Evaluation of Blood Pressure in Children Treated with Ceftriaxone: A Case-Control Study

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ABSTRACT

Background: In children, high blood pressure can develop into hypertension and its consequences during puberty and adulthood. High blood pressure in children is often secondary to other causes, including renal diseases. Nephrolithiasis is one of the causes of secondary hypertension. The extensive use of cephalosporins in hospitals, particularly ceftriaxone, can result in nephrolithiasis. Therefore, the purpose of this study was to assess the relationship between ceftriaxone treatment and elevated blood pressure in children.

Method: The research was conducted as a case-control study over an 18-month period from 2018 to 2019. In this study, blood pressure was measured in 111 children aged 3-13 years who were hospitalized at Amir Kabir Hospital in Arak and received ceftriaxone for at least 48 hours. As a control group, 111 children who did not receive ceftriaxone had their blood pressure measured. The blood pressure levels and percentiles of children in the two groups were then compared.

Result: In the case and control groups, the mean age was 5.1±1.61 and 6.04±2.4 years, and the mean height was 109.17±10.71 and 114.86±12.95 cm, respectively. A slightly higher mean systolic blood pressure percentile was observed in the case group (65.59±18.17) than in the control group (65.28±14.51) (P=0.112), and the mean diastolic blood pressure percentile was also slightly higher in the case group (58.89±18.88) than in the control group (54.85±19.28) (P=0.317). The difference in diastolic blood pressure was greater than in systolic blood pressure. However, these detected differences were slight and not statistically significant.

Conclusion: This study showed no association between blood pressure levels and ceftriaxone treatment in children older than three years who received the medicine for at least 48 hours. However, additional research is suggested, focusing on the effects of the medicine at higher doses and over a longer period of time following administration.

Keywords: ceftriaxone; hypertension; blood pressure; nephrolithiasis; children.

1. INTRODUCTION

The global age-standardised prevalence of hypertension in adults in 2019 was estimated to be 32% in women and 34% in men (1). However, children and adolescents have a lower prevalence of hypertension than adults (2). Several population-based and school-based screening studies indicate that the prevalence of 95th percentile hypertension in children increased from the late 1980s to the early 2000s (3). Evidence suggests that hypertension persists from childhood into adulthood, making it increasingly important to manage elevated blood pressure in children and adolescents (4). In children, systemic hypertension is uncommon, and its

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prevalence is less than 1%, but if present, it often indicates the course of the primary disease (secondary hypertension) (5). The incidence and potential causes of secondary hypertension vary with age. Renal parenchymal disease and coarctation of the aorta are the most common causes in children (6, 7). Blood pressure should be measured routinely in all children over three, either during routine care or during emergency visits (8).

Adult hypertension is defined as blood pressure of 130/80 mmHg or above, regardless of body size, gender, or age (9, 10). This clinical definition is based on the findings of large studies on the influence of antihypertensive drugs on the risk of cardiovascular diseases and mortality and establishes a connection between blood pressure and the risk of cardiovascular events (11). This definition is inapplicable to children since cardiovascular events, except for ventricular hypertrophy, do not usually occur until adulthood (5). Thus, the definition of hypertension in childhood is based on the distribution of normal blood pressure levels in healthy children (12).

Body size is the most influential factor in determining blood pressure levels in children and adolescents. For a more precise classification of blood pressure levels based on the normal growth rate of children, numerous variables, including height, age, and gender, have been considered (5, 13).

Cephalosporins are the most frequently used beta-lactam class and one of the most commonly used antibiotics for treating common infections, and their use has increased over time (14, 15). Ceftriaxone, a third-generation cephalosporin, is a low-risk drug with a longer serum half-life than other cephalosporins, often eliminating the need for repeated injections (16). Due to these features, ceftriaxone is one of the most commonly used medicines in this class. Ceftriaxone has been approved for the treatment of certain types of bacterial meningitis, as well as severe infections caused by penicillin-resistant pneumococcal strains (17).

The common side effects of cephalosporins are divided into two categories: Allergies and toxicity (18). The majority of cephalosporins are metabolized in the liver, and the main route of excretion is renal via active tubular secretion. Renal excretion of ceftriaxone is approximately 33-67%, with the residue being excreted in the bile. Because ceftriaxone appears to have less renal excretion, its renal complications and toxicity are reduced (14, 17). However, renal disorders with ceftriaxone have been documented, including renal stones and nephrolithiasis (19-21), and acute renal failure (22, 23).

Numerous studies have demonstrated an association between nephrolithiasis and hypertension (24). Due to the potential risk of nephrolithiasis, long-term ceftriaxone users are likely to develop hypertension. However, no research has yet studied the relationship between ceftriaxone administration and blood pressure. The purpose of this study was to determine the association between ceftriaxone use and elevated blood pressure in children, as well as to monitor blood pressure in children treated with ceftriaxone.

2. MATERIAL AND METHOD

Study design and patient recruitment

This case-control study included 222 children who were admitted to Amirkabir Hospital in Arak over the course of 18 months between 2018 and 2019. Of these, 111 children aged 3-13 years who were hospitalized and treated with ceftriaxone for any reason for at least 48 hours were included in the study, and their blood pressure was measured. This age range was chosen since blood pressure classification based on percentile is applicable until the age of 13 (25). All these patients were hospitalized due to pyelonephritis. Another group of 111 children aged 3-13 years without specific diseases, who visited the hospital for outpatient care or came to the hospital as patient companions during visiting hours and had not taken ceftriaxone, were also measured for their blood pressure as a control group. The case group members were matched to the control group in terms of gender. Exclusion criteria included the presence or

diagnosis of an underlying or specific condition in the child, as well as the absence of parental consent for participation in the study.

Blood pressure measurement

First, written consent was obtained from the children's parents. All children in both groups rested for at least 30 minutes before their blood pressure was measured. To increase the accuracy of the measurements and reduce possible mistakes, the blood pressure measurements in the case group, who were hospitalized, were repeated twice at intervals of at least 3 hours. Blood pressure was taken from the right arm, as the right arm is more appropriate for hypertension screening (26, 27). Elevated blood pressure was defined as prehypertension (above the 90th percentile and below the 95th percentile), Stage 1 hypertension (above the 95th percentile and below the 99th percentile + 5 mmHg), and Stage 2 hypertension (above the 99th percentile + 5 mmHg) (28) in both groups. If the blood pressure was above the 95th percentile, the blood pressure in the left arm was also measured. In the event of abnormal blood pressure, parents were asked to return to the clinic two weeks later for a second blood pressure measurement. This was done because pyelonephritis can also induce hypertension, and after the completion of the treatment period (14 days), this elevation in blood pressure will resolve as a result of the disease's treatment. This was performed in both the case and control groups. Three sphygmomanometers of varying sizes were used for measurements based on the size of the child's arm. Simultaneously with blood pressure measurements, the children's age, gender, and height were recorded. The measured blood pressure values were classified based on age, gender, and height into the relevant blood pressure percentiles. The height percentile was calculated for all children based on their age and height using the growth charts available on the "Centres for Disease Control and Prevention" website (29). The tables in the "Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" (28) were used to calculate blood pressure percentiles in all children based on age, gender, and height percentile.

Statistical analysis

After entering the data into SPSS software version 23, central and dispersion indices were utilized for statistical analysis. Categorical variables were presented as percentages, and continuous variables were presented as the mean and standard deviation. To evaluate and compare blood pressure values between the case and control groups, data were analysed using the Mann-Whitney U test with a 5% level of significance.

3. RESULTS

The first section of the statistical analysis evaluated the sample's demographic characteristics. In the case group, 58 children (52.3%) were female, and 53 (47.7%) were male. In the control group, 58 (52.3%) were female, and 53 (47.7%) were male. Additional demographic data are presented in Table 1. There were no significant differences between the two groups in terms of demographic parameters ($P > 0.05$).

Table 1. Demographic characteristics

Demographic characteristics	Group	Mean	Standard deviation	Lowest	highest
Age	Case	5.10	1.61	3	10
	Control	6.04	2.04	3	13
Height	Case	109.17	10.71	91	139
	Control	114.86	12.95	92	151
Height percentile	Case	50.22	21	7	98
	Control	48.27	19.88	7	93

In the case group, the mean systolic blood pressure was 98.91 ± 6.64 mmHg (range 80-115), while in the control group, it was 100.14 ± 13.6 mmHg (range 86-117). The mean diastolic blood pressure in the case group was 56.31 ± 7.09 mmHg (range 40-76), and in the control group, it was 56.18 ± 6.69 mmHg (range 43-75). Additionally, the mean systolic blood pressure percentile in the case group was 65.59 ± 18.17 (range 14-94), and in the control group, it was 65.28 ± 14.51 (range 31-95). The mean diastolic blood pressure percentile in the case group was 58.89 ± 18.88 (range 13-94), and in the control group, it was 54.85 ± 19.28 (range 19-94).

In the second measurement for the case group, the mean systolic blood pressure was 99.05 ± 6.35 mmHg (range 82-114), and the mean diastolic blood pressure was 56.07 ± 7.20 mmHg (range 40-75). The mean systolic blood pressure percentile was 66.27 ± 16.71 (range 17-97), and the mean diastolic blood pressure percentile was 58.09 ± 18.87 (range 14-91). Notably, the mean and percentile of blood pressure in the case group did not change significantly between the first and second measurement.

Out of the 111 children whose blood pressure was measured twice in the case group, seven had blood pressure levels above the normal range. Four of these children had blood pressure levels above the 90th percentile in both measurements, two in the first measurement, and one in the second measurement. Six out of these seven children with elevated blood pressure had prehypertension, and only one had blood pressure above the 95th percentile, indicating the first stage of hypertension. The left arm blood pressure of the child with blood pressure higher than the 95th percentile was similarly above the 95th percentile. Parents of these seven children were asked to bring their child for blood pressure re-measurement two weeks later, but ultimately, only five of them had their blood pressure re-measured. Two out of these five children continued to have blood pressure above the 90th percentile, whereas the remaining three had blood pressure below the 90th percentile. In the control group, six out of the 111 children whose blood pressure was measured had higher than normal blood pressure. Five children in this group were in the prehypertension stage, and one was in stage 1 hypertension. Two weeks later, blood pressure measurements were repeated for these children, with only two of them returning for re-measurement, and one of these two still had blood pressure above the 90th percentile.

Tables 2 and 3 display blood pressure and blood pressure percentile comparisons between the case and control groups. As shown in the tables, there were no significant differences in blood pressure levels between children who received ceftriaxone and those who did not.

Table 2. Comparison of blood pressure in the two groups based on Mann-Whitney U test

Variable	Group	Mean	Standard deviation	P-value
Systolic blood pressure	Case	98.91	6.64	0.221
	Control	100.14	6.13	
Diastolic blood pressure	Case	56.31	7.09	0.485
	Control	56.81	6.69	

Table 3. Comparison of blood pressure percentile in the two groups based on Mann-Whitney U test

Variable	Group	Mean	Standard deviation	P-value
Systolic blood pressure	Case	65.59	18.17	0.112
	Control	65.28	14.51	
Diastolic blood pressure	Case	58.89	18.88	0.317
	Control	54.85	19.28	

4. DISCUSSION

In the case and control groups, the mean age was 5.1 ± 1.61 and 6.04 ± 2.4 years, respectively, and the mean height was 109.17 ± 10.71 and 114.86 ± 12.95 cm, respectively. Both groups' blood pressure levels and percentiles were compared. According to statistical analysis, the difference in systolic and diastolic blood pressure values between the two groups was not statistically significant at the 5% significance level. However, since blood pressure in children varies with age, gender, and height, the blood pressure percentiles obtained in the two groups were also compared. After adjusting for children's height and age, which were greater in the control group than in the case group ($P > 0.05$), blood pressure percentiles were found to be higher in the case group, although this difference was not statistically significant. This suggests that there may be underlying causes for the observed elevated blood pressure in children receiving ceftriaxone.

Ceftriaxone use can result in renal complications (19, 30, 31). Nephrolithiasis is a possible side effect of ceftriaxone. At therapeutic levels, ceftriaxone crystallizes with calcium in the urine and adheres to the surface of renal tubular cells (32). Approximately 1.4-7.8% of ceftriaxone-treated individuals develop renal calculi within 7 days of completing the normal course of treatment (32, 33). Typically, ceftriaxone renal stones are small, asymptomatic, and require no special therapy. Following discontinuation of ceftriaxone treatment, the stones usually pass naturally, but in some cases, they can be large and cause nephrolithiasis (22). Nephrolithiasis can lead to hypertension. In both nephrolithiasis and hypertension, alterations in calcium metabolism may play a significant role in the pathophysiology (34). Since the use of ceftriaxone is associated with increased urinary calcium excretion (35) and the development of renal stones, an elevation in blood pressure can be expected in patients receiving ceftriaxone. Moreover, urinary tract obstruction caused by severe nephrolithiasis can result in ceftriaxone-associated postrenal acute kidney injury (AKI) (22, 36). AKI is associated with CKD and hypertension (37, 38). As a result, ceftriaxone may cause an elevation in blood pressure in a variety of ways.

One of the factors that may interfere with the diagnosis of the primary cause of elevated blood pressure in children receiving ceftriaxone is the infectious condition for which ceftriaxone is prescribed. Ceftriaxone is administered every 24 hours to hospitalized children with severe pyelonephritis until they are clinically improved and have been fever-free for 24 hours (39). Severe pyelonephritis is the leading cause of acquired renal scarring in childhood, which, in a small but significant proportion of patients, may progress to hypertension (40).

If the medication is effective, this increase in blood pressure will subside. Therefore, in our study, the blood pressure of children with high blood pressure was re-measured after two weeks at the end of the treatment period. Since some children's blood pressure had returned to normal while others still had elevated blood pressure, the impact of this factor cannot be ruled out in this study.

One limitation of the study was that the dose of injectable medicine for children was not considered a variable, and children treated with any drug dose were included. Additionally, the duration of ceftriaxone administration was not compared, and all participants who received ceftriaxone for more than 48 hours were placed in the same group. Another limitation of this study was that all children treated with ceftriaxone in this center were hospitalized due to pyelonephritis. It is recommended that future research include children treated with ceftriaxone for other reasons. To obtain more accurate results, it is also suggested that the study be conducted with a larger sample size and a longer duration of follow-up.

5. CONCLUSION

Although this study did not find a correlation between hypertension in children and ceftriaxone use, it is advisable to avoid prescribing this medication without a clear

medical indication to prevent unnecessary expenses and potential adverse consequences on the kidneys. Furthermore, for future studies, it is recommended to assess blood pressure at various intervals after ceftriaxone treatment. On the other hand, since adverse effects of the medication may become more apparent at higher doses, it is suggested that future research considers evaluating the drug's dosage in addition to the duration of drug use.

Conflicts of Interest

The authors disclose no conflict of interest.

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Ethical approval

Ethical approval was granted by the Ethics Committee of Arak University of Medical Sciences. (Ethical number: IR.ARAKMU.REC.1396.116)**.**

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تقييم ضغط الدم في الأطفال الذين يتلقون علاجًا بالسيفترياكسون: دراسة حالة وشاهد

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ملخص

الخلفية: في الأطفال، يمكن أن يتطور ارتفاع ضغط الدم إلى ارتفاع ضغط الدم ومضاعفاته خلال فترة البلوغ والبلوغ. يكون ارتفاع ضغط الدم في الأطفال غالبًا ثانويًا لأسباب أخرى بما في ذلك الأمراض الكلوية. حصوة الكلية هي واحدة من أسباب ارتفاع ضغط الدم الثانوي. يمكن أن يؤدي الاستخدام المكثف للسيفالوسبورينات في المستشفيات، ولا سيما السيفترياكسون، إلى حصوة الكلية. لذلك، كانت الغاية من هذه الدراسة هي تقييم العلاقة بين علاج السيفترياكسون وارتفاع ضغط الدم لدى الأطفال.

الطريقة: تمت الدراسة كدراسة حالة وشاهد خلال فترة 18 شهرًا بين عامي 2018 و2019. في هذه الدراسة، تم قياس ضغط الدم في 111 طفلاً تتراوح أعمارهم بين 3 و13 عامًا وتم نقلهم إلى مستشفى أمير كبير في عراق وتلقوا السيفترياكسون لمدة 48 ساعة على الأقل. كمجموعة ضابطة، تم قياس ضغط الدم لدى 111 طفلاً لم يتلقوا السيفترياكسون. ثم تم مقارنة مستويات ضغط الدم والنسب المئوية للأطفال في المجموعتين.

النتيجة: في مجموعة الحالات ومجموعة الضابطة، كانت الأعمار المتوسطة 5.1 ± 1.61 و6.04 ± 2.4 سنة، وكانت الأطوال المتوسطة 109.17 ± 10.71 و114.86 ± 12.95 سم. لوحظت نسبة متوسطة أعلى لضغط الدم الانقباضي في مجموعة الحالات (65.59 ± 18.17) مقارنة بمجموعة الضابطة(P = 0.112) (14.51 ± 65.28) ، وكانت نسبة ضغط الدم الانبساطي المتوسطة أيضًا أعلى في مجموعة الحالات (58.89 ± 18.88) مقارنة بمجموعة الضابطة (P = 0.317). (19.28 ± 54.85)كان الاختلاف في ضغط الدم الانبساطي أكبر من ضغط الدم الانقباضي. ومع ذلك، فإن الاختلافات المكتشفة طفيفة وغير ذات دلالة إحصائية.

الاستنتاج: أظهرت هذه الدراسة عدم وجود ارتباط بين مستويات ضغط الدم وعلاج السيفترياكسون في الأطفال الذين تزيد أعمارهم عن ثلاث سنوات والذين تلقوا الدواء لمدة لا تقل عن 48 ساعة. ومع ذلك، يُقترح إجراء بحوث إضافية تركز على تأثيرات الدواء عند جرعات أعلى وعلى مدى فترة أطول بعد الإعطاء.

الكلمات الدالة: سيفترياكسون؛ ارتفاع ضغط الدم؛ ضغط الدم؛ حصوات الكلى؛ الأطفال.

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