ORIGINAL ARTICLE

Cardiac effects of a single course of antenatal betamethasone in preterm infants

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Aim: To show the effects of a single course of antenatal betamethasone on cardiac measurements and systolic functions in premature newborn infants.

Methods: Seventy six newborn infants with a gestational age of 25–33 weeks were included in the study. They were first classified according to their gestational age: 25–29 weeks (n = 28) and 30–33 weeks (n = 48). They were then reclassified as betamethasone positive (mother received one course of betamethasone) or betamethasone negative (mother did not receive any antenatal glucocorticoid treatment). Cross sectional M mode echocardiographic scans were performed during the first three postnatal days and at the end of the first and third weeks. Left interventricular septum (IVS), left ventricular posterior wall (LVPW), left ventricular end diastolic (LVED), and left ventricular end systolic (LVES) dimensions, aortic root (AO), and left atrial diameters (LAs) were measured. The IVS to LVPW ratio was calculated to identify asymmetrical septal hypertrophy.

Results: In neither group was any statistically significant difference noted in IVS, LVED, LVES, LVPW, LA, and AO measurements during the three cardiac ultrasonography scans. Systolic function, as assessed by fractional shortening, was not significantly different in infants who received betamethasone antenatally, in either age group. There was no difference in the IVS/LVPW ratios between those who received antenatal steroid and those who did not for the 25–29 week and 30–33 week groups during these three consecutive scans.

Conclusion: One course of antenatal betamethasone did not affect the cardiac wall thicknesses and systolic function in premature infants.

Antenatal steroid treatment before preterm delivery is one of the best documented and most cost effective life saving treatments in perinatal medicine.¹ The recommended glucocorticoid regimens consist of two 12 mg doses of betamethasone given intramuscularly 24 hours apart or four 6 mg doses of dexamethasone given intramuscularly 12 hours apart. Multiple studies have documented improved outcomes of preterm infants born to mothers treated antenatally with glucocorticoids. Antenatal glucocorticoid administration to the mothers improves postnatal outcomes of the neonates by decreasing the incidence of respiratory distress syndrome, intraventricular haemorrhage, retinopathy of prematurity, and neonatal ductus arteriosus.^{2–5} The consensus statement of the American National Institutes of Health recommends administration of antenatal corticosteroids to all patients at risk of preterm delivery before 34 weeks gestation.⁶ However, some neurological adverse effects, such as decreased head circumference at birth and delayed psychomotor development, have been noted, particularly for those who received multiple courses of antenatal corticosteroids.^{7–8} Although some adverse cardiac effects (increased septal and left posterior wall thickness and decreased left ventricular filling) of postnatal corticosteroid treatment have been reported, to the best of our knowledge, there has been no prospective study that investigated the effects of antenatal glucocorticoid administration on cardiac dimensions of human newborn infants.^{9–10} In this study we aimed to determine the effects of a single course of antenatal betamethasone on cardiac measurements and systolic function in premature newborn infants.

METHODS

This prospective cohort study was carried out in the neonatal intensive care unit of Cerrahpasa Medical Faculty Hospital

between August 2003 and January 2005. Seventy six newborn infants with a gestational age of 25–33 weeks were included in the study. The patients were first classified according to their gestational age: 25–29 weeks and 30–33 weeks. They were then reclassified as betamethasone positive (mother received two 12 mg doses of betamethasone given intramuscularly 24 hours apart) or betamethasone negative (mother did not receive any antenatal glucocorticoid treatment). Infants who did not receive a complete antenatal treatment regimen and those who received multiple courses (more than two injections) were excluded from the study. Infants who were not born within two weeks of the last dose of betamethasone and those who were born before a period of 12 hours had elapsed after the last injection were also excluded. As antenatal glucocorticoid was systematically administered in our maternity hospital (12 mg betamethasone intramuscularly repeated once in 24 hours for two doses) to patients at risk of premature delivery at 24–33 weeks gestation, this classification was not performed randomly, and the betamethasone negative group was composed of mothers who were not followed up in our hospital.

Echocardiographic scans were obtained during the first three postnatal days and at the end of the first and third weeks with a Philips ATL HDI-3500, using a 7–4 MHz transducer. Patients were examined in the supine position; the left ventricle was studied from cross sectional, parasternal long axis views on cross sectional M mode echocardiography. The following dimensions were measured by M mode examinations at mitral chord level: left interventricular

Abbreviations: AO, aortic root; IVS, left interventricular septum; LA, left atrial diameter; LVED, left ventricular end diastolic dimension; LVES, left ventricular end systolic dimension; LVPW, left ventricular posterior wall

Table 1 Characteristics of newborn infants in study

	Gestational age 25–29 weeks			Gestational age 30–33 weeks		
	Betamethasone positive	Betamethasone negative	p Value	Betamethasone positive	Betamethasone negative	p Value
Number	14	14		23	25	
Gestational age (weeks)	27.3 (1.3)	28.1 (0.9)	0.063	31.5 (1.3)	31.0 (0.9)	0.579
Apgar 1 minute	3.3 (1.8)	4.5 (2.4)	0.222	4.9 (1.8)	4.4 (2.3)	0.394
Apgar 5 minute	6.0 (1.8)	6.2 (2.0)	0.793	6.9 (1.4)	6.7 (1.9)	0.99
CRIB score	5.6 (2.6)	5.4 (3.7)	0.676	1.6 (1.1)	2.9 (2.8)	0.058
Age at 1st cardiac ultrasonography	2.2 (1.5)	1.9 (1.1)	0.804	2.5 (1.3)	2.1 (0.9)	0.441
Age at 2nd cardiac ultrasonography	7.0 (1.0)	7.3 (1.3)	0.517	7.7 (0.8)	7.3 (1.1)	0.056
Age at 3rd cardiac ultrasonography	21.0 (1.1)	21.3 (0.8)	0.141	24.3 (5.6)	22.3 (2.5)	0.784

Values are mean (SD).

CRIB, Clinical risk index for babies.

septum (IVS), left ventricular posterior wall (LVPW), left ventricular end diastolic dimension (LVED), and left ventricular end systolic dimension (LVES). Aortic root (AO) and left atrial diameters (LAs) were measured in diastole at the level of the aortic valves. The IVS to LVPW ratio was calculated to identify asymmetrical septal hypertrophy. The measurements were carried out using cutting edge methodology following the American Society of Echocardiography recommendations,¹¹ as adapted by Silverman¹² for premature babies. All measurements were repeated three times during the same echocardiographic examination, and results were averaged. The observer's (VM) own variability was evaluated, and measurements showed consistent variations of less than 4%. The observer was completely unaware of the classification of the newborns. Newborns with any major cardiac malformations or infants of diabetic mothers were excluded from the study. None of the infants received postnatal corticosteroid treatment. Gestational age was calculated from the date of the last menstrual period for those women who were certain of this date and confirmed by an ultrasonographic examination when possible. In case of any doubt, a physical examination was performed to determine gestational age.¹³

The ethics committee of Cerrahpasa Medical Faculty approved the study, and all parents of participating patients gave informed consent.

Statistical analyses were performed using χ^2 analysis for categorical data and the Mann-Whitney U test for continuous data. Statistical significance was defined as $p \leq 0.05$. All data are given as mean (SD) unless otherwise indicated.

RESULTS

Seventy six infants were enrolled in the study. Twenty eight were in the group with gestational age 25–29 weeks, and the remaining 48 in the group with gestational age 30–33 weeks.

Newborns in both groups were than reclassified as those who received antenatal betamethasone and those who did not. Table 1 presents the characteristics of each group (25–29 weeks and 30–33 weeks gestational age).

In neither group was there any statistically significant differences in gestational age, Apgar score, CRIB score, or the age at first, second, or third ultrasonographic scan. In the 25–29 week group, four infants were from a multiple pregnancy (two in the betamethasone positive group and two in the betamethasone negative group). In the 30–33 week group, 18 infants were from a multiple pregnancy (11 in the betamethasone positive group and seven in the betamethasone negative group). The median of the period between the last injection and birth was one day and 2.5 days for the 25–29 week and 30–33 week groups respectively. In neither group was any significant difference in IVS, LVED, LVES, LVPW, LA, and AO measurements noted during the three cardiac ultrasonographic scans. Systolic function, as assessed by fractional shortening, was not significantly different in infants who received betamethasone antenatally, in either age group. There was no difference in the IVS/LVPW ratio between those who received antenatal steroid and those who did not for either gestational age group during the three scans. Tables 2–4 present these results.

Developmental changes in IVS and LVPW dimensions were evaluated by looking at the differences in measurements between the first and second and first and third ultrasonographic scans (table 5). Small changes were noted for both the 25–29 and 30–33 week infants, but no significant differences were found between the betamethasone positive and negative groups.

DISCUSSION

In this study, we investigated whether antenatal betamethasone administration had an effect on cardiac dimensions or

Table 2 Cardiac dimensions of newborn infants at the first ultrasonographic scan

	Gestational age 25–29 weeks			Gestational age 30–33 weeks		
	Betamethasone positive	Betamethasone negative	p Value	Betamethasone positive	Betamethasone negative	p Value
Number	12	12		23	21	
IVS (cm)	0.31 (0.05)	0.33 (0.09)	0.516	0.36 (0.08)	0.36 (0.07)	0.522
LVED (cm)	1.15 (0.17)	1.26 (0.13)	0.062	1.34 (0.18)	1.38 (0.18)	0.588
LVES (cm)	0.77 (0.16)	0.82 (0.16)	0.061	0.83 (0.15)	0.89 (0.14)	0.241
LVPW (cm)	0.21 (0.03)	0.22 (0.04)	0.546	0.28 (0.04)	0.25 (0.05)	0.175
LA (cm)	0.75 (0.16)	0.84 (0.17)	0.149	0.82 (0.15)	0.83 (0.14)	0.915
AO (cm)	0.64 (0.08)	0.66 (0.08)	0.093	0.79 (0.09)	0.76 (0.11)	0.417
FS (%)	0.36 (0.06)	0.34 (0.08)	0.621	0.38 (0.04)	0.36 (0.05)	0.078
IVS/LVPW ratio	1.48 (0.31)	1.57 (0.27)	0.411	1.29 (0.29)	1.49 (0.46)	0.226

IVS, Left interventricular septum; LVED, left ventricular end diastolic dimensions; LVES, left ventricular end systolic dimensions; LVPW, left ventricular posterior wall; LA, left atrium; AO, aortic root; FS, fractional shortening.

Table 3 Cardiac dimensions of newborn infants at the second ultrasonographic scan

	Gestational age 25–29 weeks			Gestational age 30–33 weeks		
	Betamethasone positive	Betamethasone negative	p Value	Betamethasone positive	Betamethasone negative	p Value
Number	11	10		23	25	
IVS (cm)	0.35 (0.07)	0.34 (0.05)	0.875	0.38 (0.06)	0.38 (0.06)	0.533
LVED (cm)	1.03 (0.10)	1.13 (0.12)	0.056	1.38 (0.17)	1.31 (0.17)	0.261
LVES (cm)	0.62 (0.06)	0.68 (0.10)	0.055	0.89 (0.14)	0.79 (0.16)	0.052
LVPW (cm)	0.25 (0.05)	0.26 (0.07)	0.815	0.26 (0.05)	0.26 (0.05)	0.581
LA (cm)	0.73 (0.13)	0.75 (0.13)	0.638	0.85 (0.17)	0.78 (0.17)	0.172
AO (cm)	0.68 (0.06)	0.69 (0.09)	0.879	0.81 (0.08)	0.79 (0.12)	0.751
FS (%)	0.41 (0.06)	0.40 (0.06)	0.696	0.36 (0.04)	0.39 (0.08)	0.052
IVS/LVPW ratio	1.44 (0.36)	1.36 (0.21)	0.663	1.55 (0.48)	1.54 (0.36)	0.799

IVS, Left interventricular septum; LVED, left ventricular end diastolic dimensions; LVES, left ventricular end systolic dimensions; LVPW, left ventricular posterior wall; LA, left atrium; AO, aortic root; FS, fractional shortening.

systolic function or produced cardiac hypertrophy in preterm neonates. We did not observe any significant differences in cardiac dimensions, fractional shortening, or IVS/LVPW ratio during the first three days or after the first and third week of life between neonates whose mothers did or did not receive antenatal betamethasone.

Both dexamethasone and betamethasone readily cross the placenta, are active for longer than cortisol, and are weakly immunosuppressive and devoid of mineralocorticoid activity.¹⁴ Antenatal betamethasone is becoming more widely used for women at risk of preterm delivery, especially for its beneficial effects on pulmonary morbidity of the premature newborn. In a recent meta-analysis, in which randomised antenatal corticosteroid administration was investigated in 3700 preterm babies, its use was found to be associated with decreased mortality and lower incidence of respiratory distress syndrome and intraventricular haemorrhage.¹⁵ In an observational cohort study of surviving infants with birth weight less than 1250 g, Higgins *et al*¹⁶ showed that antenatal dexamethasone administration decreased the incidence of severe retinopathy of prematurity. Postnatal use of steroids, especially dexamethasone, has also been well investigated in animal and human studies. Muangmingsuk *et al*¹⁷ showed in an animal model that dexamethasone induced cardiac hypertrophy in newborn rats through its effect on myosin heavy chain phenotype and gene transcription.

The effects of corticosteroids on cardiac wall measurements have also been shown in human neonates, although the mechanism of the effect is not well understood. In the era when chronic lung diseases were treated for long periods with dexamethasone, Bensky *et al*¹⁸ investigated very low birthweight infants who received either a 42 day tapering course of dexamethasone or a saline placebo. Patients receiving dexamethasone showed a significantly larger

increase in septal thickness on days 7, 14, and 28 and in LVPW thickness on day 14.

Skelton *et al*¹⁹ also showed that left ventricular hypertrophy developed in almost all preterm neonates receiving a 2–3 week course of dexamethasone, but it was of little clinical importance and always resolved. They found that the left ventricular hypertrophy associated with dexamethasone was quite uniform, affecting the septum and free wall to the same extent. This distribution was different from those seen in other conditions. In familial hypertrophic cardiomyopathy and infants born to diabetic mothers, the hypertrophy affected the septum rather than the LVPW. Glennon *et al*²⁰ explained this cardiac hypertrophy as being a result of hypertrophy of the myocytes, rather than division, through synthesis of various intracellular cardiac proteins, rather than deposition of substances, at a cellular level. Synthesis of such cardiac proteins could occur within 48 hours of an appropriate stimulus on cardiac receptors.

Yunis *et al*²¹ reported on three infants whose mothers had received repeated (five to sixteen) courses of antenatal corticosteroids. All three infants developed transient hypertrophic cardiomyopathy in a dose dependent fashion.

Skelton *et al*²² in another study in which they tried to establish reference ranges for cardiac dimensions and blood velocity in preterm infants, reported that there was no difference in IVS and LVPW dimensions of babies who received antenatal dexamethasone compared with those who did not. In fact, the main aim of that study was not to show the effect of dexamethasone on cardiac dimensions, and therefore no basic non-clinical data or cardiac dimensions were reported for the two populations. Although both betamethasone and dexamethasone are recommended by the American National Institutes of Health when there is a risk of preterm delivery, betamethasone has become the

Table 4 Cardiac dimensions of newborn infants at the third ultrasonographic scan

	Gestational age 25–29 weeks			Gestational age 30–33 weeks		
	Betamethasone positive	Betamethasone negative	p Value	Betamethasone positive	Betamethasone negative	p Value
Number	11	13		23	21	
IVS (cm)	0.36 (0.07)	0.37 (0.08)	0.536	0.38 (0.07)	0.37 (0.08)	0.814
LVED (cm)	1.13 (0.12)	1.22 (0.09)	0.078	1.49 (0.13)	1.45 (0.19)	0.349
LVES (cm)	0.70 (0.13)	0.78 (0.14)	0.176	0.96 (0.09)	0.90 (0.17)	0.229
LVPW (cm)	0.027 (0.08)	0.32 (0.08)	0.156	0.27 (0.06)	0.27 (0.05)	0.501
LA (cm)	0.85 (0.14)	0.92 (0.12)	0.396	1.07 (0.19)	0.94 (0.23)	0.055
AO (cm)	0.69 (0.07)	0.74 (0.05)	0.396	0.86 (0.08)	0.83 (0.14)	0.298
FS (%)	0.38 (0.05)	0.39 (0.07)	0.071	0.36 (0.04)	0.38 (0.06)	0.232
IVS/LVPW ratio	1.41 (0.42)	1.20 (0.30)	0.341	1.40 (0.52)	1.42 (0.37)	0.991

IVS, Left interventricular septum; LVED, left ventricular end diastolic dimensions; LVES, left ventricular end systolic dimensions; LVPW, left ventricular posterior wall; LA, left atrium; AO, aortic root; FS, fractional shortening.

Table 5 Developmental changes in IVS and LVPW dimensions

	Gestational age 25–29 weeks			Gestational age 30–33 weeks		
	Betamethasone positive	Betamethasone negative	p Value	Betamethasone positive	Betamethasone negative	p Value
Difference between 1st and 2nd scan						
Number	10	9		20	20	
IVS (cm)	0.030 (0.082)	0.0330 (0.087)	0.927	0.028 (0.083)	0.018 (0.062)	0.385
LVPW (cm)	0.040 (0.051)	0.056 (0.073)	0.707	(–)0.029 (0.09)	(–)0.003 (0.073)	0.438
Difference between 1st and 3rd scan						
Number	10	11		19	18	
IVS (cm)	0.029 (0.081)	0.046 (0.103)	0.501	0.022 (0.101)	0.001 (0.076)	0.562
LVPW (cm)	0.048 (0.084)	0.100 (0.077)	0.138	(–)0.010 (0.075)	0.018 (0.069)	0.274

IVS, Left interventricular septum; LVPW, left ventricular posterior wall.

preferred drug because it reduces neonatal mortality and decreases periventricular leucomalacia compared with dexamethasone.^{15–23}

Our study is the first prospective study that is specially designed to evaluate the effects of antenatal betamethasone treatment on cardiac dimensions and function. As, in our maternity unit, antenatal betamethasone is administered systematically to mothers with a risk of premature birth at 24–34 weeks gestation, it was not possible to randomise patients. That is why mothers who did not receive this treatment are generally those not followed up in our hospital.

Reference ranges for cardiac dimensions in 79 preterm infants of 23–33 weeks gestation were reported by Skelton *et al.*²² Most of our results were similar to those reported in that study. We found no difference between betamethasone positive and betamethasone negative groups in either gestational age group throughout the period of the three scans.

A ratio of more than 1.3 is usually taken in adult cardiology to indicate asymmetrical septal hypertrophy. This ratio is less accurately defined for newborns, especially preterm newborns. Skelton *et al.*²² showed that normal preterm infants may have asymmetrical septal hypertrophy. Although they reported that the IVS/LVPW ratio was above 1.3 in 12% of babies, they did not give the absolute values. Tables 2–4 show our IVS/LVPW ratios. We also found that there was a tendency towards asymmetrical septal hypertrophy in our group of premature newborns, but no significant differences were noted between groups. We think that this asymmetrical septal hypertrophy should be considered a physiological one. We show that antenatal betamethasone did not change this ratio.

One of our aims was to show if antenatal betamethasone had any effect on IVS and LVPW dimensions during a defined period after birth. We followed our patients until the chronological age of 3 weeks and studied the changes in these cardiac dimensions over time. Like Skelton *et al.*²² we also noted some small changes in most of the measurements in both gestational age groups between the first and second and first and third ultrasonographic scans. These differences were noted in both betamethasone positive and negative groups but were not significant. We considered this to be normal progression of cardiac dimensions over time. Antenatal betamethasone had no effect on the development of either IVS or LVPW.

The results of our study suggest that antenatal betamethasone does not have any effect on cardiac wall thicknesses and systolic function. Although antenatal corticosteroid application has different influences on pulmonary and vascular structures and although postnatal corticosteroid administration may be accompanied by increased cardiac wall thickness, the mechanism of the effect of corticosteroids on the heart and its clinical correlation are still under investigation. An interesting point is why antenatal administration of

What is already known on this topic

- Antenatal betamethasone has positive effects on different systems (increased pulmonary maturation, decreased risk of intraventricular haemorrhage, etc)
- Postnatal corticosteroid treatment has the risk of increasing cardiac wall thickness

What this study adds

- One course of antenatal betamethasone did not alter cardiac wall thickness, systolic function, or IVS/LVPW ratio in infants born within two weeks of the last injection

betamethasone does not cause any differences in cardiac indices whereas postnatal treatment does. The pharmacokinetics of betamethasone in pregnant women in preterm labour is not very well understood. It is even less well understood when the pregnancy is a multiple one. Betamethasone is probably mainly eliminated in the liver.²⁴ Ballabh *et al.*²⁵ showed that the half life of betamethasone in mothers with twin pregnancies was significantly (20%) shorter than in mothers with singleton pregnancies. In our study, 13 of the 37 newborn infants in the betamethasone positive group were from multiple pregnancies. Multiple fetoplacental units in multiple pregnancies probably result in greater metabolism of betamethasone. This may be one reason why a difference in cardiac dimensions was not detected in our group of neonates who received antenatal betamethasone compared with those who did not. We do not know the precise betamethasone concentrations required to induce either lung maturation or cardiac wall hypertrophy. We can speculate that transplacental transport of betamethasone was not sufficient in our group of infants to increase the heart wall dimensions.

Another important point is the time between the last dose of betamethasone and delivery. Ballabh *et al.*²⁵ showed that the longer the interval between the last dose of betamethasone and delivery the higher the cord and maternal blood betamethasone ratios in both singleton and twin pregnancies. They reported that the mean ratio of maternal and cord blood betamethasone was 3:1. However, when the last dose of betamethasone and delivery was more than five days, the ratio was reversed. In our study, it is unlikely that any hypertrophy due to antenatal betamethasone could resolve in the period between the last injection and birth, so we would not have been able to detect it even it had existed after the

treatment. To minimise the effect of this factor, we did not include infants born more than two weeks after the last (second) injection. The median time between the last injection and birth was one and 2.5 days for the 25–29 and 30–33 week group respectively. We think that this timescale for inclusion was justified. The data from the study of Skelton *et al.*¹⁹ in which they investigated very closely the natural history of left ventricular hypertrophy in premature infants who had received a three week course of postnatal dexamethasone, support our opinion. They show that the median time for maximum hypertrophy and resolution of hypertrophy were 10 and 26 days respectively after the beginning of the treatment. As all of our patients were investigated within two weeks of the last betamethasone injection (median times of one and 2.5 days for the two groups) and as they were followed until the chronological age of 3 weeks, we reason that no hypertrophy due to antenatal treatment could be missed.

Multiple courses (more than two betamethasone injections) were commonly used in the past if the interval between the last dose of corticosteroid and birth was longer than one week. In view of animal and postnatal data on neurological disability, repetition of antenatal corticosteroid courses is considered unnecessary.¹ To have a more homogeneous group of premature infants and to avoid the possible cumulative effects of multiple courses on the heart, only infants who had received one course (two injections) of betamethasone were included in our study.

In this study, we show that one course of antenatal betamethasone did not change the cardiac wall thicknesses, systolic function, and IVS/LVPW ratio in infants born within two weeks of the last injection. This antenatal treatment can be used safely without any cardiac side effects. In future studies, cardiac effects of antenatal betamethasone could be determined even more precisely by also incorporating fetal echocardiography.

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