Antenatal Corticosteroids Promote Survival of Extremely Preterm Infants Born at 22 to 23 Weeks of Gestation

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Objective To evaluate the effectiveness of antenatal corticosteroid (ACS) to improve neonatal outcomes for infants born at <24 weeks of gestation.

Study design We performed a retrospective analysis of 11 607 infants born at 22 to 33 weeks of gestation between 2003 and 2007 from the Neonatal Research Network of Japan. We evaluated the gestational age effects of ACS administered to mothers with threatened preterm birth on several factors related to neonatal morbidity and mortality.

Results By logistic regression analysis, ACS exposure decreased respiratory distress syndrome and severe intraventricular hemorrhage in infants born between 24 and 29 weeks of gestation. Cox regression analysis revealed that ACS exposure was associated with a significant decrease in mortality of preterm infants born at 22 or 23 weeks of gestation (adjusted hazard ratio, 0.72; 95% CI, 0.53 to 0.97; $P = .03$). This effect was also observed at 24 to 25 and 26 to 27 weeks of gestation and in the overall study population.

Conclusions ACS exposure improved survival of extremely preterm infants. ACS treatment should be considered for threatened preterm birth at 22 to 23 weeks of gestation. *(J Pediatr 2011;159:110-4)*.

Preterm birth is the main cause of perinatal mortality and morbidity.[1] In 1993, the survival rate of infants born at 22 to 23 weeks of gestation was reported to be 18%.[2] Since then, there has been a steady increase in the survival of extremely preterm infants in Japan. During 2005, the survival rate of infants born at 22 and 23 weeks of gestation was 41.2% and 60.3% at the 28 days of age, respectively.[3] Despite improvements in intensive care and increase in the survival of extremely preterm neonates, their treatment continues to be a challenge because of the associated acute complications such as respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH).[4]

Women with threatened preterm birth are treated with antenatal corticosteroid (ACS) because evidence from randomized, placebo-controlled trials and meta-analyses demonstrate their benefit in decreasing neonatal mortality and morbidity in preterm infants, especially in the first 48 hours of life.[5] Recent literature indicates that ACS treatment is indicated for women at high risk of preterm delivery at 24 to 34 weeks of gestation.[5,6] However, there is wide international and regional variation in ACS use.[6,7] Furthermore, although ACS use has increased significantly over the years, it has remained low, at 22 to 26 weeks of gestation.[8]

The MOSAIC study compared obstetric interventions in extremely preterm infants and also found large regional differences by gestational age.[9] Our group had previously reported intercenter differences in the morbidity and mortality of 2145 very low birth weight infants from 37 tertiary care centers included in the Neonatal Research Network (NRN) data base in Japan.[10] As of April 2008, 87 perinatal centers were participating in the network. The NRN database is the only extensive source of information on extremely preterm infants born at 22 to 23 weeks of gestation in Japan. Considering the differences in the treatment and outcomes of preterm infants and the variation in ACS use by gestational age, we conducted a retrospective data base analysis to evaluate the effectiveness of ACS treatment in improving the outcomes of preterm infants by gestational age, especially for preterm births at <24 weeks of gestation.

Methods

Patient data were obtained from the NRN database established in 2003 with a grant from the Ministry of Health, Labor, and Welfare, Japan. This data base contains information on the morbidity and mortality of very low birth weight

ACS	Antenatal corticosteroid
CLD	Chronic lung disease
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NRN	Neonatal Research Network
PDA	Patent ductus arteriosus
RDS	Respiratory distress syndrome

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infants with birth weight ≤1500 g and born in the participating hospitals or admitted to these facilities within 28 days of birth. All tertiary neonatal units designated by the government except three units participate in this data base in Japan. Data for infants who were born alive but died in the delivery room are also included.[10] Each tertiary neonatal center designated by the government has a responsibility to care for sick newborn infants in the designated area. When the data were collected, the clinician's attitude on active treatment or withdrawal of the care toward preterm labor and infants at 22 and 23 weeks of gestation in Japan depended on the general status of fetus or infant. After 24 weeks of gestation, the great majority of clinicians made efforts to save the infants. This retrospective data base analysis included infants born at 22 to 33 weeks of gestation between 2003 and 2007. The data were analyzed according to gestational age: 22 to 23 weeks, 24 to 25 weeks, 26 to 27 weeks, 28 to 29 weeks, 30 to 31 weeks, and 32 to 33 weeks. We studied the effect of ACS on RDS, use of surfactant, duration of O_2 use, chronic lung disease (CLD), PDA, IVH, severe IVH, NEC, and mortality in preterm infants. The definition of RDS was a diagnosed RDS by clinical and radiographic findings; the grade of IVH was diagnosed with cranial echography according to the classification of Papile and were grades III and IV severe IVH. Definition of NEC was according to Bell classification stage II or greater.

Data were not available for the types, doses, and timing of ACS given to the mothers. Administration of any dose of ACS was defined as ACS given. Neonatal mortality was defined as mortality of infants before the age of 28 days. Covariables included in the analysis as confounders were maternal age, parity, multiplicity, gestational diabetes mellitus, hypertension, premature rupture of membranes, mode of birth, sex of the infant, place of birth (inborn or outborn), and birth weight (plus gestation for the overall study population).

The baseline characteristics of the no-ACS control group and ACS-exposed group were compared using χ^2 test and *t* test as appropriate. Multivariate logistic regression analyses were performed to assess the effect of ACS treatment on the neonatal morbidities. Odds ratios or coefficients adjusted for confounding variables and 95% CIs were calculated. Many extremely preterm infants survive with intensive care for longer than 28 days, and the logistic regression analysis on neonatal mortality was limited to reflect the short time survival of such infants in modern neonatal intensive care. A survival analysis using a Cox regression model was conducted to compare mortality between the two populations, taking the observational period into account. The observational period in the model was defined as between the date of admission and the date of discharge. The time of origin was set as date of birth, and the end point was mortality or survival at discharge from the neonatal unit. Statistical analysis was performed using Stata version 10.0 (StataCorp LP, College Station, Texas). Statistical significance was considered at $P < .05$.

All information about the infants was collected anonymously and unlinked from the original data. The internal review board from Tokyo Women's Medical University approved the study.

Results

Data of 11 607 infants were available for the period 2003 to 2007 and were included in the analysis. The demographic and baseline characteristics of the study population are shown in Table I. Significant differences in several baseline characteristics were observed between the no-ACS and ACS groups. Multivariate logistic regression analysis was performed with adjustment for maternal age, parity, multiplicity, gestational diabetes mellitus, hypertension, premature rupture of membranes, mode of birth, sex of infant, place of birth (inborn or outborn), and birth weight (plus gestation for the overall study population).

ACS use resulted in a significant reduction in RDS in infants born at a gestational age of 24 to 25 weeks and 28 to 29 weeks and in the overall study population; surfactant use in the 28- to 29-week group; and the duration of O_2 use in the 24- to 25-week group and the overall study population (Table II). Furthermore, ACS use was associated with a significant reduction in both IVH and severe IVH in infants born at a gestational age of 24 to 29 weeks as well as in the overall study population. However, ACS use was not associated with a significant reduction in CLD, PDA, or NEC in any gestational age group or overall.

Logistic regression analyses on neonatal mortality, as well as survival analyses by a Cox regression model, was conducted to assess the effect of ACS use on the survival of preterm infants by gestational age (Table III). There was no evidence of differences in the logistic regression analysis between the two groups on mortality to 28 days. When the analysis was expanded to include survival to hospital discharge, the survival analyses showed that ACS treatment was associated with a significant reduction in mortality of preterm infants born at a gestational age of 22 to 23 weeks (adjusted hazard ratio, 0.72; 95% CI, 0.53 to 0.97; $P = .03$). This effect was also seen in infants born at a gestational age of 24 to 25 weeks and 26 to 27 weeks, as well as in the

Table I. Demographics and baseline characteristics

Characteristic	No ACS (n = 6767)	ACS (n = 4840)	*P* value
Maternal age, years, mean (SD)	30.7 (5.3)	31.0 (5.03)	.006
Primiparous	53.5%	55.3%	.06
Singleton	75.0%	67.0%	<.001
Diabetes	1.82%	1.32%	.04
Hypertension	20.0%	15.4%	<.001
Chorioamnionitis	18.8%	19.6%	.32
PROM	24.2%	35.8%	<.001
Cephalic position	68.3%	69.6%	.15
Cesarean section	74.6%	79.6%	<.001
Age on admission, days, mean (SD)	0.22 (1.92)	0.05 (0.89)	<.001
Male sex	50.1%	52.2%	.03
Outborn	12.5%	5.7%	<.001
Apgar score <7 (1 min)	62.4%	55.1%	<.001
Apgar score <7 (5 min)	29.7%	22.0%	<.001
Birth weight, grams, mean (SD)	1011 (305)	998.0 (990)	.02

PROM, premature rupture of membranes.