

Research Paper

The Effects of Antenatal Corticosteroids on Short- and Long-Term Outcomes in Small-for-Gestational-Age Infants

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Abstract

Aim: To evaluate the effect of antenatal corticosteroids (ANS) on short- and long-term outcomes in small-for-gestational age (SGA) infants.

Methods: A retrospective database analysis was performed. A total of 1,931 single infants (birth weight <1,500 g) born at a gestational age between 22 weeks and 33 weeks 6 days who were determined to be SGA registered in the Neonatal Research Network Database in Japan between 2003 and 2007 were evaluated for short-term outcome and long-term outcome.

Results: ANS was administered to a total of 719 infants (37%) in the short-term outcome evaluation group and 344 infants (36%) in the long-term outcome evaluation group. There were no significant differences between the ANS group and the no-ANS group for primary short-term outcome (adjusted odds ratio (OR) 0.73; 95% confidence interval (CI) 0.45-1.20; P-value 0.22) or primary long-term outcome (adjusted OR 0.69; 95% CI 0.40-1.17; P-value 0.17).

Conclusions: Our results show that ANS does not affect short- or long-term outcome in SGA infants when the birth weight is less than 1500 g. This study strongly suggests that administration of ANS resulted in few benefits for preterm FGR fetuses.

Key words: fetal growth restriction; glucocorticoids; infant; infant mortality; premature birth; small for gestational age

Introduction

Antenatal corticosteroid (ANS) administration in women who are at risk for preterm labor reduces the incidence of neonatal respiratory distress syndrome [1], intraventricular hemorrhage (IVH), necrotizing

enterocolitis (NEC), and neonatal mortality [2]. Although administration of ANS is the most effective intervention for risks associated with preterm birth, the effect in some subgroups is limited. The effects of

ANS in multiple pregnancies, in cases of chorioamnionitis (CAM) [3], and in cases of growth-restricted fetuses [4] are unclear. In addition, there is considerable controversy about the effectiveness of ANS in fetal growth restriction (FGR) [5].

The Neonatal Research Network Database is the largest database of level III perinatal centers in Japan. The database includes infants with birth weights at or less than 1,500 g, herein referred to as very-low-birth-weight (VLBW) infants, who were treated at participating neonatal centers. Considering the nation-wide population of VLBW infants born in Japan during the study period, more than 50% of VLBW infants in Japan were registered in the registry [6]. This database contains the factors of the maternal course (administered ANS or not), short-term outcomes, and long-term outcomes.

In this study, we conducted a retrospective analysis of the effectiveness of ANS on the short- and

long-term outcomes in small-for-gestational-age (SGA) VLBW infants, which is a very high-risk group among preterm infants.

Materials and Methods

This was a retrospective analysis of the Neonatal Research Network Database created with a grant from the Ministry of Health, Labor, and Welfare of Japan in 2004. The 82 level III perinatal centers in Japan are registered in the database (listed in the Acknowledgments). Data include infants with birth weight less than 1,500 g. Infants who were born alive but died in the delivery room were also included. The clinician's perspective on active treatment or withdrawal of care for preterm infants born at 22 and 23 weeks of gestation depended on the clinical status of the infants. After 23 weeks of gestation, most clinicians attempted to save the infants. All other factors were defined as reported previously [7].

There were 10,394 clinical cases between 2003 and 2007 (Fig. 1). Exclusion criteria were multiple pregnancies, 34 weeks of gestation or more, uncertain gestational age, uncertain administration of ANS, major congenital malformation, and hospitalization following an out-of-hospital birth. Short-term outcome evaluation was available in 5,853 cases. Of those, 3,063 cases dropped out of the follow-up before 3 years of age; therefore, long-term outcome was evaluated in 2,790 cases.

These cases were classified as either SGA or non-SGA. A birth weight below the 10th percentile for gestational age was classified as SGA. Birth weight for gestational age was determined using the percentile scale derived from the formula used in Japan [Itabashi, Fujimura, Kusuda, Tamura, Hayashi, et al. (2011) The new standard of birth weight for gestational age. *J Jpn Pediatr Soc* 114: 1271–1293 [In Japanese]].

ANS usage was defined as the administration of any corticosteroids to accelerate fetal lung maturity. ANS was provided based on the clinician's policy or perspective. The time from ANS administration to delivery and the type of corticosteroid used were not described in the database. It is inferred that betamethasone was used in most of the cases because betamethasone is the only drug that is officially recognized in the health insurance system of Japan for the acceleration of fetal lung maturation.

The primary short-term outcome was evaluated based on death occurring before

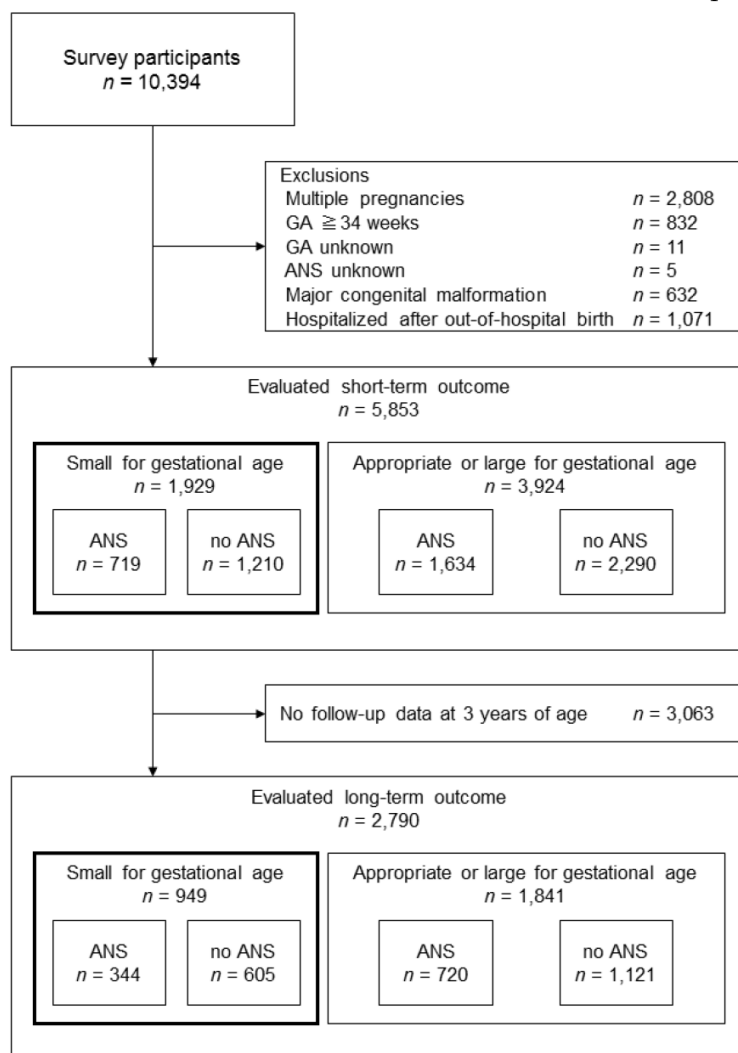


Figure 1. Study inclusion process for the short-term outcome evaluation group and the long-term outcome evaluation group. ANS, antenatal corticosteroids; GA, gestational age

discharge from a participating neonatal intensive care unit (death in NICU). Intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), respiratory distress syndrome (RDS), chronic lung disease of prematurity (CLD), sepsis, late-onset adrenal insufficiency, symptomatic patent ductus arteriosus (PDA), and necrotizing enterocolitis (NEC) were also evaluated. IVH was defined as Papile grade I or more. The diagnosis of PVL was made based on either head ultrasound or cranial MRI scans performed at 2 weeks of age or later. RDS was diagnosed based on the clinical and radiographic findings. CLD was defined when an infant continued to receive supplemental oxygen on the 28th day after birth, and 36-week CLD was defined when an infant continued to receive supplemental oxygen at the 36th week based on postmenstrual age. PDA was diagnosed based on both the echocardiographic findings and clinical evidence of a volume overload due to a left-to-right shunt. NEC was defined according to a Bell classification [8] of stage II or greater.

For surviving VLBW infants, the follow-up protocol consisted of routine physical and neurological evaluations and developmental assessments at 3 years (36-42 months) of chronological age at each participating center, as reported previously [9]. The primary long-term outcome was evaluated based on death before 3 years of age or neurodevelopmental impairment (NDI). Infants with cerebral palsy (CP), a development quotient (DQ) < 70, and severe hearing impairment and visual impairment were designated as having neurodevelopmental impairment (NDI). CP was defined as a non-progressive central nervous system disorder characterized by abnormal muscle tone in at least one extremity and abnormal control of movement and posture [10]. DQ was determined using the Kyoto Scale of Psychological Development (KSPD) test applied by psychologists at each participating center [11]; when the DQ was < 70, the infant was judged as "delayed". Severe hearing impairment included the need for hearing aids. Visual impairment was defined as unilateral or bilateral blindness diagnosed by an ophthalmologist.

The results are expressed as the mean \pm SD or median (range). Statistical analysis was performed using the Chi² test and t-test, as appropriate. Multivariable logistic regression analyses were performed to assess the effect of ANS on the short- and long-term outcomes. Odds ratios (OR) or confidence interval (CI) were adjusted for confounding variables, and 95% confidence intervals were calculated. Multivariate logistic regression analysis was performed after adjusting for maternal age, parity, preeclampsia, preterm rupture of membranes (PROM), non-reassuring fetal status (NRFS), mode of delivery, gestational age

of delivery, birth weight, gender of the infant, and histological CAM (\geq stage 2 according to Blanc's classification [12]).

Statistical analyses were performed using JMP, version 9.0.2J (SAS Institute, Cary, North Carolina, USA). Differences were considered to be statistically significant at $P < 0.05$.

All information about the infants was collected anonymously, and the stored data were unlinked from individual data. The protocol of this study was approved by the central internal review board at Tokyo Women's Medical University, where all data were collected and stored.

Results

Short-term outcome

A total of 10,394 infants were registered in the database between 2003 and 2007. In total, 4,541 infants were excluded. A total of 5,853 patients were evaluated for short-term outcomes. A total of 1,929 infants (33%) were classified as SGA, and the 3,924 remaining infants were classified as appropriate or large for gestational age. ANS was administered to 719 of the SGA patients (37%).

Table 1 compares the clinical characteristics of the ANS group and the no-ANS group in SGA infants. The incidence of preeclampsia was low, and the incidence of PROM was high in the ANS group. The ratio of cesarean section to vaginal birth was higher in the ANS group. Gestational age at delivery was earlier and birth weight was lower in the ANS group. Although RDS and CLD were more common in the ANS group, there was no difference in the primary short-term outcome (incidence of death before NICU discharge) and other short-term outcome factors between the ANS group and the no-ANS group based on univariate analysis.

To evaluate the effect of ANS on short-term outcome in SGA infants, further analysis was performed using logistic regression analysis. Table 2 shows the odds ratios of the ANS group compared with the no ANS group in SGA infants. Although the incidence of PVL demonstrated a trend toward a lower rate in the ANS group, the adjusted OR (95% CI) was 0.73 (0.45-1.20) for the primary short-term outcome in the ANS group compared to the no-ANS group, significant effect of ANS was not observed in SGA infants.

Long-term outcome

A total of 3,063 infants were excluded because of the lack of follow-up data until 3 years of age. A total of 2,790 patients were evaluated for long-term outcome. Of those, 949 (34%) infants were classified as SGA. ANS was administered to 344 of the SGA infants

(36%). The administration rate of ANS was similar to that of the SGA infants in the short-term evaluation group.

Table 3 shows a comparison of the clinical characteristics of the ANS group and the no-ANS group of SGA infants. The incidence of preeclampsia was low, and the incidence of PROM was high in the ANS group. Gestational age at delivery was lower, and birth weight was lower in the ANS group. Although severe hearing impairment was uncommon in the ANS group, there was no difference in the incidence of death before 3 years of age and other neurodevelopment impairment factors between the ANS group and the no-ANS group based on the univariate analysis.

To evaluate the effect of ANS on long-term outcome in SGA infants, further analysis was performed using logistic regression analysis. Table 4 shows the odds ratios of the ANS group compared to the no-ANS group of SGA infants. The adjusted OR (95% CI) was 0.69 (0.40-1.17) for the primary long-term outcomes in the ANS group compared to the no-ANS group; a significant long-term effect of ANS was not found in SGA infants.

Table 1. Comparison of the clinical characteristics and the results of the univariate analysis of the ANS group and the no-ANS group in the short-term outcome evaluation group of SGA infants (n=1929)

	ANS (n=719)	no ANS (n=1210)	P value
Maternal age	32.0 ± 4.9	32.1 ± 5.0	.50
Nulliparous	437/719 (61%)	746/1210(62%)	.70
Preeclampsia	318/719 (44%)	605/1209 (50%)	.0134*
Diabetes	8/719 (1%)	25/1210 (2%)	.11
PROM	124/719 (17%)	118/1210 (10%)	< .0001*
NRFS	309/719 (43%)	530/1209 (44%)	.71
Cesarean section	661/719 (92%)	1058/1210 (87%)	.0018*
GA at delivery	29.1 ± 2.6	29.7 ± 2.7	< .0001*
Birth weight	886±298	959±313	< .0001*
Male gender	386/717 (54%)	615/1209 (51%)	.21
Histological CAM (≥stage 2)	46/507 (9%)	46/838 (5%)	.0129*
Clinical CAM	43/717 (6%)	75/1199 (6%)	.82
Death during NICU hospitalization	56/719 (8%)	92/1210 (8%)	.88
IVH	54/719 (8%)	99/1210 (8%)	.60
PVL	11/719 (2%)	28/1210 (2%)	.23
RDS	341/719 (47%)	510/1210 (42%)	.0241*
CLD	194/719 (27%)	250/1210 (21%)	.0015*
Sepsis	51/719 (7%)	75/1210 (6%)	.44
Late-onset adrenal insufficiency	53/719 (7%)	67/1210 (5%)	.11
PDA	175/719 (24%)	268/1210 (22%)	.27
NEC	13/719 (2%)	15/1210 (1%)	.31

ANS, antenatal corticosteroids; PROM, preterm rupture of membranes; NRFS, non-reassuring fetal status; GA, gestational age; CAM; chorioamnionitis; NICU, neonatal intensive care unit; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; CLD, chronic lung disease of prematurity; PDA, symptomatic patent ductus arteriosus; NEC, necrotizing enterocolitis.

Table 2. The results of multiple logistic analysis of the short-term outcome showing the adjusted odds ratio of the ANS group compared to the no-ANS group

	Adjusted OR†	95% CI	P value
Death during NICU hospitalization	0.73	0.45-1.20	.22
IVH	0.79	0.51-1.21	.28
PVL	0.44	0.17-1.03	.06
RDS	1.10	0.84-1.44	.48
CLD	1.18	0.87-1.62	.29
Sepsis	0.95	0.59-1.53	.84
Late-onset adrenal insufficiency	0.94	0.59-1.50	.80
PDA	1.01	0.76-1.34	.96
NEC	1.04	0.43-2.48	.92

ANS, antenatal corticosteroids; NICU, neonatal intensive care unit; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; CLD, chronic lung disease of prematurity; PDA, symptomatic patent ductus arteriosus; NEC, necrotizing enterocolitis.

†Adjusted for maternal age, parity, preeclampsia, PROM, NRFS, mode of delivery, gestational age at delivery, birth weight, gender of the infant, and histological CAM (≥ stage 2).

Table 3. Comparison of the clinical characteristics and the results of the univariate analysis of the ANS group and the no-ANS group in the long-term outcome evaluation group of SGA infants (n=949)

	ANS (n=344)	no ANS (n=605)	P value
Maternal age	32.2 ± 4.9	32.1 ± 5.0	.68
Nulliparous	215/344 (63%)	391/605 (65%)	.51
Preeclampsia	135/344 (39%)	307/605 (51%)	.0006*
Diabetes	5/344 (1%)	15/605 (2%)	.27
PROM	67/344 (19%)	55/605 (9%)	< .0001*
NRFS	148/344 (43%)	277/605 (46%)	.41
Cesarean section	314/344 (91%)	534/605 (88%)	.14
GA at delivery	28.7 ± 2.7	29.2 ± 2.8	.0025*
Birth weight	829 ± 294	900 ± 320	.0005*
Male gender	190/342 (56%)	316/604 (52%)	.33
Histological CAM (>stage 2)	28/234 (12%)	23/436 (5%)	.0024*
Clinical CAM	24/344 (7%)	43/598 (7%)	.90
Death before 3 years of age	59/344 (17%)	100/605 (16%)	.81
Neurodevelopment impairment	66/285 (23%)	93/505 (18%)	.11
Cerebral palsy	19/278 (7%)	25/498 (5%)	.30
DQ<70	51/271 (19%)	70/486 (14%)	.12
Severe hearing impairment	0/277 (0%)	5/502 (1%)	.0357*
Visual impairment	1/275 (0%)	3/490 (1%)	.64
Death before 3 years of age or NDI	125/344 (36%)	193/605 (31%)	.16

ANS, antenatal corticosteroids; PROM, preterm rupture of membranes; NRFS, non-reassuring fetal status; GA, gestational age; CAM; chorioamnionitis; DQ, development quotient; NDI, neurodevelopmental impairment.

Table 4. The results of multiple logistic analysis of the long-term outcome showing the adjusted odds ratio of the ANS group compared with the no ANS group

	Adjusted OR†	95%CI	P value
Death before 3 years of age	0.69	0.40-1.17	.17
Neurodevelopment impairment	1.03	0.62-1.70	.90
Cerebral palsy	1.12	0.41-2.96	.82
DQ<70	1.08	0.63-1.85	.78
Severe hearing impairment	-	0.00-1.42	.08
Visual impairment	1.03	0.02-36.15	.99
Death before 3 years of age or NDI	0.83	0.54-1.27	.39

ANS, antenatal corticosteroids; DQ, development quotient; NDI, neurodevelopmental impairment.

†Adjusted for maternal age, parity, preeclampsia, PROM, NRFS, mode of delivery, gestational age at delivery, birth weight, gender of the infant, and histological CAM (≥stage 2).

Discussion

Despite the established benefits of antenatal glucocorticoids for neonatal lung function and viability in normal-size premature infants, there is considerable controversy concerning the effectiveness of ANS in growth-restricted premature infants.

A large retrospective study found that the ANS affects fetal outcome even in cases of SGA. According to "The Vermont Oxford Network", ANS lowered the incidence of RDS, IVH, and perinatal death in both normal and growth-restricted newborns from 25 to 30 weeks gestation. The authors concluded that the benefits of ANS are not dependent on fetal growth [13].

In contrast, another study showed that ANS resulted in few benefits in cases of FGR. Elimian et al. found that there was no difference due to ANS in the incidence of RDS, IVH, PVL, NEC, and neonatal mortality in a retrospective study [4]. The case-control study of 62 pairs with growth-restriction due to placental insufficiency indicated that the survival rate without disability or handicap at 2 years corrected age was higher in the ANS group, but there was a statistically significant negative effect on physical growth in the long-term follow-up at school age. Schaap et al. concluded that the benefits from ANS for growth-restricted infants outweigh the possible adverse effects [14].

Several mechanisms of the ANS effect on FGR have been proposed. Early studies showed that plasma cortisol levels in SGA fetuses were higher than in appropriate-for-gestational-age infants, suggesting that the ANS effect was attenuated [15]. Accordingly, the risk of RDS in FGR fetuses without ANS should decrease, but in fact, it increases [16]. A recent study of sheep fetuses with uterine artery ligation (an induced FGR model) showed no changes in surfactant protein gene expression when plasma cortisol concentrations were increased [17]. These studies suggest reactivity to corticosteroid concerning the pulmonary maturity deficits in FGR.

Administration of ANS for FGR might compromise cardiovascular function. A sheep study demonstrated that carotid blood flow decreased after the administration of betamethasone in an induced FGR model [18]. In contrast, human growth-restricted fetuses showed absent or reversed end-diastolic umbilical artery flow. Blood flow in umbilical arteries and veins increased after intramuscular injections of betamethasone in some cases [19]. Thus, the effects of ANS on the cardiovascular system and on prognosis warrant further investigation.

Our study demonstrated that ANS has no effect on the short- and long-term outcome in SGA infants. Mori et al. demonstrated that ANS improved short-term outcome using the same database [20], but

their study did not delineate between SGA infants and non-SGA infants. This is the first large sample size retrospective study examining the effect of ANS on long-term outcomes in SGA infants.

The strength of this study is its large sample size. In addition, little distortion of the results due to inconsistent neonatal medical care is expected because the same health insurance system of Japan is provided to most inhabitants.

The limitations of our study are that it is a retrospective and multicenter study. The type of ANS and the days from ANS to delivery are not described in this database and are expected to vary. Although we excluded major malformation, the causes of SGA vary and are not described in the database, and it is expected that the response to ANS varies according to the cause of SGA. Another limitation is that the ANS administration rate was low. We suppose the reason for this was that ANS was not authorized in the public insurance institution of Japan until 2009; our study subjects were born between 2003 and 2007.

In summary, ANS is not effective to improve the short- or long-term outcome of SGA infants when the birth weight is less than 1500 g. This study strongly suggests that the administration of ANS resulted in few benefits for preterm FGR fetuses. For randomization to be ethically justified, further study is needed to clarify ANS activity for FGR fetuses.

Abbreviations

ANS: antenatal corticosteroids; SGA: small-for-gestational age; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; CAM: chorioamnionitis; FGR: fetal growth restriction; VLBW: very-low-birth-weight; SGA: small-for-gestational-age; NDI: neurodevelopmental impairment; CP: cerebral palsy; DQ: development quotient

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Competing Interests

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