Antenatal Betamethasone: A Prolonged Time Interval from Administration to Delivery Is Associated with an Increased Incidence of Severe Intraventricular Hemorrhage in Infants Born before 28 Weeks Gestation

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Objective To examine the effects of antenatal steroids on severe intraventricular hemorrhage (IVH) in infants born during the IVH vulnerable period (<28 weeks gestational age) and to evaluate rates of IVH correlated with the time interval between treatment or retreatment and birth.

Study design A total of 429 infants (<28 weeks gestation), who delivered ≥24 hours after the first betamethasone (BMZ) course (2 doses), were divided into groups based on the interval between the first course of BMZ and delivery: <10 days or ≥10 days. The primary outcome was severe IVH. Multiple regression analyses were performed to adjust for potential confounders.

Results Three hundred ninety-two infants delivered after a single BMZ course (312 delivered <10 days; 80 ≥10 days). The incidence of severe IVH was 17% for infants delivered ≥10 days and 7% for those delivered <10 days after a single BMZ course (aOR 4.16; 95% CI 1.59-10.87, $P = .004$); 37 infants (born ≥10 days from the first BMZ course) received a second/rescue BMZ course. The incidence of severe IVH among infants receiving a second/rescue course was 8%, which was similar to the incidence among infants born <10 days (aOR 1.7; 95% CI 0.41-6.6, $P = .48$).

Conclusions In infants born before 28 weeks gestation, delivery ≥10 days from the first BMZ course is associated with a higher incidence of severe IVH; a second/rescue course may reverse this effect. *(J Pediatr 2016;177:114-20).*

Although randomized controlled trials (RCTs) demonstrate that infants exposed to antenatal corticosteroids have a decreased incidence of death, respiratory distress syndrome (RDS) and severe grades (grades 3 and 4)[1] of intraventricular hemorrhage (IVH),[2] there are unanswered questions about the duration of the beneficial effects and whether retreatment is required. In vitro[3] and in vivo[4] studies suggest that betamethasone (BMZ)'s beneficial effects on the preterm lung are reversible and begin to wane after the first week. In addition, a meta-analysis of the RCTs that examined the use of repeat doses of corticosteroids in women still at risk of preterm birth 1-2 weeks after an initial course found that retreatment decreases the incidence of RDS.[5]

Whether the beneficial effects of antenatal corticosteroids on other morbidities (eg, severe IVH) also wane with time is much less clear. None of the corticosteroid retreatment RCTs[5] found a difference in the incidence of severe IVH between infants who received a single course and those who received repeat dosing.[5-11] Although these findings suggest that retreatment may not affect the incidence of severe IVH and that the beneficial effects of corticosteroids on severe IVH may not wane with time, there are important considerations that need to be examined before one can accept this conclusion. Severe IVH occurs almost exclusively in infants born before 28 weeks gestation; the incidence is 27% among infants born below 26 weeks, but less than 2% among those born at 28 weeks gestation or older.[12] Unfortunately, the infants who delivered before 28 weeks gestation in the "retreatment" RCTs made up only 7% (range 0%-16%) of the study population, and the overall incidence of severe IVH was only 2.6% (range 0%-5%).[6-11] Therefore, we designed an observational study to examine the effects of antenatal steroids on severe IVH in infants born during the IVH vulnerable period (<28 weeks gestation). We hypothesized that the beneficial effects of antenatal steroids on severe IVH are time-limited and wane with time in neonates born before 28 weeks gestation, and that retreatment with a second course of antenatal BMZ can restore its beneficial effects.

BMZ	Betamethasone
BPD	Bronchopulmonary dysplasia
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
RCTs	Randomized controlled trials
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity

Methods

This project was approved by the University of California San Francisco's Institutional Review Board. A single neonatologist prospectively evaluated and recorded the perinatal and neonatal risk factors and outcome measures from all infants born at ≤27[6/7] weeks gestation and admitted, within the first 24 hours of birth, to the William H. Tooley Intensive Care Nursery at the University of California San Francisco between January 1998 and December 2015. Infants with major congenital malformations were excluded. Six hundred sixty-seven patients were eligible for the study. Perinatal characteristics of the study population are listed in **Table I** (available at www.jpeds.com).

Criteria used to evaluate specific neonatal and perinatal risk factors that may affect the incidence of severe IVH have been previously described.[13,14] Gestational age was determined by the date of last menstrual period and early ultrasounds (before 24 weeks gestation). If there were discrepancies, the early ultrasound dating was used. Intrauterine growth restriction was defined as birth weight less than the tenth-percentile for gestational age using the growth curves from Olsen et al.[15]

Detailed descriptions of our approach to respiratory and hemodynamic support have been published elsewhere.[13,16,17] Oxygen saturation target limits for this population were 88%-94% throughout the study period.

All infants were examined with serial bedside cranial ultrasounds that included a study on postnatal day 3 or 4, followed by weekly or biweekly studies for the first 4 weeks. A single neonatologist prospectively reviewed all of the cranial ultrasound examinations with an ultrasonographer. IVH was classified using the 4-level grading system.[2] Grades 3 and 4 IVH were considered "severe IVH."[2]

Bronchopulmonary dysplasia (BPD) was defined by a modified physiologic room-air challenge test performed between 36 and 37 weeks postmenstrual age.[18]

Necrotizing enterocolitis (NEC) was defined as Bell's classification II or greater (this included NEC that was treated medically or surgically, and "spontaneous perforations" that occur before 7 days).[19]

The criteria for diagnosis, follow-up, and treatment of retinopathy of prematurity (ROP) have been previously described.[14]

Infants were divided into groups depending on the interval between the first dose of the first course of antenatal BMZ and delivery. A complete course of antenatal BMZ consisted of two 12-mg doses that were administered 24 hours apart. Group A consisted of infants who were either never treated or delivered within 6 hours of the initiation of antenatal BMZ. Group B consisted of infants who delivered between 7 and 23 hours of the initiation of antenatal BMZ. Group C consisted of infants who delivered between 24 hours and 9 days (group C-1, between 24 and 47 hours; group C-2, between 48 hours and 7 days; and group C-3 between 8 and 9 days) after the initiation of antenatal BMZ. Group D consisted of infants who delivered 10 days or more after the initiation of antenatal BMZ.

Statistical Analyses

Statistical analyses were performed using STATA (Stata Statistical Software: Release 14; StataCorp LP, College Station, Texas). A χ^2 test was used to compare categorical baseline characteristics between infants who delivered at different times after the initiation of antenatal BMZ treatment. The Student t test was used to compare continuous parametric variables (gestational age, birth weight).

Because our study period spanned 17 years, we were concerned that unmeasured changes in practice or risk factors may have occurred that could have affected the rates of our primary study outcome (severe IVH). Therefore, we created a categorical variable ("birth year epoch") that divided the study period into the 3 epochs (1998-2003, 2004-2009, and 2010-2015). We included the "birth year epoch" variable in all of our multivariate regression analyses to adjust for any unmeasured practice changes that may have occurred over time as discussed below.

We first examined the relationship between the time interval from the first dose of BMZ to delivery and neonatal morbidity by conducting a multivariate regression analysis. Logistic regression was used for categorical outcomes, and linear regression was used for continuous outcome variables. Regression covariates were selected a priori. For these analyses, the following covariates were included in the model: gestational age, birth year epoch, pregnancy complications (small for gestational age, multiple gestation, gestational diabetes, chorioamnionitis, and preeclampsia), delivery mode, out born status, and race. For all regression models, sensitivity analyses were conducted for other baseline characteristics (including male sex, prophylactic indomethacin, and 5-minute Apgar score) that were not included in the primary models. Addition of these variables to the model did not change the point estimates.

We next investigated the waning effects of a complete (2-dose) course of BMZ on neonatal morbidity by examining a subset of our population who either delivered between 24 hours and 9 days (group C), or delivered 10 days or more (group D) after the initiation of antenatal BMZ. Multivariate regression model covariates were selected a prior and included gestational age, birth year epoch, small for gestation, preeclampsia, multiple gestation, and gestational diabetes. Variation inflation factors were used to check for collinearity between variables in our models. If the distribution of an outcome variable was skewed, bootstrapping (with 100 repetitions) was employed to overcome the normality assumption of the linear regression model, and bias corrected CIs were calculated and reported. For all statistical tests, a P value of .05 was considered significant.

Results

Among the 667 infants in the study, 28% delivered prior to or within 6 hours of the first dose of BMZ, 8% delivered between 7 and 23 hours of the first dose, and 64% delivered after completing the full 2-dose course of BMZ (≥24 hours after the first dose). We first examined the relationship between