Clin Pediatr Endocrinol 2019; 28(2), 25–30

Original Article

Treatment of adrenal crisis in patients with primary hypoadrenalism can lead to hypertension

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Abstract. Hypertension is one of the most serious side effects of glucocorticoid therapy. We retrospectively investigated the frequency of hypertension during treatment of adrenal crisis and analyzed the factors associated with its development. Patients who were admitted for primary hypoadrenalism due to diagnosed or suspected adrenal crisis were included. In the analysis, the subjects were divided into two groups: the hypertensive group (group H) and non-hypertensive group (group Non-H). The primary endpoint was the difference in the hourly therapeutic hydrocortisone (HDC) dosage between the two groups. The hourly therapeutic HDC dose in the two groups was defined as the hourly HDC dose from the start of HDC infusion until the development of hypertension in group H or until the last blood pressure measurement in group Non-H. Nine of 19 crises led to hypertension. There was no significant difference in the therapeutic HDC dosage between the groups ($p = 0.108$). In conclusion, hypertension developed in some patients during treatment for adrenal crisis. There was no significant difference in the therapeutic HDC dosage between groups H and Non-H.

Key words: adrenal crisis, hypertension, hydrocortisone, primary hypoadrenalism

Introduction

Primary hypoadrenalism refers to glucocorticoid deficiency in the setting of adrenal dysfunction (1). Adrenal crisis, an acute clinical manifestation of primary and secondary hypoadrenalism, can occur in patients with primary hypoadrenalism and is precipitated by various stressors such as infection or insufficient glucocorticoid treatment. The administration of glucocorticoids, including hydrocortisone (HDC), which is mainly used for pediatric patients, should be increased in the treatment of adrenal crises. The Japanese Society for Pediatric Endocrinology guidelines recommend an intravenous injection of HDC 50 mg/m^2 followed by a continuous intravenous infusion of HDC 50–100 mg/m^2/d (2). A similar recommendation has been published elsewhere (3).

Although the dosage of HDC for adrenal crisis should be tapered as the patient's condition improves, the method of tapering is controversial. Currently, tapering is done at the discretion of the primary physician or institution. The American Medical Association guidelines for adrenal supplementation therapy recommend

Received: December 1, 2018
Accepted: February 14, 2019
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that patients be given HDC 100–150 mg/d on the day of the procedure only and that the dose be rapidly decreased to maintenance levels over the following few days even in the presence of severe stress caused by pancreatitis or major surgery (4). The Japan Endocrine Society guidelines recommend that HDC 100–150 mg/d be given on the first day of acute adrenal crisis, then tapered from the second day of treatment until a maintenance dose is achieved after 3–5 days (5).

The method of tapering the dose is of vital clinical importance. Prolonged exposure to glucocorticoids may induce adverse effects such as hypertension, hyperglycemia, altered wound healing, and acute corticosteroid-induced psychosis (4). On the other hand, too rapid tapering can worsen the clinical course (4).

Hypertension is one of the most serious side effects of glucocorticoid therapy. Since hypertension can be life-threatening, minimizing its frequency and severity is important. In this study, we retrospectively investigated the frequency of hypertension during treatment for adrenal crisis by focusing on the HDC dosage to identify factors possibly related to the development of hypertension.

Subjects and Methods

Subjects

The electronic medical records of patients with primary hypoadrenalism at Tokyo Metropolitan Children's Medical Center, aged 1–15 yr, were retrospectively reviewed. Of these, we enrolled patients who received HDC and fludrocortisone (FC) and were admitted for diagnosed or suspected adrenal crisis between November 2010 and March 2017.

Adrenal crisis was defined in this study as a profound impairment of general health with 1) at least two of the clinical features of severe fatigue, nausea or vomiting, somnolence, hypotension, hyponatremia (< 132 mmol/L) or hyperkalemia, or hypoglycemia as well as 2) clinical deterioration precipitated by a glucocorticoid-deficient state or clinical improvement after the administration of glucocorticoid (6).

Patients with 1) no documentation of blood pressure after admission; 2) complications affecting blood pressure, such as asthma treated with methylprednisolone; and 3) hypertension before starting treatment for adrenal crisis, were excluded.

Methods

The following data were collected for each subject: 1) primary disease, 2) reason for admission (including the presence of adrenal crisis), 3) age at discharge, 4) duration of hospitalization, 5) presence and timing of hypertension during hospitalization, 6) therapeutic HDC dose after starting treatment for adrenal crisis (total therapeutic and hourly therapeutic HDC dosage as explained below), 7) maintenance (pre-admission) HDC and FC dosage before admission, 8) plasma renin activity before admission, and 9) body mass index (BMI) SD score (SDS) on admission.

The subjects were divided into two patient groups: hypertensive patients (group H) and non-hypertensive patients (group Non-H).

Blood pressure was initially measured before starting treatment and at least once a day during hospitalization. The sex, age, and height-corrected scores for systolic blood pressure were recorded in accordance with the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (7). Hypertension was defined as a systolic blood pressure above the 95th percentile recorded twice consecutively.

In our hospital, the therapeutic HDC dose for adrenal crisis consists of an intravenous infusion of 20–25 mg/m^2 followed by a continuous infusion of 100 mg/m^2/d on the first day of hospitalization. Our department has no unified method of decreasing the HDC dosage in the days after admission, with the actual method used depending on the patient's physical condition.

The total therapeutic HDC (tHDC) dosage

(mg/m^2) was defined in group Non-H as the total HDC dosage from the start of HDC infusion to the last blood pressure measurement. For group H, the tHDC dosage was calculated as the sum of the infusion HDC doses until the development of hypertension as described above. The hourly therapeutic HDC (hHDC) dosage was calculated as the sum of the tHDC doses divided by the number of hours from the start of the HDC infusion to the last blood pressure measurement or the timing of hypertension confirmation in groups Non-H and H, respectively. The hHDC dosage was calculated because three of nine patients in group H showed hypertension within only 3 h from the start of the HDC infusion.

The primary endpoint was the difference in hHDC dosage between the groups. The secondary endpoints were the difference in the tHDC dosage, maintenance HDC dosage, maintenance FC dosage, plasma renin activity before admission, age, and BMI SDS on admission between the two groups.

Statistical analysis

Statistical analysis was performed using EZR software (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html). The Mann-Whitney U test with a significance level of $p < 0.05$ was used.

Ethics approval

This study was approved by the research ethics review board of Tokyo Metropolitan Children's Medical Center (approval number: H29b-55).

Results

Twenty-six adrenal crises were initially included. Seven adrenal crises with preexisting hypertension were excluded. The remaining 19 crises were analyzed (including 10 patients). Fourteen crises (eight patients) involved 21-hydroxylase deficiency, three (one patient) involved congenital adrenal hypoplasia with *NR0B1* mutations, and two (one patient) involved cytochrome P450 oxidoreductase deficiency.

Eleven crises satisfied the criteria for an adrenal crisis, four did not, and four were indeterminate owing to insufficient information in the medical records. Eleven crises had received emergency adrenal crisis treatment with steroids (HDC conversion 20–25 mg/m^2/dose) at home, as prescribed by a physician, just before admission.

Hypertension developed in nine of the 19 crises (47%) and were placed in group H as explained above. Of these nine crises, hypertension developed in five on the first day of admission. None of the nine crises presented any serious signs or symptoms related to hypertension.

The accurate timing of the initiation of HDC was not available for five of the 19 crises, which were therefore excluded when calculating the hHDC and tHDC dosages. Six of the 14 crises that were not excluded were finally placed in group H, and eight were placed in group Non-H. The data on blood pressure and duration from the start of HDC infusion to the appearance of hypertension in each case are shown in Table 1. There was no significant difference in the duration from the start of HDC infusion to the confirmation of hypertension among the patients in group H or from the start of HDC infusion to the last blood pressure measurement in group Non-H.

There was no significant difference in the hHDC dosage (median: 11.2 mg/m^2/h in group H vs. 4.6 mg/m^2/h in group Non-H, $p = 0.108$) (Table 2) or the tHDC dosage (104.4 vs. 199.6 mg/m^2, $p = 0.142$) between the groups. The maintenance HDC dosage (9.0 vs. 11.5 mg/m^2/d, $p = 0.11$), maintenance FC dosage (0.08 vs. 0.08 mg/m^2/d, $p = 0.74$), and plasma renin activity before admission (0.00 vs. 0.40 ng/ml/h, $p = 0.24$) also showed no significant difference between the groups (Table 3). These three parameters did not show any significant difference even after the seven excluded cases (see exclusion criteria 3 in Subjects) were added to group H (data not

Table 1. Highest systolic blood pressure and duration from start of HDC infusion to highest blood pressure reading in both groups and systolic blood pressure at first occurrence of hypertension and duration until hypertension confirmation in the hypertensive group

Group Non-H

Crisis No.	Sex	Age (yr)	Duration from start of HDC infusion to last blood pressure reading	Highest systolic blood pressure	Duration from start of HDC infusion to highest blood pressure reading	Systolic blood pressure above 95th percentile
1	F	1	37 h 6 min	114 *	37 h 6 min	105
2	F	3	18 h 28 min	110 *	1 h 43 min	105
3	M	6	62 h 47 min	115	62 h 47 min	117
4	F	7	114 h 5 min	114	66 h 2 min	116
5	F	8	116 h 31 min	103	1 h 25 min	116
6	F	8	92 h 38 min	116	52 h 48 min	118
7	M	9	8 h 29 min	105	8 h 29 min	118
8	M	9	12 h 30 min	99	Before starting HDC	118

Group H

Crisis No.	Sex	Age (yr)	Systolic blood pressure at first occurrence of hypertension	Duration from start of HDC infusion to hypertension confirmation	Highest systolic blood pressure	Duration from start of HDC infusion to highest blood pressure reading	Systolic blood pressure above 95th percentile
9	M	1	102	0 h 45 min	137	25 h 27 min	101
10	F	4	111	1 h 6 min	135	32 h 32 min	107
11	F	4	114	38 h 5 min	125	86 h 28 min	112
12	F	5	121	2 h 31 min	121	2 h 31 min	112
13	F	5	115	46 h 1 min	118	70 h 22 min	111
14	F	5	107	58 h 41 min	117	82 h 42 min	107

H, hypertensive; HDC, hydrocortisone. * The scores were higher than the normal upper limit but not recorded twice consecutively.

shown).

Age (4.0 vs. 7.5 yr, p = 0.02) differed significantly between groups H and Non-H. However, the BMI SDS did not differ significantly between the groups (0.73 vs. 0.15) although a tendency toward a higher BMI SDS was observed in group H (p = 0.053).

Discussion

In this retrospective study, the frequency of hypertension during therapy for adrenal crisis was 47% (n = 9 of 19). Five crises developed into hypertension on the first day of admission. There was no significant difference in the hHDC dosage between groups H and Non-H.

There are no reports of hypertension in patients with primary hypoadrenalism who received HDC for the treatment of adrenal crisis. As far as we know, this study is the first to show that some patients with primary hypoadrenalism presented hypertension soon after receiving HDC therapy for adrenal crisis.

At least two similar studies have been published. Bonfig et al. studied blood pressure in patients with 21-hydroxylase deficiency

Table 2. HDC dose for adrenal crisis and intergroup differences (excluding patients with unknown starting time for HDC therapy for adrenal crisis)

	Unit	Group H (n = 6)	Group Non-H (n = 8)	P value
		Median (range)	Median (range)	
Total therapeutic HDC dose for adrenal crisis	(mg/m^2)	104.4 (28.1; 366.1)	199.6 (60.3; 476.3)	0.142
Hourly therapeutic HDC dose for adrenal crisis	($mg/m^2/h$)	11.2 (3.8; 37.5)	4.6 (2.3; 9.0)	0.108

H, hypertensive; HDC, hydrocortisone.

Table 3. Data from each group and intergroup differences

	Unit	Group H (n = 9)	Group Non-H (n = 10)	P value
		Median (range)	Median (range)	
Maintenance HDC dose	($mg/m^2/d$)	12.1(7.4; 19.7)	12.2 (7.2; 24.5)	0.78
Maintenance FC dose	($mg/m^2/d$)	0.08 (0; 0.12)	0.08 (0; 0.16)	0.74
Plasma renin activity before admission	(ng/ml/h)	0.00 (0; 2.4)	0.40 (0; 6.60)	0.24
Age	(yr)	4.0 (1.0; 5.0)	7.5 (1.0; 9.0)	0.02
BMI-SDS		0.73 (–0.20; 1.84)	0.15 (–0.51; 1.82)	0.053

BMI, body mass index; FC, fludrocortisone; H, hypertensive; HDC, hydrocortisone; SDS, SD score.

(21OHD) at an outpatient clinic and found no correlation between blood pressure and the average HDC dosage. Instead, they showed a significant correlation between blood pressure and FC dosage, age, and BMI SDS (8). In another study based on a cohort of patients with 21OHD, hypertension was associated with younger age and suppressed plasma renin activity in children with classical 21OHD (9). In our study, there was no significant correlation between hypertension and FC dosage or plasma renin activity despite the exclusion of seven crises owing to the presence of hypertension before HDC therapy. The similarly higher frequency of hypertension in younger children in the aforementioned study may be related to issues with blood pressure measurement (8).

There were at least two limitations to our retrospective study. First, the subject pool was too small for us to analyze statistically. Second, we were unable to compare blood pressure before and after admission. A carefully designed prospective study will doubtless be able to rectify these problems.

In summary, we demonstrated that some patients with primary hypoadrenalism presented with hypertension during their treatment for adrenal crisis. Further prospective research is needed to verify these findings.

Acknowledgments

We are indebted to Mr James R Valera for his assistance in editing this manuscript.

References

1. Stewart PM, Newell-price JDC. The Adrenal Cortex. Williams textbook of Endocrinology, 13th ed: Elsevier; 2015. p.524.
2. Ishii T, Anzo M, Adachi M, Onigata K, Kusuda S, Nagasaki K, *et al*. Mass Screening Committee Japanese Society for Pediatric Endocrinology Japanese Society for Mass Screening.

Guidelines for diagnosis and treatment of 21-hydroxylase deficiency (2014 revision). Clin Pediatr Endocrinol 2015;24: 77–105. [Medline] [CrossRef]
3. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, *et al*. Diagnosis and treatment of primary adrenal insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2016;101: 364–89. [Medline] [CrossRef]
4. Coursin DB, Wood KE. Corticosteroid supplementation for adrenal insufficiency. JAMA 2002;287: 236–40. [Medline] [CrossRef]
5. Yanase T, Kasayama S, Iwasaki Y, Mune T, Sugawara A, Oki Y, *et al*. The guideline for diagnosis and treatment for hypoadrenalism including adrenal crisis (final edition). Folia Endocrinologica Japonica. 2015;91(Suppl): 1–78 (In Japanese).
6. Odenwald B, Nennstiel-Ratzel U, Dörr HG, Schmidt H, Wildner M, Bonfig W. Children with classic congenital adrenal hyperplasia experience salt loss and hypoglycemia: evaluation of adrenal crises during the first 6 years of life. Eur J Endocrinol 2016;174: 177–86. [Medline] [CrossRef]
7. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES National Institutes of Health National Heart, Lung, and Blood Institute. the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. 2005. https://www.nhlbi.nih.gov/files/docs/resources/heart/hbp_ped.pdf.
8. Bonfig W, Roehl FW, Riedl S, Dörr HG, Bettendorf M, Brämswig J, *et al*. AQUAPE CAH Study Group. Blood pressure in a large cohort of children and adolescents with classic adrenal hyperplasia (cah) due to 21-hydroxylase deficiency. Am J Hypertens 2016;29: 266–72. [Medline] [CrossRef]
9. Finkielstain GP, Kim MS, Sinaii N, Nishitani M, Van Ryzin C, Hill SC, *et al*. Clinical characteristics of a cohort of 244 patients with congenital adrenal hyperplasia. J Clin Endocrinol Metab 2012;97: 4429–38. [Medline] [CrossRef]