Association of Rewarming Rate on Neonatal Outcomes in Extremely Low Birth Weight Infants with Hypothermia

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Objective To explore the possible association between rewarming rate and neonatal outcomes in extremely low birth weight infants (ELBWIs) with hypothermia.

Study design All ELBWIs with hypothermia (temperature <36.0°C) on neonatal intensive care unit (NICU) admission were retrospectively evaluated. Rewarming rate was analyzed as both a dichotomous (≥0.5°C/h rapid group; <0.5°C/h slow group) and a continuous variable. Multivariable analysis was performed to explore the relation between rewarming rate and several outcomes, adjusting for clinically relevant confounders.

Results Hypothermia on NICU admission was present in 182 out of 744 ELBWIs (24.5%). The rewarming rate was slow in 109 subjects (59.9%) and rapid in 73 subjects (40.1%), with a median rewarming rate of 0.29°C/h (IQR 0.2-0.35) and 0.76°C/h (IQR 0.61-1.09), respectively ($P < .0001$). The median rewarming time was 340 minutes (IQR 250-480) and 170 minutes (IQR 110-230), respectively ($P < .0001$). After adjusting for clinically relevant confounders, we did not find significant associations between rewarming rate group (≥0.5°C/h vs <0.5°C/h) and neonatal outcomes. When we considered the rewarming rate as continuous variable, a higher rewarming rate was identified as a protective factor for respiratory distress syndrome (OR 0.39, 95% CI 0.17-0.87; $P = .02$).

Conclusions In ELBWIs with hypothermia upon NICU admission, there were no significant differences between rapid or slow rewarming rate and major neonatal outcomes. A higher rewarming rate was associated with a reduced incidence of respiratory distress syndrome. *(J Pediatr 2015;167:557-61)*.

Hypothermia is a worldwide problem in preterm newborns, especially in extremely low birth weight infants (ELBWIs), because of inadequate heat production and increase of heat loss.[1] In ELBWIs, hypothermia is an independent risk factor for death, cerebral hemorrhage, and late-onset sepsis.[1-3] Several interventions to prevent heat loss at birth have been evaluated, and the importance of hypothermia was highlighted in the last version of the international guidelines for neonatal resuscitation.[4] Previous studies have evaluated the rewarming approach of newborns with hypothermia,[5-9] but this continues to remain controversial. Detailed guidelines for warming a preterm infant with hypothermia are not available. Slow rewarming is the suggested strategy in consideration of its alleged protective effects on cerebral flow and rapid cardiovascular changes.[10-12] However, observational studies and case reports suggest that rapid rewarming may be the preferred approach in the management of infants with hypothermia.[9,13-15] In the past, rapid rewarming was generally avoided because of anecdotal cases where complications such as hyperthermia, convulsions, and episodes of apnea were described.[10,11,16] Therefore, it is not known whether a rapid instead of a slow rewarming strategy could have an effect on neonatal outcomes. Previous studies are dated and focused on limited populations. No studies reported on ELBWIs admitted to a modern neonatal intensive care unit (NICU).[5-8] We explored the possible association between rewarming rate and neonatal outcomes in ELBWIs with hypothermia.

Methods

The study was conducted at the Department of Women's and Children's Health, University of Padua, Azienda Ospedaliera di Padova. The protocol was approved by the ethical committee for human investigation at each participating center. We retrospectively reviewed the medical records of all infant newborns ≤28 weeks gestation and/or birth weight ≤1000 g, who were hypothermic (temperature <36.0°C) on admission to the NICU, between January 1, 2003, and December 31, 2013. Exclusion criteria were outborn infants admitted to the NICU at a postnatal age >24 hours; inborn infants transferred to another hospital immediately after birth; death before achieving

BPD	Bronchopulmonary dysplasia
ELBWI	Extremely low birth weight infant
GA	Gestational age
NICU	Neonatal intensive care unit
RDS	Respiratory distress syndrome

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normothermia (≥36.5°C); and major congenital anomalies. Patients were divided into 2 groups (rapid vs slow rewarming) based on rewarming rate: ≥0.5°C/h (rapid) and <0.5°C/h (slow). This cut-off was arbitrarily chosen based on the rewarming rate used in asphyxiated infants treated with therapeutic hypothermia.[17]

Rewarming rate was calculated based on the following formula:

$$\text{Rewarming rate} = \frac{\text{first normothermic value (36.5}-\text{37.5°C)}-\text{admission temperature}}{\text{time (hours)}}$$

Management of ELBWIs

Our local protocol for temperature management of ELBWIs is based on gestational age (GA) and birth weight. Incubator temperature and humidity are set to 36°C-37°C and 70-80%, respectively, for infants with GA <26 weeks and/or BW <750 g, and to 35°C-37°C and 70%, respectively, for infants with GA 26-29 weeks and/or birth weight 750-1000 g. When an infant with moderate hypothermia (temperature <36.0°C) is admitted, the incubator temperature is set 1°C over the recommended range. During the first postnatal days, axillary temperatures are manually checked by the attending nurse every hour in infants with hypothermia and at least every 3 hours in stable patients. The servo-control system is not used. Temperature is measured by using a digital thermometer (Terumo Digital Clinical Thermometer C202; Terumo Corporation, Tokyo, Japan).

Neonatal Outcomes

We collected maternal history, anthropometric characteristics, admission temperature, rewarming time, and neonatal outcomes including mortality, intraventricular hemorrhage, convulsions, late onset sepsis, hypoglycemia, respiratory distress syndrome (RDS), apnea of prematurity, duration of mechanical ventilation and supplemental oxygen, bronchopulmonary dysplasia (BPD), death/BPD, and length of hospitalization.

Intraventricular hemorrhage was defined according to the cranial ultrasound classification described by Papile et al.[18] Convulsions required documentation by electroencephalogram within the first 48 hours of life. Late onset sepsis was defined as positive results on one or more blood cultures, in the presence of clinical signs or symptoms suggestive of infection, after 72 hours of life.[19] Hypoglycemia was defined as blood glucose level below the 47 mg/dL.[20] RDS was defined as a need for supplemental oxygen in conjunction with characteristic radiographic findings.[21] BPD was defined as an oxygen requirement at corrected age of 36 weeks. Apnea of prematurity was defined as sudden cessation of breathing for at least 20 seconds or if accompanied by bradycardia or oxygen desaturation.[22]

Statistical Analyses

Continuous data were expressed as median and IQR. Sample characteristics were compared between slow and rapid rewarming groups using Fisher test (categorical data) and Mann-Whitney test (continuous data). Correlation between temperature at NICU admission and rewarming rate as a continuous variable was evaluated using Spearman rank correlation coefficient. Multivariable analysis (logistic regression model or linear regression model, according to type of dependent variable) was performed to explore the relation between rewarming rate and each outcome, adjusting for clinically relevant confounders (birth weight, GA, sex, small for GA, temperature at NICU admission, Apgar at 5 minutes, and need for intubation at birth).

We planned a priori to analyze the rewarming rate as both dichotomous and continuous variables. A secondary multivariable analysis also included twin pregnancy, antenatal steroids, preeclampsia, and placenta abruption among confounders was performed in order to take into account the possible effect of obstetric variables. A P value of less than .05 was considered significant. Statistical analysis was performed using R 2.12 language.

Results

The percentages of infants with hypothermia at NICU admission decreased over the years of the study (**Figure 1**). During the study, 744 ELBWIs (GA ≤28 weeks and/or birth weight ≤1000 g) were admitted to the NICU. Hypothermia was reported in 182 (24.5%) (**Figure 2**; available at www.jpeds.com). All infants were cared for in an incubator and had umbilical catheters inserted during the time of rewarming.

The rewarming rate was slow in 109 subjects (59.9%) and rapid in 73 (40.1%), with a median rewarming rate of 0.29°C/h (IQR 0.2-0.35) and 0.76°C/h (IQR 0.61-1.09), respectively ($P < .0001$). The median rewarming time was 340 minutes (IQR 250-480) and 170 minutes (IQR 110-230), respectively ($P < .0001$). Rewarming rate was inversely correlated to temperature at NICU admission (Spearman correlation coefficient −0.43, $P < .0001$).

Maternal and neonatal characteristics of the 2 groups are shown in **Table I**. The temperature at NICU admission was lower in the rapid group than in the slow rewarming group (median 35.0°C vs 35.5°C, respectively; $P < .0001$). The 2 groups were comparable for maternal and neonatal characteristics, apart from the blood sugar levels ($P = .01$) and the rates of twin pregnancy ($P = .04$), preeclampsia/eclampsia/HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome ($P = .01$), and placenta abruption ($P = .01$).

Neonatal Outcomes and Rewarming Rate as Dichotomous Variable

Neonatal outcomes in slow and rapid groups are reported in **Table II** (available at www.jpeds.com). When adjusting for clinically relevant confounders, rewarming rate as a dichotomous variable did not show any statistically significant effect on outcomes. Patients in the rapid rewarming group had a slightly lower risk of hypoglycemia (OR 0.46, 95% CI 0.20-1.07; $P = .07$). The aORs with 95%