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Çocuklarda Kortikosteroid Tedavisinin Kardiovasküler Yan Etkisi

Adverse Cardiovascular Effect of Corticosteroid Therapy in Children

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ÖZ

GİRİŞ ve AMAÇ: Kortikosteroidler pediatri pratiğinde birçok klinik durum için sıkça kullanılır. Steroidlerin kronik kullanımına bağlı yan etkiler iyi bilinmesine rağmen, kısa süre kullanımda ortaya çıkan yan etkiler bakımından daha az farkındalık vardır. Bu çalışmada biz düşük, orta ve yüksek doz kortikosteroidle tedavi edilen hastalarda ilaç öncesi ve ilaç sonrası kan basınçlarını ve nabız hızlarını değerlendirmeyi amaçladık. Kortikosteroid kullanımının klinik yansımalarını tanımlamak için, kortikostroidle tedavi edilen ve edilmeyenlerin bulgularını karşılaştırdık.

YÖNTEM ve GEREÇLER: Çalışmaya akut viral bronşiolitis ve nefrotik sendrom nedeniyle kortikosteroid tedavisi alan, 0-16 yaş arasındaki hastalar dahil edildi. Hastalar alınan kortikosteroid dozuna göre üç alt gruba bölündü. Kontrol grubu corticosteroid tedavisi almayan hastalardan oluşturuldu.

BULGULAR: Hem kontrol grubunda, hem de grup-I ve grup-II de ilaç öncesi ve ilaç sonrası nabız hızları ortalaması arasında fark varken, pulse kortikosteroid alan grup-III'de ilaç öncesi ve ilaç sonrası ortalama nabız hızları arasında fark yoktu. Aşikar kardiak disritmi hiçbir grupta gözlenmedi.

TARTIŞMA ve SONUÇ: Bizim çalışmamız gösterdi ki, kortikosteroid kullanımı ile kardiak disritmiler arasında doğrudan bir nedensel ilişki yoktur. Muhtemeldir ki, kortikosteroid tedavisi sonrası gelişen disritmiler multi faktorialdir. Dolayısıyla, bu konuda herhangi bir yargıya varılmadan önce daha kapsamlı çalışmalar yapılmalıdır. Sebep ne olursa olsun, özellikle karaciğer hastalığı olan, kardiyak patolojisi olan veya kardiyak ilaç alan hastalar, disritmiler konusunda yakından izlenmelidir. Kortikosteroidlerin, aksi ispatlanana kadar kardiyak disritmileri presipite edebileceğinin farkında olunması önemlidir.

Anahtar Kelimeler: Kardiak disritmiler, kortikosteroidler, nabız hızı, yan etki

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SUMMARY

INTRODUCTION: Corticosteroids are widely used for many clinical conditions in pediatric practice. Although the adverse effects arising from the use of chronic corticosteroids are well-known, there is less awareness regarding the side effects emerging from use in short period. We aimed at evaluating the measurements of pre- and post-drug blood pressure and pulse rates in the patients treated with low, medium, and high doses of corticosteroids. To define the clinical reflections of corticosteroid treatment, we compared the findings of those treated with and without corticosteroids.

METHODS: Patients between 0-16 years of age who received corticosteroid treatment for acute viral bronchiolitis and nephrotic syndrome were included in the study. Patients were divided into three subgroups with respect to corticosteroid doses. The control group consisted of patients who did not receive corticosteroid treatment.

RESULTS: While there was difference between pre-drug and post-drug mean pulse rates in control group and group-I and group-II in the steroid group; there was no difference in group-III who received pulse corticosteroid therapy. No evident cardiac dysrhythmia was observed in any group.

DISCUSSION and CONCLUSION: Our study showed that there is no direct causal relationship between corticosteroid use and cardiac dysrhythmias. It is likely that dysrhythmias developing after corticosteroid treatment are multifactorial. So, more comprehensive studies must be performed before any judgment is reached in this topic. Whatever the reason, particularly patients with liver disease and those with cardiac pathology or taking cardiac drug must be closely monitored regarding dysrhythmias. It is important to be aware that corticosteroids can precipitate cardiac dysrhythmias until proven otherwise in other studies in large cohorts.

Keywords: Cardiac dysrhythmia, corticosteroids, pulse rate, side effect

Introduction

Corticosteroids are widely used for many clinical conditions in pediatric practice. However, they have some adverse effects, such as increased appetite, hyperglycemia, hypertension, mood changes, depression, osteoporosis, and Cushing's syndrome. Although the adverse effects arising from the use of chronic corticosteroids are well-known, there is less awareness regarding the side effects emerging from high doses used in short period. The rhythm changes due to corticosteroid therapies have mostly been reported in adults in recent years. These rhythm changes may be seen in the form of either tachyarrhythmias or bradyarrhythmias (1). Among these dysrhythmias are atrial fibrillation, premature atrial contractions, premature ventricular contractions and sinus tachycardia or bradycardia (2). Although generally asymptomatic and treated with simple observation, arrhythmias can sometimes cause symptoms, such as palpitation, chest pain, loss of consciousness, and even cardiac arrest (1-3). In this instance, arrhythmias are treated with chronotropic and antiarrhythmic agents, or temporary cardiac pacing administration.

How steroids cause dysrhythmias still remains a controversial entity. However, it has been shown in animal studies that high dose methyl-prednisolone has various effects on cardiovascular system, such as blunting of chronotropic response to catecholamines, particularly through β-1 receptor sensitivity (4). These effects may be due to both the direct action on electron exchange in myocardial cell membrane and alterations in sinoatrial node sensitivity to catecholamines (4-6). In addition, hypertension caused by corticosteroids and stimulating the baroreceptor-mediated reflex, and the resultant reduction in heart rate are other plausible explanations leading to bradyarrhythmias (1).

In our clinic, the sinusal bradycardia was noticed in two children treated with corticosteroid in the last several years. Upon scanning literature, we realized that the number of publications investigating the association between dysrhythmias and corticosteroids is limited. Moreover, most of the previous studies were case reports where adult patients had been investigated. Whereupon, the present case-control study was planned in order to investigate the association between corticosteroids and dysrhythmias. Given the widespread use of corticosteroids in the treatment of various ailments, it is important for physicians to be aware of their cardiac adverse effects.

In the present study, we aimed at evaluating the measurements of pre- and post-drug blood pressure (BP) and pulse rates in the patients treated with low, medium, and high doses of corticosteroids. To define the clinial reflections of corticosteroid treatment, we compared the findings of those treated with and without corticosteroids.

Methods

A total of 195 patients receiving corticosteroid treatment for acute viral bronchiolitis and nephrotic syndrome (NS) between 0-16 years of age were included into the study. Those with any cardiac pathology, undergoing cardiac surgery, or receiving cardiac drug were excluded from the study. All patients were monitored continuously during pre- and post-drug periods. The vital findings of the study participants, such as systolic and diastolic BP and pulse rates were measured before receiving drugs, and between the hours 0-6, 6-12, 12-18, 18-24, 24-48 and 96-104 after receiving drugs were recorded. To improve the reliability of the measurements, mean values were calculated for the patients with multiple measurements. The measurements performed when the patients had fever were ignored.

The patients were divided into three subgroups in accordance with corticosteroid doses as group-I (2mg/kg/day), group-II (10 mg/kg/day) and group-III (30 mg/kg/day). The control group consisted of the patients not receiving steroid treatment.

All statistical analyses were performed using SPSS for Windows, release 22.0 (SPSS, Chicago, IL, USA). The normality of data was tested using the Kolmogorov-Smirnov test. The descriptive statistical analyses were performed to calculate the averages and frequencies. The two-related samples test was used to compare the mean values of pre- and post-drug heart rate. The results were expressed as mean±standard deviation (SD), and a $p< 0.01$ value was accepted as statistical significance. The study was approved by the local ethics committee.

Results

The first patient inspiring the study was a 14-year-old male adolescent. After the oral methyl-prednisolone treatment was started at 2 mg/kg/day with the diagnosis of acute rheumatic fever (ARF), the patient developed bradycardia less than 50% of the baseline heart rate on the theurapeutic 3rd day. Atropine infusion was started, when the pulse rate dropped to 42/min, and a complaint of fatigue was detected in the patient. The bradycardia lasted for 8 days and resolved spontaneously. The second patient was also 13-years-old male adolescent. He was also given oral methyl-prednisolone therapy at a dose of 2 mg/kg/day with ARF diagnosis, and developed bradycardia less than 50% of the baseline heart rate on the theurapeutic 3rd day. Although the pulse rate fell under 48/min, the case was not symptomatic. Thus, atropine infusion was not initiated. The bradycardia in the second patient lasted for 4 days and resolved without intervention.

The entire study group consisted of 195 patients. Of all patients, 160 (82.1%) had been followed-up and treated due to acute viral bronchiolitis, and 35 (17.9%) due to NS (Table 1). Of the patients receiving corticosteroid treatment, 50 (34.5%) had received lower dose corticosteroids, and 74 (51%) had received middle dose, while 21 (14.5%) were treated with high dose corticosteroids. The control

group receiving no corticosteroid therapy was also composed of 50 patients. Mean age of the cases in the entire study group was 2 years [IQR 1.5-3] (min 1, max 16). Of all cases, 108 (55.4%) were boys, while 87 (44.6%) were girls.

Table 1. The some clinical features and distribution of groups.

	Indication					
	Acute Viral Bronchiolitis (n=160)				**Nephrotic Syndrome (n=35)**	
	Controls	Group-I	Group-II	Group-III	Group-I	Group-III
Subject (n)	50	36	74	0	14	21
Age	2±0.7 (min 1, max 3)				8.7±4.4 (min 1.5, max 16)	
Gender	88 (55%) male / 72 (45%) female				20 (57.1%) male/15 (42.9%) female	

Mean pre-drug pulse rates and post-drug pulse rates of the entire study group measured at the second-6th hours were 140±24.7 and 135.9±19.4, respectively (Table 2). A difference was observed between mean pre- and post-drug pulse rates in the entire study group ($p< 0.01$).

Table 2. Comparisons of pre-drug and post-drug pulse rates of groups.

Groups	Pre-drug pulse	Post-drug first 6th hours pulse	Post-drug second 6th hours pulse	p
Entire study groups	140±24.7	138.9±13.8	135.9±19.4	< 0.01*
Controls	143.4±16.3	130.9±11.8	136.5±14	< 0.01#
Group-I	132.4±21.1	133.2±10.5	137.5± 26.9	< 0.01£
Group-II	149.9±19.6	144.9±14.7	140.4±18.6	< 0.01§
Group-III	102.3±13.5	103.3±21.4	109.1±25.6	> 0.01¥

**: The difference was between pre-drug and post-drug second 6th hours pulse rates;*
#: The difference was between both pre-drug and post-drug first 6th hours and between pre-drug and post-drug second 6th hours pulse rates;
£: The difference was between pre-drug and post-drug second 6th hours pulse rates;
§: The difference was between pre-drug and post-drug second 6th hours pulse rates;
¥: No the difference was between both pre-drug and post-drug first 6th hours and between pre-drug and post-drug second 6th hours pulse rates.

Mean pre- and post-drug pulse rates of the control group at the second-6th hours were 143.4±16.3 and 136.5±14, respectively. There was a difference between mean pre- and post-drug pulse rates in control group ($p< 0.01$). Mean pre- and post-drug pulse rates of group-I at the second-6th hours were 132.4±21,1 and 137.5± 26.9, respectively. A difference was also detected between mean pre- and post-drug pulse rates in group-I ($p< 0.01$). Mean pre- and post-drug second-6th hours pulse rates of group-II were 149.9±19,6 and 140.4±18.6, respectively, and there was a difference between mean pre- and post-drug pulse rates in group-II ($p< 0.01$). Mean pulse rates of group-III measured before drug intake and during infusion were 102.3±13.5 and 97.08±15.6, respectively, and no difference was observed

between mean pre-drug and during infusion pulse rates in group-III. Mean post-drug pulse rate of group-III taken at the second 6th hours was 109.1±25.6. No difference was found between mean pre- and post-drug pulse rates in group-III. Mean post-drug pulse rates of group-III were 104.6±24.6 on the second day and 94.2±9.7 on the fourth day. There was no difference between mean pre-drug pulse rate, and post-drug pulse rates on the second and fourth days in group-III.

Mean pre-drug and during infusion systolic BP rates of group-III were 100.6±25 and 108.4±12 mmHg, respectively. There was no difference between mean pre-drug and during infusion systolic BP rates in group-III. Mean pre- and during infusion diastolic BP rates of group-III were 63.6±6.9 and 67.5±10.4 mmHg, respectively, and no difference was found between mean pre- and during infusion diastolic BP rates in group-III.

To test whether the indication of corticosteroid administration was influential on the cardiac side effects, mean pre-drug pulse rate and post-drug pulse rate measured at the second 6th hours were separately compared in both the patients with acute viral bronchiolitis and those with NS. Mean pre- and post-drug pulse rates taken at the second 6th hours of those with bronchiolitis were found as 148±18.4and 138.7±16.5, respectively. There was a difference between mean pre- and post-drug pulse rates in the patients with acute viral bronchiolitis ($p< 0.01$). In NS group, mean pre-drug pulse rate and post-drug pulse rate measured at the second 6th hours were also determined as 103.9±14.3 and 102.9±20.8, respectively. There was no difference between mean pre- and post-drug pulse rates at the second 6th hours in those with NS.

Discussion

The reports of dysrhythmias, especially those related to sinus bradycardia, arising from steroid therapy, are usually anecdotal (1,2,7,8). The our knowledge, the single case-control study investigating the association between dysrhythmias and steroid therapy has been performed by Nagakura et al. (9) The researchers advocating this idea suggest that high dose methyl-prednisolone alters the sensitivity threshold of myocardial cells (1) While some authors assert that corticosteroids lead to the expansion of plasma volume by changing the physiology of sodium and water, triggering a reflexive bradycardia by pressure on baroreceptors (10), others propose a predisposing mechanism of myocardium to corticosteroids (11). Corticosteroids may cause transient shifts both in renal electrolyte excretion and across myocardial cell membrane, leading to cardiac dysrhytmia. In a study performed by Fujimoto et al.(6), it was suggested that electrolyte monitoring during corticosteroid therapy is essential, especially in patients at risk for electrolyte imbalance. The authors also recommend the Holter electrocardiogram monitoring with regard to cardiac dysrhythmias.

Steroid-induced dysrhythmias have been reported after both single and repetitive doses of steroids, and the onset of dysrhythmias may be as early as during the infusion of the medicament, or as late as a few days (12-14). In a study, Akikusa et al. reported that prolonged sinus bradycardia developed in 5 of the patients receiving pulse methyl-prednisolone treatment because of acute rheumatic disease (1). In their case study, mean time until the development of bradyarrhythmia was reported as 44 hours (min 24, max 60). In our study, however, when mean pre-drug pulse rates of the patients receiving pulse methyl-prednisolone therapy were compared with those taken during infusion and post-drug follow-ups, no difference was observed between the averages. Akikusa et al. also suggested that pulse methyl-prednisolone cause reflex bradycardia by raising systemic BP, and the development of bradycardia may be delayed until the 2nd or 3rd days. In our study, no significant difference was found between the averages of both pre- and post-systolic BP measurements, and pre- and post-diastolic BP measurements in those receiving pulse methyl-prednisolone treatment. In addition, there was also no difference between the averages of pre- and post-drug pulse rates of this group measured on the 2nd and 4th days.

Some researchers suggest that anti-inflammatory effects of corticosteroids may suppress the cytokine production and the function of sympathetic nervous system, resulting in bradycardia (9). Conversely, other researchers advocate that the decrease observed in pulse rate during the corticosteroid treatment cannot be due to the decrease of inflammation, but a real effect plays a role. The advocates of the latter notion report that they observed an improvement in bradycardia, when the corticosteroid treatment was discontinued. In our study, while a difference was present between mean pre- and post-drug pulse rates at the second-6th hours in the patients receiving the corticosteroid treatment and those diagnosed with viral bronchiolitis, there was no difference between mean pre- and post-drug pulse rates at the second-6th hours in the patients receiving the corticosteroid treatment due to the diagnosis of NS. This status can be explained by the clinical course of the disease rather than the pharmacodynamics of the corticosterids. While such factors as relief in the clinical presentation through oxygen and bronchodilator treatment sapplied to those with bronchiolitis, and smoothing of the worries such as white uniform anxiety experienced during the first admisson may have caused a decrease in pulse rate, the decrease expected in NS group showing a more consistent course may not have been observed. However, this hypothesis is inadequate for explaining the decrease in pulse rates dropping below normal values in index cases.

Some authors report that other drugs administered together with corticosteroids may also contribute to dysrhythmias. In particular, phosphate-containing drugs can cause the formation of calcium and phosphate salts that precipitates sudden decreases in ionized calcium content, leading to a predispositing effect on cardiac dysrhythmias (15-16). In a case report performed by Pryse-Phillips et al., an anaphylactic reaction was observed in a patient given pulse methyl-prednisolone for the treatment of multiple sclerosis (17). In addition, in another study, it was suggested that corticosteroids are metabolized in the liver, so that conditions affecting the liver enzymatic system may change

pharmacokinetics of corticosteroids, and the level of their active metabolites may increase in blood (18).

The reports investigating the effects of corticosteroids on dysrhythmias give controversial information on dose and duration of drug regime. Some authors report that arrhythmias develop after a single dose or multiple doses, or with routine doses, as well as others stating that arrhythmias develop with pulse doses (1,12,14,15). In addition, the types of arrhythmias may also be different. While some studies report the development of bradycardia, others report the development of tachycardia (15). This discrepancy has created doubts or confusions about the arrhythmogenic effects of corticosteroids. In a limited number of cases in literature, it is reported that arrhythmias and associated symptoms resolved on their own in a few days (1.12). In their study performed in the patients with Kawasaki disease, Nagakura et al. reported the rate of bradycardia as 79.1% in those given standard dose prednisolone treatment (9). In the same study, it was reported that bradycardia was observed in half of the the patients on the average 2.6th day, while it was seen in the other half in one week. In our index cases, bradycardia started on the third day of the corticosteroid treatment and resolved spontaneously on the 8th days in the first patient and on the 4th day in the second patient. In our study, although the average of pre-drug pulse rates was higher than the average of post-drug heart rates on the 4th day, no statistical difference was found between the averages. This difference can also be interpreted as the improvement in the clinic of the patients due to the treatment. These findings suggest that the development of dysrhythmias is multifactorial and may be associated with an underlying disease, other accompanying pathologies such as liver disease, co-administered drugs, age of the patient or idiosyncrasis (15,19). Both of our index cases were followed due to the diagnosisof ARF. Considering that ARF is a pancarditis, it can be suggest that both the sinoatrial node and the pathways of communication will be affected by this situation. Therefore, bradycardia may have developed as a result of either direct carditis or decreased catecholamine sensitivity due to corticosteroids. In a study by Miura et al., bradycardia was reported to develop in 82% of 22 cases receiving pulse methyl-prednisolone therapy due to Kawasaki disease (20). Even so, in another study by Jain et al., bradycardia was reported as 30% in the patients with pemphigus receiving corticosteroids (21). The fact that bradycardia occuring at a higher rate in the treatment of cardiac disorders such as Kawasaki disease is seen in the patients with pemphigus at a lower rate supports our hypothesis, suggesting that bradycardia may be associated with an underlying disorder.

There are some limitations in our study. First, our study had non-homogeneous indications for the administration of corticosteroids. We administered corticosteroid therapy due to two different indications. The study could have been performed with one indication, but the number of subjects would not be enough to make statistics. Finally, the factors affecting patients' mood such as crying, sleeping or playing and relevant to the assessment of heart rate were not assessed because of the retrospective design of the study.

Our study showed that there is no direct causal relationship between the use of corticosteroids and cardiac dysrhythmias. It is likely that dysrhythmias developing after corticosteroid treatment are multifactorial. Dysrhythmias may be dependent on an underlying disease, adjuvant treatments applied, or other accompanying pathologies, such as liver disease and idiosyncrasies. So, we consider that further and more comprehensive studies should be performed to reach any judgement related to the topic. Whatever the reason, particularly the patients with liver disease and those with cardiac pathologies or taking cardiac drugs should be closely monitored in terms of dysrhythmias, if treated with corticosteroids. It is important to be aware that corticosteroids can precipitate cardiac dysrhythmias, until proven otherwise.

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