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/m² followed by a continuous intravenous infusion of HDC 50–100 mg/m²/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
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/m² followed by a continuous
infusion of 100 mg/m²/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/m²) 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/m²/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/m²/h in group H vs. 4.6 mg/m²/h in group Non-H, p = 0.108) (Table 2) or the tHDC dosage (104.4 vs. 199.6 mg/m², p = 0.142) between the groups. The maintenance HDC dosage (9.0 vs. 11.5 mg/m²/d, p = 0.11), maintenance FC dosage (0.08 vs. 0.08 mg/m²/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
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.
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(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.

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