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Original article

Effect of antenatal betamethasone on early systemic inflammatory indices in preterm infants with gestational age < 32 weeks

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Abstract

Introduction: Antenatal glucocorticoid (AGC) therapy is routinely given to pregnant women when preterm delivery is expected. Systemic inflammatory indices are thought to have predictive value in some neonatal diseases. However, the effect of AGC on systemic inflammatory indices is unknown. The aim of this study was to evaluate the effect of AGC treatment on systemic inflammatory indices, morbidities and mortality in preterm infants.

Methods: All preterm babies born at < 32 weeks of gestation were evaluated retrospectively and included in the study. Systemic inflammatory indices, demographic characteristics and clinical results were compared by dividing the babies into groups based on the application of AGC to their mothers (24 mg betamethasone, 12 mg betamethasone and non-AGC).

Results: A total of 869 preterm infants were evaluated in the study. As the use of AGC increased, respiratory distress syndrome and mortality were found to decrease significantly ($p < 0.001$ and $p = 0.018$, respectively). No effect of AGC on other preterm morbidities and systemic inflammatory indices was detected ($p > 0.05$).

Conclusion: AGC had no effect on systemic inflammatory indices in preterm infants. The effect of AGC, especially on the lung, may be due to local effects rather than systemic effects.

Keywords

Antenatal steroid, betamethasone, newborn, premature, systemic inflammatory indices, morbidity.

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Introduction

Presently, there is an increased risk of preterm birth especially due to assisted reproductive techniques, increased number of multiple pregnancies, advanced maternal age and some additional reasons. Subsequently, premature morbidity and mortality are increasing due to the increased frequency of preterm birth. Therefore, additional interventions to reduce preterm morbidity and mortality are considered for pregnant women at risk of preterm delivery [1, 2]. Antenatal glucocorticoid (AGC) administration has been used as a part of standard care for the risk of preterm birth after its first appearance in 1972 [3, 4].

AGC treatment reduces preterm morbidities such as systemic infections, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC) and mortality [1-3, 5]. In accordance with the recommendations of the American College of Obstetricians and Gynecologists (ACOG), the Turkish Society of Neonatology's *Guideline on the management of respiratory distress syndrome and surfactant treatment* recommends performing AGC to all pregnant women at risk of preterm delivery [3, 6].

The effect of glucocorticoids on the clinical outcomes of preterm infants is thought to be due to their anti-inflammatory properties. However, little is known about the effect of AGC on systemic inflammation in preterm neonates [5]. There are conflicting results regarding AGC in studies evaluating interleukin and C-reactive protein (CRP) levels as indicators of postnatal inflammation in preterm infants [1, 2, 5]. Additionally, it is thought that ACG exerts its effect through the number and functions of natural killer, lymphocyte, and neutrophil cells [7-9]. In a small number of studies on systemic inflammatory indices in newborns, some systemic inflammatory indices have been found to be significant parameters that can be used in the diagnosis of hypoxic ischemic encephalopathy, patent ductus arteriosus (PDA), sepsis, retinopathy of prematurity (ROP), IVH, and NEC [10-15]. However, the effect of ACGs on early systemic inflammatory indices has not been evaluated before. According to the hypothesis of our study, systemic inflammatory indices may be affected in preterm infants due to the anti-inflammatory properties of ACG. Therefore, our study aimed to evaluate the possible effect of ACG on early systemic inflammatory indices, preterm morbidity and mortality in preterm babies born < 32 weeks of gestational age (GA).

Methods

Study design and patient selection

Our hospital serves as a reference hospital with a level 3 Neonatal Intensive Care Unit (NICU) with 150 incubators. In addition to approximately 16,000 births each year, 3,500 newborn babies are treated annually.

The study was performed between September 2019 and December 2021 on preterm infants born at < 32 weeks of gestation who were admitted to the NICU.

Inclusion criteria: infants < 32 weeks of gestation, all premature babies born in our hospital and admitted to the NICU as alive from the Delivery Room were included in the study.

Exclusion criteria: infants ≥ 32 weeks of gestation, those who died in the Delivery Room, those who were born in an external center and referred to our NICU, infants with major congenital anomalies, those with genetic diseases (e.g., trisomies), those with congenital hematological diseases were not included in the study.

The data of the infants included in the study were obtained from the hospital medical records. Demographic and clinical characteristics, complete blood count values of the patients were recorded.

Ethical approval was obtained from the Institutional Review Board.

Demographic and clinical characteristics

GA, birth weight (BW), gender, modes of delivery, preeclampsia, prolonged premature rupture of membranes (PPROM), chorioamnionitis, administration of antenatal steroid, Apgar score (at 5 minutes) were recorded.

Rupture of membranes occurring before 37 weeks of gestation was defined as PPROM. Chorioamnionitis is an infection with resultant inflammation of any combination of the amniotic fluid, placenta, fetus, fetal membranes, or decidua due to ascending polymicrobial bacterial infection. Diagnostic criteria for clinical chorioamnionitis are described as maternal fever with two of the following: maternal tachycardia, fetal tachycardia, uterine tenderness, foul odor of amniotic fluid, or maternal leukocytosis. Preeclampsia is identified by a blood pressure (BP) of 140/90 mmHg or greater after 20 weeks of gestation in a woman with previously normal BP and who has proteinuria (≥ 0.3 g protein in 24-h urine specimen).

Preterm morbidities

RDS, severe IVH (stage ≥ 3), hemodynamically significant PDA (hsPDA), early-onset sepsis (EOS), NEC (stage > 2), moderate/severe bronchopulmonary dysplasia (BPD), ROP and mortality were recorded.

Infants who needed surfactant due to respiratory distress were defined as RDS [3]. Patients with severe IVH (stage ≥ 3) identified by cranial ultrasonography were recorded [16]. Patients with hsPDA determined by Doppler echocardiography examination at the 72nd hour postpartum in addition to clinical findings were recorded [17]. EOS was defined as clinical or blood culture-positive sepsis starting at < 72 postnatal hours [18]. Infants with moderately or advanced (stage ≥ 2) NEC were enrolled [19]. Preterm infant was defined as moderate BPD if he or she needed < 30% oxygen at the postmenstrual age of 36 weeks, or severe BPD if he or she received positive pressure respiratory support or ≥ 30% oxygen demand [20]. Patients requiring treatment for ROP according to the preterm infant ROP screening program were enrolled [21].

Complete blood count analysis and systemic inflammatory indices

In accordance with the NICU protocol, blood samples are routinely taken at the postnatal 6th hour after delivery.

Complete blood count analysis was performed from blood samples taken into ethylenediaminetetraacetic acid tubes. Cell-Dyn 3700 automatic hemocytometer (Abbott, Abbott Park, IL, USA) device was used for analysis. Leukocyte (10^3/μL), platelet (10^3/μL), neutrophil (10^3/μL), monocyte (10^3/μL), lymphocyte (10^3/μL) count values obtained from complete blood count results were recorded.

N/L formula to calculate neutrophil-to-lymphocyte ratio (NLR), P/L formula for platelet-to-lymphocyte ratio (PLR), M/L formula for monocyte-to-lymphocyte ratio (MLR), P x N/L formula for systemic immune-inflammation index (SII), N x M/L formula for systemic inflammation response index (SIRI), and P x N x M/L formula for pan-immune-inflammation value (PIV) were used. Systemic inflammatory indices did not have a unit as they were ratios [10].

After the blood samples were centrifuged at 4,000 rpm, CRP (CRP latex HS, Roche kit, Roche Diagnostics, GmbH, Mannheim, Germany) and interleukin-6 (IL-6) (Siemens Diagnostic Product Corporation, Los Angeles, CA, USA) levels were studied.

Administration of antenatal glucocorticoids

AGC was applied to all pregnant women at risk of preterm delivery in accordance with the recommendations of ACOG and the Turkish Society of Neonatology.

Pregnant women were administered betamethasone at a dose of 12 mg intramuscularly twice, every 24 hours. The optimal benefit of first cure treatment continues from 24 hours to 7 days after the first dose. A complete administration could have been done 1 to 7 days (or more) [3, 6].

If the mother's cervix was fully dilated at the time of admission to the hospital, and if there was a risk situation for the mother or the fetus, emergency delivery was performed. Either AGC (betamethasone) could not be given to the pregnant women who had an emergency delivery or they gave birth after a single dose.

If delivery did not occur after the first dose, a second dose of steroid was administered at the 24th hour of the first dose and a cure was completed.

Pregnant women with threatened preterm labor received a second cure steroid regimen 2 weeks after the first cure.

Preterm infants were divided into three groups according to the administered AGC dose: 24 mg betamethasone (full course), 12 mg betamethasone (incomplete course) and non-AGC in the first cure.

These three groups were compared in terms of demographic features, clinical characteristics,

complete blood count analysis and systemic inflammatory indices, morbidities and mortality.

Data analysis

Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS®), version 20.0 (SPSS Inc, Chicago, IL, USA) program. The Kolmogorov-Smirnov test, which includes histograms and analytical methods, was used to examine the distribution of patients' variables. Fisher's Exact test or Pearson Chi-Square test was used for the analysis of categorical variables. The Mann-Whitney U test or t test was used for statistical analysis of continuous variables. Normally distributed continuous variables were expressed as mean ± standard deviation (SD), abnormally distributed continuous variables were expressed as median and interquartile range (IQR), and categorical variables were expressed as frequency. One-way ANOVA test was used to compare more than two groups. If p-value was < 0.05, it was considered statistically significant.

Results

A total of 911 patients with < 32 week of gestation were evaluated during the study period. According to exclusion criteria, 42 patients were excluded from the study. As a result, a total of 869 preterm infants born at GA < 32 weeks were included in the study. 24 mg AGC was used in 40.5% (n = 352) of the patients, 12 mg AGC was used in 28.1% (n = 244) and 31.4% (n = 273) of the patients did not use AGC (non-AGC group).

In our study, the results were similar among the three groups in terms of GA, BW, gender, cesarean section, preeclampsia, PPROM, chorioamnionitis, Apgar score (at 5 minutes), IVH, hsPDA, EOS, NEC, BPD and ROP (p > 0.05). It was found that the frequency of RDS and mortality decreased significantly as the application dose of AGC increased (p < 0.001 and p = 0.018, respectively) (**Tab. 1** and **Tab. 2**). There was no statistically significant difference among the groups in terms of leukocyte, platelet, neutrophil, monocyte, lymphocyte count, NLR, MLR, PLR, PIV, SII, SIRI, CRP and IL-6 (p > 0.05) (**Tab. 3**).

Table 1. Comparison of demographic characteristics in the groups.

Characteristics	24 mg AGC (n = 352, 40.5%)	12 mg AGC (n = 244, 28.1%)	Non-AGC (n = 273, 31.4%)	ANOVA p-value
GA (weeks), mean ± SD	28.2 ± 1.1	28.3 ± 1.2	28.0 ± 1.2	0.113
BW (g), mean ± SD	1,073 ± 221	1,039 ± 230	1,062 ± 231	0.194
Male gender, n (%)	183 (51.9)	120 (49.1)	137 (50.1)	0.785
Cesarean section, n (%)	297 (84.3)	203 (83.1)	233 (85.3)	0.789
Preeclampsia, n (%)	71 (20.1)	51 (20.9)	54 (19.7)	0.590
PPROM, n (%)	86 (34.4)	45 (18.4)	47 (17.2)	0.056
Chorioamnionitis, n (%)	71 (20.1)	27 (11.0)	32 (11.7)	0.076
Apgar score (at 5 minutes), median (IQR)	8 (1)	7 (2)	7 (2)	0.066

AGC: antenatal glucocorticoid (betamethasone); BW: birth weight; GA: gestational age; IQR: interquartile range; PPROM: prolonged premature rupture of membranes; SD: standard deviation.

Table 2. Comparison of clinical outcomes in the groups.

Characteristics	24 mg AGC (n = 352, 40.5%)	12 mg AGC (n = 244, 28.1%)	Non-AGC (n = 273, 31.4%)	ANOVA p-value
RDS, n (%)	137 (38.9)	128 (52.5)	186 (68.1)	**< 0.001** [a]
Severe IVH (stage ≥ 3), n (%)	26 (7.3)	20 (8.2)	29 (10.6)	0.204
hsPDA, n (%)	114 (32.3)	100 (40.9)	103 (37.7)	0.088
EOS, n (%)	36 (10.2)	39 (15.9)	49 (17.9)	0.053
NEC (stage ≥ 2), n (%)	8 (2.2)	9 (3.6)	3 (1.1)	0.074
BPD, n (%)	47 (13.3)	46 (18.8)	52 (19.0)	0.187
ROP, n (%)	28 (7.9)	23 (9.4)	24 (6.8)	0.995
Mortality, n (%)	43 (12.2)	45 (18.4)	55 (20.1)	**0.018** [a]

[a] P-value < 0.05 was considered statically significant.
AGC: antenatal glucocorticoid (betamethasone); BPD: bronchopulmonary dysplasia; EOS: early-onset sepsis; hsPDA: hemodynamically significant patent ductus arteriosus; IVH: intraventricular hemorrhage; NEC: necrotising enterocolitis; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity.

Table 3. Systemic inflammatory indices according to antenatal steroid therapy administration.

Parameters	24 mg AGC (n = 352, 40.5%)	12 mg AGC (n = 244, 28.1%)	Non-AGC (n = 273, 31.4%)	ANOVA p-value
Leukocyte count ($10^3/\mu$L), median (IQR)	11.05 (8.00)	11.30 (8.40)	11.30 (9.67)	0.326
Platelet count ($10^3/\mu$L), median (IQR)	231 (105)	220 (96)	227 (110)	0.116
Neutrophil count ($10^3/\mu$L), median (IQR)	2.32 (2.40)	2.08 (2.63)	2.34 (2.86)	0.428
Monocyte count ($10^3/\mu$L), median (IQR)	0.66 (0.75)	0.67 (0.67)	0.67 (0.72)	0.329
Lymphocyte count ($10^3/\mu$L), median (IQR)	7.00 (5.71)	7.43 (6.70)	7.56 (6.58)	0.326
NLR, median (IQR)	0.31 (0.32)	0.31 (0.44)	0.31 (0.40)	0.092
MLR, median (IQR)	0.09 (0.05)	0.08 (0.06)	0.09 (0.06)	0.105
PLR, median (IQR)	32.76 (30.40)	31.88 (28.36)	33.76 (33.60)	0.064
PIV, median (IQR)	48.62 (46.62)	42.09 (51.53)	44.59 (56.07)	0.350
SII, median (IQR)	75.34 (81.73)	68 (75.73)	79.54 (65.58)	0.315
SIRI, median (IQR)	0.21 (0.30)	0.19 (0.33)	0.20 (0.37)	0.242
CRP (mg/L), median (IQR)	1.00 (1.51)	1.19 (1.36)	1.3 (1.58)	0.056
IL-6 (pg/mL), median (IQR)	39.15 (105.23)	35.50 (89.10)	43.17 (133.43)	0.751

AGC: antenatal glucocorticoid (betamethasone); CRP: C-reactive protein; IL-6: interleukin 6; IQR: interquartile range; MLR: monocyte-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PIV: pan-immune-inflammation value; PLR: platelet-to-lymphocyte ratio; SII: systemic immune inflammation index; SIRI: systemic inflammation response index.

Discussion

AGC treatment, which is one of the standard treatments applied to pregnant women who are expected to have preterm birth, to increase the pulmonary maturity of the babies, can reduce some preterm morbidities and mortality [3]. Similar to previous studies, we showed that AGC treatment had no effect on premature morbidity and could only reduce the frequency of RDS and mortality [1, 2]. It has been shown that AGC treatment has no effect on leukocyte lineage cells, CRP and IL-6. Additionally, we determined for the first time that AGC had no effect on early postnatal systemic inflammatory indices in premature infants.

Glucocorticoids play an important role in perinatal and neonatal medicine. The use of glucocorticoids has positive effects on many systems such as lung, brain and gastrointestinal system of preterm infants. The precise mechanisms underlying the beneficial effects of perinatal glucocorticoids have not yet been clarified. The genomic effects of glucocorticoids are known to occur through the binding of ligand-dependent transcription factors to the glucocorticoid receptor (GR), a member of the nuclear receptor family. Glucocorticoids can then alter the expression of specific target genes. However, given specific disease models, it is unclear whether the specific effects of glucocorticoids occur through this mechanism or through other non-genomic effects [22, 23].

In our study, it was found that the frequency of RDS decreased significantly as the dose of AGC increased. This is due to the important effects of AGC on the developing fetal lung during the maturation process of the lung, including alveolar differentiation, thinning of the alveolar septa and capillary walls, and upregulation of surfactant production [24]. In addition to these effects on pulmonary development, AGC accelerates normal lung development by increasing antioxidant activity and decreasing reactive oxygen species [25]. As in our study, although the mechanisms of AGC are unclear, it decreases RDS by increasing fetal pulmonary adaptation at birth [23]. In addition, AGC can reduce mortality with its positive respiratory effects, as it was found in our results [3, 23].

Antenatal steroids are known to alter functions such as cell proliferation, apoptosis, phagocytosis and the production of colony-stimulating factors and anti-inflammatory cytokines. Steroids may have effects such as an increase in leukocyte and neutrophil counts, and a decrease in lymphocyte and monocyte counts [1, 7, 26, 27]. However, conflicting results have been reported by previous studies regarding the effects of AGCs on hematological parameters [1, 2, 7, 8, 26]. In our results, no effects of AGC on hematological parameters and systemic inflammatory indices were demonstrated. In addition, CRP and IL-6 levels do not seem to be affected. The possible reason why AGCs do not affect hematological parameters may

be due to the local effects of AGCs, especially on the pulmonary receptor and gene regulation, rather than their systemic effects in preterm infants [28].

To understand the effects of glucocorticoids, it is necessary to understand the role of the intracellular and predominantly cytoplasmic receptor, the GR. Even in early pregnancy, GR is abundant in human fetal tissues. However, the number of receptors varies depending on cell types and GA. In the second month of pregnancy, cortisol binds to human fetal lung tissues with high affinity. In this period, there is intense GR expression in the bronchial epithelium and terminal sac canaliculi in the lung. Subsequently, high local glucocorticoid concentrations are observed in human fetal lung tissue with increased GR expression. Although the exact cellular localization of GR in fetal lung tissue has not been determined, abundant GR mRNA and GR are found in all cells of the adult lungs and airways.

The presence of steroid receptor gene expression in the fetus suggests that glucocorticoids are an important regulatory factor. High GR levels are found mainly in airway epithelial cells, bronchial vessels, and alveolar wall, in addition to inflammatory cells such as mast cells, eosinophils, T-lymphocytes, dendritic cells, and monocytes/macrophages. Most of these cells respond to corticosteroids and may explain the local effects of the glucocorticoids [28, 29]. As in our study, the mechanism underlying the reduction of RDS by AGC without affecting the number of leukocyte immune cell lines and systemic inflammatory indices can be explained in this way. In addition, induction of antioxidant enzymes and up-regulation of genes occur in fetal lung when beta-receptors are stimulated via AGC. Thus, the release of surfactant into the alveoli and the absorption of sodium and lung fluid from the pulmonary epithelium occur after birth. As a result, AGC leads to structural and biochemical changes that improve both lung mechanics and gas exchange by accelerating the development of type 1 and type 2 pneumocytes [30, 31].

It has been shown that genes such as *ERK3* positively affect bronchial and saccular development in the lung, increase surfactant production from type II alveolar cells, and accelerate epithelial maturation [32]. Glutathione-S-transferase-P1 I105V (*GST-P1*) gene polymorphism has also been shown to have an effect on lung development [22]. Therefore, the effects of AGC on gene expression are mediated by pulmonary receptors rather than its systemic effect, while AGC has a positive effect on RDS. The fact that it has no effect on hematological parameters and systemic inflammatory indices can be explained in this way. Our results found that AGC basically reduced RDS, and this result supports the knowledge that AGCs are more effective on preterm problems, especially in the first 48 hours, in addition to reducing mortality in preterm infants [1-3]. Based on those findings, the effectiveness of AGC in reducing mortality in our patients seems to be an expected result.

In adult studies, some systemic inflammatory indices have been shown to have both diagnostic and prognostic value in infectious diseases, malignancies, cardiac and pulmonary diseases [33-36]. Studies on the use of systemic inflammatory indices in the diagnosis and follow-up in the field of neonatology are few. It has been reported that while NLR, PIV, SII, and SIRI increase in HIE in term infants, MLR decreases significantly [10]. It was reported that PLR increases in hsPDA; NLR and PLR increase in EOS; NLR increases in IVH, NEC and ROP [11-15]. These results show that systemic inflammatory indices can be used in the diagnosis and follow-up of neonatal diseases. Moreover, it is noteworthy that some indices become significant in neonatal diseases, while others are meaningless. This may be due to the fact that neonatal diseases have different pathophysiologies. Therefore, the relationship between systemic inflammatory indices should be evaluated separately according to each gestational week and diagnosis of each neonatal disease.

The effect of ACGs on systemic inflammatory indices has not been evaluated before. According to the hypothesis of our study, considering the effects of steroids on the immune system, AGCs may affect the systemic inflammatory indices. Thus, changes in systemic inflammatory indices may affect clinical outcomes in preterms. In our study, the possible effect of AGC on the most frequently examined systemic inflammatory indices in the literature was evaluated. However, it was found that AGC did not affect either immune cell counts or systemic inflammatory indices. According to our results, AGC does not affect systemic inflammatory indices, and it may mean that it does not affect preterm morbidities. In fact, the cause of many preterm morbidities is not only prenatal and natal. In addition, an increase in morbidity may develop as a result of adverse conditions (such as sepsis, mechanical ventilation)

experienced by the preterm baby in the postnatal period [20]. Therefore, it can be concluded from our results that the positive effect of AGC on RDS is probably due to its local effect on the pulmonary system [22, 28, 29, 32].

Limitations

Our study has some limitations as it was conducted in a single center and the data were obtained retrospectively. In addition, we did not have maternal hematological parameters. The leukocyte subsets, functions of immune cells (apoptosis, phagocytosis, and chemotaxis), receptor and genetic relationship could not be evaluated. In our study, complete blood count was evaluated at the postnatal 6th hour. However, the postnatal complete blood count results of the patients and the effect on the clinical results could not be evaluated. Considering the shortcomings of our study, future studies may bring up the use of inflammation indicators such as systemic inflammatory indices more efficiently in preterm diseases.

Conclusion

The use of systemic inflammatory indices in neonatology is a new approach. In our study, it was found that AGC did not affect early systemic inflammatory indices in preterm infants with GA < 32 weeks, and did not change preterm morbidities, except for RDS. Also mortality did change. As the effect of AGC on the immune system in preterms becomes clear, its effect on systemic inflammatory indices can be better understood. Thus, significant progress can be made in immunological improvements in neonatal care. For this purpose, stronger randomized controlled prospective studies are needed.

Declaration of interest

The Authors declare no conflict of interests. The study did not receive any funding.

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