0°C) | 6 (18) | 2 (6) | .12 |
| Admission temperature (°C)* | 36.9 (0.9) | 36.5 (0.9) | 0.06 |
| **≥26 wk of GA** | **Heated-humidified (n = 98)** | **Unconditioned (n = 106)** | ***P* value** |
| Hypothermia (<36.5°C) | 26 (27) | 48 (45) | <.01 |
| Mild hypothermia (36.0°C -36.4°C) | 14 (14) | 32 (30) | <.01 |
| Moderate hypothermia (32.0°C -35.9°C) | 12 (12) | 16 (15) | .6 |
| Severe hypothermia (<32.0°C) | 0 (0) | 0 (0) | |
| Normothermia (36.5°C -37.5°C) | 55 (56) | 40 (38) | <.01 |
| Hyperthermia (>37.5°C) | 17 (17) | 18 (17) | .95 |
| Hyperthermia (>38.0°C) | 5 (5) | 4 (4) | .64 |
| Admission temperature (°C)* | 36.8 (0.8) | 36.6 (0.8) | .10 |

Data presented are counts (percentages) unless otherwise stated.
*Mean (SD).

Respiratory outcomes and other major neonatal morbidities were comparable between the 2 groups (**Table III**), including within GA subgroups. There were no differences in any secondary outcomes, with the exception of a lower incidence of severe (grade 3 or 4) intraventricular hemorrhage (IVH) in the heated-humidified group.

## Discussion

Our study found a significant reduction in the incidence of admission hypothermia in infants <30 weeks of GA when



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**Table III. Respiratory outcomes and associated morbidities**

| | Heated-humidified (n = 132) | Control (n = 141) | *P* value |
|---|---|---|---|
| Surfactant ≥1 dose | 75 (57) | 85 (60) | .56 |
| Maximum $FiO_2$ in first 24 h* | 36 (26-52) | 40 (30-50) | .47 |
| Inotropes within first 24 h | 18 (14) | 23 (16) | .54 |
| Pneumothorax | 7 (5) | 10 (7) | .54 |
| Culture positive sepsis† | 36 (27) | 40 (28) | .84 |
| PDA medical treatment | 39 (30) | 55 (39) | .10 |
| IVH ≥grade 3 | 2 (2) | 10 (7) | .02 |
| PVL | 5 (4) | 7 (5) | .64 |
| Death before discharge | 11 (8) | 11 (8) | .87 |
| BPD | 52 (39) | 64 (45) | .32 |
| BPD or death before discharge | 59 (45) | 72 (51) | .29 |
| Days of respiratory support* | 39 (10-65) | 43 (19-72) | .08 |
| Length of hospital stay (d)* | 79 (63-103) | 82 (63-106) | .46 |

*BPD*, bronchopulmonary dysplasia defined as respiratory support or oxygen requirement at 36 weeks corrected GA; *PDA*, patent ductus arteriosus; *PVL*, periventricular leukomalacia.
Data presented are counts (percentages) unless otherwise stated.
*Median (IQR).
†Three infants had episode of fungal and bacterial sepsis (2 in heated-humidified group, 1 in control group).

heated-humidified medical gases were used during stabilization after birth. Our findings are comparable with those of the only existing randomized trial of delivery room humidification. Meyer et al studied 203 preterm infants of mean GA 29 weeks and reported an increase in normothermia in the intervention group.[21]

Measures to prevent hypothermia may increase the risk of hyperthermia. McCarthy et al compared the combination of an exothermic mattress plus a polyethylene bag with the use of polyethylene bags alone, and noted an increased rate of hyperthermia in infants managed with both.[22] In a large randomized controlled trial comparing a plastic wrap with no wrap, Reilly et al[8] found a hyperthermia rate of 4.5% with the majority (88%) in the intervention group. In contrast, we found no difference in the overall rate of hyperthermia, although there was a shift (statistically nonsignificant) to higher rates of hyperthermia in the lower GA subgroup. Our overall result is consistent with the findings of Meyer et al, and an earlier observational study of 112 infants <32 weeks of GA assessed before and after the introduction of heated-humidified gases to the delivery room.[20,21] Reassuringly, the majority of hyperthermic infants in our study had mild hyperthermia (37.5°C-38°C) (**Table II**).

The incidence of hyperthermia in our study was higher than expected, including in the control group. A possible explanation may be a heightened awareness of thermoregulatory practices in the delivery room by clinical staff during the study period, and an earlier, consistent approach to measuring NICU admission temperature.

Our results showed a trend toward an increased incidence of hyperthermia in the heated-humidified group in the lower GA infants. These infants are at highest risk of heat loss, with recommended temperature management strategies already in place. During this study, the effects of the interventions were neither monitored nor servo-controlled during stabilization in the delivery room or during transfer to the NICU. This trend toward higher rates of hyperthermia in the smallest infants suggests a need for caution when introducing additional thermal control measures to prevent hypothermia in the delivery room.[22] Servo-control was not standard practice in the recruiting centers and was not introduced during the study, but use in the delivery room and during transport should be explored as a potential method of maintaining normothermia in these infants.

The use of unconditioned ventilator gases has been shown to have a detrimental effect on mucociliary clearance, respiratory function, mucous viscosity, and ciliary function.[23,24] Injury is proportional to the duration of ventilation with unconditioned gases.[23] Animal studies have shown that, as early as after 1 hour of ventilation with unconditioned gases, structural and functional damage of the airway is evident[25]; with 3 or more hours exposure further injury is seen, with inflammation, necrosis, and blistering of the trachea.[26,27] The use of unconditioned gases in the delivery room may adversely influence respiratory outcomes in very preterm infants. However, we did not detect any significant differences in respiratory outcomes in this study. This may be because this study was underpowered to detect such differences, or because the exposure time to unconditioned gases in our study was relatively short (median 26 minutes), and the absolute difference in admission temperature between groups was small (0.3°C). It may also be because the majority of infants in our study were not intubated in the delivery room and received respiratory support with continuous positive airway pressure applied via a face mask (64% in the heated-humidified group vs 63% in the control group; $P = .93$). Previous animal and laboratory work investigating unconditioned ventilation has mostly used endotracheal ventilation and with prolonged exposure to unconditioned gases.[26-28] The use of an endotracheal tube means that the upper airways, the natural conditioning pathways, are completely bypassed. Therefore, the adverse effects seen in the airways of intubated animals receiving unconditioned gases may be more severe than those seen when noninvasive respiratory support is used.

Our study was not powered to find significant differences in mortality, respiratory outcomes, or neonatal morbidities. We did, however, observe an apparent reduction in severe IVH with the use of conditioned gases. In other studies, the association of admission hypothermia and IVH is inconsistent[4,29,30] and, although this result is statistically significant, its clinical importance is unclear and should not be over interpreted.

The main limitations of our study were that researchers and caregivers were not blinded to the treatment allocation and that the study was underpowered to show differences in the GA subgroups, particularly for the most immature infants, at highest risk of hypothermia. A further weakness in our study was the number of postrandomization exclusions. However, these were similar in both arms of the trial (15% in the intervention group and 14% in the control arm), which suggests that these exclusions did not introduce bias. Studies of emergency medical interventions, such as neonatal resuscitation, are difficult if prior consent is required. The use of deferred consent improves recruitment rate and makes results more generalizable. Sixty-five



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percent of postrandomization exclusions were due to consent being declined, however, none of the parents who were approached expressed anger that their child had already been randomized into the study. Parental opinion of the use of deferred consent in neonatal studies warrants further evaluation.

The application of the intervention was straightforward. The equipment used in the heated-humidified group was similar to the standard equipment used with the unconditioned circuit and did not interfere with the operator's ability to administer effective ventilation. No warm-up time for the humidifier was stipulated; previous data demonstrated that this humidification system delivers gas at 25°C and >70% relative humidity within 1 minute, and reaches international standards (>32°C and >95% relative humidity) within 3 minutes.[17] During the period of our study, there was 1 recorded incidence of failure of circuit pressure in the heated-humidified group because of gas leak via a loose temperature probe. In addition, there were 2 incidents where the humidification system overheated, also because of loose temperature probes. All 3 incidents occurred prior to patient use, appropriately triggered the system to alarm and were quickly rectified. However, these incidents highlight the need to balance the potential benefits of an additional piece of equipment in the delivery room against any potential risks before recommending it for general use.

A further limitation to consider is that although polyethylene bags, woolen hats and radiant warmers were used as standard thermoregulatory measures in this study, neither center was able to consistently achieve the recommended ambient temperature.[14] Although the use of the intervention in this trial demonstrated a reduction in hypothermia at NICU admission, we cannot exclude the possibility that the use of additional low-cost interventions that are easier to apply, such as increasing the ambient temperature, or using exothermic mattresses, may have shown the same effect.

When deciding whether to recommend heated-humidified gases during stabilization, the duration of exposure to otherwise unconditioned gases, the lack of difference in neonatal morbidities, and the small absolute difference in admission temperature should be considered. Individual units should determine the incidence and severity of hypothermia in their local population and the time spent in the delivery room when considering the potential benefits and risks of introducing this intervention in their center. There are potential cost implications in the implementation of this intervention as the single-use humidification circuit and chamber costs approximately US$50 more than the standard circuit and T-piece used in this study. Units may wish to consider other interventions that have previously been shown to be effective at maintaining normothermia, such as increasing ambient temperature and the use of exothermic mattresses,[13] in combination with radiant warmers and polyethylene bags, as these may be more readily available and cost effective. Adding additional interventions to minimize heat loss to those already in place in the delivery room could potentially result in an increased incidence of hyperthermia.[22] Therefore, admission temperatures should be carefully monitored following introduction of any new practice.

This randomized controlled trial found that the use of heated-humidified gases during stabilization significantly reduced the rate of hypothermia on admission to NICU in preterm infants, without increasing the overall risk of hyperthermia. The trade-offs between the benefits and costs of heated-humidified gases needs to be assessed within local settings. ■

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