Admission Hypothermia in Very Preterm Infants and Neonatal Mortality and Morbidity

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Objective To investigate the association between body temperature at admission to neonatal intensive care and in-hospital mortality in very preterm infants, stratified by postnatal age of death. Moreover, we assessed the association between admission temperature and neonatal morbidity.

Study design In this cohort study from 19 regions in 11 European countries, we measured body temperature at admission for infants admitted for neonatal care after very preterm birth (<32 weeks of gestation; n = 5697) who were followed to discharge or death. Associations between body temperature at admission and in-hospital mortality and neonatal morbidity were analyzed by the use of mixed effects generalized linear models. The final model adjusted for pregnancy complications, singleton or multiple pregnancy, antenatal corticosteroids, mode of delivery, gestational age, infant size and sex, and Apgar score <7 at 5 minutes.

Results A total of 53.4% of the cohort had a body temperature at admission less than 36.5°C, and 12.9% below 35.5°C. In the adjusted model, an admission temperature <35.5°C was associated with increased mortality at postnatal ages 1-6 days, (risk ratio 2.41; 95% CI 1.45-4.00), and 7-28 days (risk ratio 1.79; 1.15-2.78) but not after 28 days of age. We found no associations between admission temperature and neonatal morbidity.

Conclusion Admission hypothermia after very preterm birth is a significant problem in Europe, associated with an increased risk of early and late neonatal death. *(J Pediatr 2016;175:61-7)*.

In newborn infants, the body temperature decreases on average 0.5°C during the first 5 minutes after birth.[1,2] In very preterm infants (<32 weeks of gestation), the immediate drop in body temperature may be more pronounced, mainly as the result of a larger surface area-to-body mass ratio and poor thermoregulation.[3,4] Wrapping the infant in a plastic bag, covering the head with a cap, as well as using radiant heaters and exothermic mattresses or skin-to-skin care may prevent rapid heat loss after delivery and preserve body temperature.[3,5,6] Placing extremely preterm infants (<28 weeks of gestation) in plastic bags or wrapping them in plastics immediately after birth, without drying, is effective to prevent hypothermia. Compared with infants who did not receive this intervention, plastic bag or wrapping increased admission temperature by on average 0.6°C-0.7°C.[5,7,8] Lately, the importance of combining a bundle of temperature preserving strategies has been emphasized.[9-11]

Despite this knowledge, recent studies indicate suboptimal compliance with current recommendations. A significant proportion of very preterm infants in high-resource countries fail to maintain normothermia after delivery. In addition, low body temperature at admission to the neonatal intensive care unit has been associated with mortality.[12-15]

We examined the incidence of hypothermia in a large population-based European cohort of very preterm infants and investigated the association between body temperature at admission to neonatal intensive care and in-hospital mortality in very preterm infants, stratified by postnatal age of death. We hypothesized that hypothermia is not only associated with immediate adverse neonatal outcomes but with increased mortality throughout the neonatal hospitalization. We also assessed the association between admission temperature and neonatal morbidity.

BPD	Bronchopulmonary dysplasia
EPICE	Effective Perinatal Intensive Care in Europe
HELLP	Hemolysis elevated liver enzymes low platelet count
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
PPROM	Preterm premature rupture of membranes
RR	Risk ratio

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Methods

Data for this population-based cohort study of very preterm infants were from the project, Effective Perinatal Intensive Care in Europe (EPICE). EPICE assessed the use of evidence-based practice in the care of the very preterm infant and its association with outcomes. The EPICE cohort was a regionally defined study of all very preterm births, stillbirths, and live births from $22^{0/7}$ to $31^{6/7}$ weeks of gestation in 19 regions in 11 European countries with more than 850 000 annual births: Belgium (Flanders); Denmark (Eastern Region); Estonia (entire country); France (Burgundy, Ile-de-France, and the Northern region); Germany (Hesse and Saarland); Italy (Emilia-Romagna, Lazio, and Marche); the Netherlands (Central and Eastern region), Poland (Wielkopolska); Portugal (Lisbon and Northern region); Sweden (greater Stockholm), and the United Kingdom (East Midlands, Northern, and Yorkshire & Humber regions). The data were collected prospectively over 12 consecutive months in 2011-2012, except in France, where data were collected for 6 months. For each study, region ethical approval was obtained from regional or hospital ethics committees, as required by national legislation.

All live born infants born in-hospital between $22^{0/7}$ and $31^{6/7}$ weeks of gestation and admitted to neonatal care were eligible for inclusion (n = 7610). We excluded infants postnatally transported to another hospital (n = 868), infants who had an admission time later than 2 hours after birth (n = 156), infants with severe congenital malformations (n = 93), infants with missing data on mortality (n = 2), and infants missing admission temperature (n = 794). After exclusions, 5697 infants were included in the primary analyses.

Investigators abstracted data from obstetric and neonatal medical records using a structured data collection instrument, tested and revised in all participating regions. Infants were followed from birth to final discharge or death. All investigators in the regions double-checked numbers of inclusions for stillbirths and livebirths with delivery or neonatal unit registers, registry offices, or equivalent data sources. Gestational age was determined by the obstetrical team caring for the pregnant woman. If several estimates were found, priority was assessed as follows: in vitro fertilization, first-trimester ultrasound scan, second- or third-trimester ultrasound scan, last menstrual period, bimanual examination (first trimester), or fundal height measurement.

Exposure Variable

The exposure, infant body temperature, was measured at admission to neonatal care either rectally or axillary according to the units' local routines. To constrict measurement time, we excluded infants with an admission time 2 hours or more after birth. The admission temperature was used in the analyses as both a continuous variable and categorized as: <35°C, 35.0°C-35.4°C, 35.5°C-35.9°C, 36.0°C-36.4°C, 36.5°C-37.5°C, 37.6°C-42.0°C, with normothermia defined as the reference group, 36.5°C-37.5°C.[16]

Outcomes

The primary outcome was in-hospital mortality; overall and stratified by time of death: <24 hours, 1-6 days, 7-28, and 28 days until discharge. We also investigated the following major neonatal morbidities as secondary outcomes: intraventricular hemorrhage (IVH) grade III or IV,[17] severe necrotizing enterocolitis (NEC), defined as peritoneal drainage or surgery for NEC, and bronchopulmonary dysplasia (BPD), defined as receiving supplemental oxygen at 36 weeks' postmenstrual age.

Covariates

Covariates were associated potentially with the exposure, the outcome, or both. Obstetric covariates included were maternal age, type of pregnancy (singleton or multiple), administration of antenatal corticosteroids (yes/no), preeclampsia/eclampsia/hemolysis elevated liver enzymes low platelet count (HELLP), preterm premature rupture of membranes (PPROM) >12 hours, and mode of delivery (vaginal or cesarean).

Infant covariates were gestational age, birth weight, infant sex; small for gestational age less than the third percentile, based on customized intrauterine growth curves[18]; birth weight z score, and Apgar score <7 at 5 minutes. Apgar score was used as a proxy variable for the infant's condition at birth.

Missing Data

The proportion of missing data was low for most of the variables: <1% for maternal age, antenatal corticosteroids, mode of delivery, 1%-3% for preeclampsia/eclampsia/HELLP, PPROM, IVH, BPD, and 5% for Apgar at 5 minutes. The exposure variable, admission temperature was missing in 794 infants (12%). In supplemental mortality analyses, final models were rerun after imputation of missing data for Apgar score (as an ordinal variable), admission temperature categories, and mode of delivery using multiple imputation chained equations.[19]

Statistical Analyses

Descriptive statistics are presented as medians and IQRs for continuous data and as numbers and proportions for categorical data. Differences in characteristics between infants with a recorded admission temperature and infants with missing admission temperature were tested using Wilcoxon rank sum test for continuous data, and χ^2 test for categorical variables. The associations between obstetric or infant characteristics and admission temperature were investigated in univariate regressions using mixed effects linear models with admission temperature as continuous variable and delivery hospital as the random effects variable. Variables with a $P < .2$ in these regressions were further investigated in multivariate regressions. Infant sex was kept in the analyses although $P = .36$, as female patients are known to have better outcomes than male patients.[20]

Unadjusted and adjusted risk ratios (RRs) with 95% CIs for mortality and morbidity were calculated with the use of mixed-effects generalized linear models to take into account