Research Article

Hydrocortisone Continuous Infusion Versus Bolus Dose on Glycemic Control in Critically Ill Subjects

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Abstract

Background: Corticosteroid therapy in patients with septic shock can improve hemodynamics but can also cause hyperglycemia. Continuous infusion (CI) hydrocortisone has limited evidence that it may reduce hyperglycemia relative to bolus dose (BD) therapy, but CI can be cumbersome and requires attention to intravenous access and drug incompatibilities. **Objective:** To compare the effects of CI hydrocortisone with BD on glycemic control. **Methods:** A matched, retrospective cohort study of blood glucose, insulin requirements, and glycemic variability was performed between patients with shock receiving CI and BD hydrocortisone. Patients were matched based on history of type 2 diabetes and intensive care unit (ICU) admission. **Results:** Baseline blood glucose was similar between groups, with higher baseline hourly insulin requirements in the CI group (CI: 12 [12.8] units, BD: 6.7 [7] units, $P = .0012$). For the first 72 hours of treatment, there was no difference in mean blood glucose with higher average hourly insulin requirements in the CI group (CI 7.8 [7.7] units, BD: 5.5 [6.9] units, $P < .0001$). There was no difference in glycemic variability between groups. **Conclusions:** CI hydrocortisone therapy for septic shock does not appear to have a favorable impact on mean blood glucose or influence glycemic variability relative to BD therapy.

Keywords

hydrocortisone, corticosteroids, shock, hyperglycemia

Introduction

Corticosteroids are recommended in critically ill patients with known or suspected adrenal insufficiency and distributive shock who are unable to achieve hemodynamic stability with adequate fluid resuscitation and vasopressor therapy.[1] These agents are useful in reducing vasopressor requirements and improving hemodynamics. However, corticosteroids increase blood glucose (BG) levels by activating enzymes involved in hepatic gluconeogenesis and inhibiting glucose uptake in skeletal muscles.[2] Hyperglycemia and hypoglycemia are associated with increased morbidity and mortality, and the variability of BG concentrations may be an important risk factor for mortality in critically ill patients.[3-5] The use of corticosteroids and the associated hyperglycemia can complicate glycemic control in this population. Clinicians have explored alternative dosing and administration strategies to help prevent or mitigate the effects of steroid-induced hyperglycemia.

In previous sepsis guidelines, the recommended dose of hydrocortisone sodium succinate (hydrocortisone) was 200 to 300 mg/d administered intravenously as a continuous infusion (CI) or in 3 to 4 divided bolus doses (BDs).[6] In clinical practice, common BD regimens were 100 mg every 8 hours or 50 mg every 6 hours. In an attempt to prevent hyperglycemia and decrease variability in BG levels, the 2012 Surviving Sepsis Campaign guidelines recommended using hydrocortisone at a dose of 200 mg/d as a CI rather than repetitive bolus injections.[7] The current 2016 guidelines recommend a dose of 200 mg/d, but no longer specify CI over BD.[1] In addition to the sepsis guidelines, the guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency support the use of hydrocortisone in patients with sepsis but do not specify an exact dose or dosing strategy.[8]

At this time, the evidence to support CI hydrocortisone to mitigate the effects on BG in critically ill patients is primarily limited to a single-center observational study consisting of 16 subjects.[9] Studies such as HYPRESS and ADRENAL utilized the CI dosing strategy; however, they were not designed to

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evaluate the effects of hydrocortisone administration on BG levels.[10,11] Although CI hydrocortisone may prevent hyperglycemic events, potential complications with its use exist. These complications include the need for additional intravenous line access, compatibility with other infusions, and ensuring the stability and sterility of a CI product, which can be problematic in critically ill patients with sepsis who are receiving several infusions. Therefore, the purpose of this study was to compare glycemic control and glycemic variability in patients with septic shock who received hydrocortisone CI versus BD hydrocortisone.

Study Methods

Design and Setting

This was a single-center, retrospective, institutional review board–approved, matched study conducted at a 900-bed tertiary care regional referral center with 128 critical care beds. It was carried out with the ethical standards set forth in the Helsinki Declaration of 1975. Critically ill adult subjects who received CI hydrocortisone between January 1, 2013, and September 1, 2014, were identified through pharmacy dispensing reports. Subjects in the BD group were identified through pharmacy dispensing records and matched working retrospectively from September 1, 2014, until the required sample size was met. Subjects were matched based on prior history of type 2 diabetes as defined by problem list and intensive care unit (ICU) admission at the time of treatment. CIs of insulin were managed using Endotool® software (Monarch Technologies) set to target a BG of 140 to 180 mg/dL. Patients were transitioned to subcutaneous insulin with clinician discretion using a protocol based on intravenous insulin requirements.

Patient Population

Adults aged 18 years or older who required vasopressor support due to hypotension were eligible for inclusion. Subjects must have received either CI hydrocortisone at a dose of 200 mg/d for at least 6 hours (a total dose of at least 50 mg) or at least one 50 mg BD of hydrocortisone while being treated in the medical, surgical, cardiac, or cardiac surgery ICUs between January 1, 2013, and September 1, 2014. Subjects were excluded if they were pregnant, had type 1 diabetes, or did not have a follow-up BG level within 6 hours of hydrocortisone administration.

Outcomes

The primary end points were the difference in mean BG levels and mean insulin requirements during the first 72 hours of treatment with intravenous BD versus CI hydrocortisone for shock with associated adrenal insufficiency. Secondary end points included time in goal BG range which we defined as 70 to 180 mg/dL, variability in BG levels and number of BG readings <70 mg/dL during the first 72 hours of treatment, in-hospital mortality, ICU and hospital length of stay, and type and route of insulin administered. Although the target BG range for insulin therapy was 140 to 180 mg/dL, for the purposes of analysis, we considered BG of 70 to 180 mg/dL to be physiologically appropriate. For analysis purposes, 1 unit of intravenous insulin was considered equivalent to 1 unit of subcutaneous insulin. The variability of glucose levels was determined using the mean and standard deviation to calculate a coefficient of variability (coefficient of variability = standard deviation of BG concentration × 100/mean BG concentration), as previously defined by Egi and colleagues.[5]

Statistical Analysis

A sample size of 110 subjects (55 per group) was needed to provide 80% power to detect a 6% difference in mean BG between groups with an alpha <.05 based on an expected standard deviation of 11.5 mg/dL. The expected standard deviation was based on the results of the previous study of CI hydrocortisone, with standard deviation estimated using the range rule.[9] Descriptive statistics were used for baseline characteristics and compared using Fisher's exact test, chi-square, unpaired *t* test for normal data, and Mann-Whitney *U* test for non-normal data. All data were assessed for normality using the Kolmogorov-Smirnov test. The primary end points of mean BG and mean insulin requirement were compared using the Mann-Whitney *U* test. Secondary end points were evaluated by Student's *t* test for continuous data and Fisher's exact test for categorical data. An alpha value of .05 or less was considered statistically significant. No financial support was provided for this study.

Results

A total of 55 subjects in the CI group met the inclusion criteria. After exclusion and matching criteria were applied, 52 subjects per group were included for primary analysis. Mean BG readings 12 hours prior to hydrocortisone initiation were slightly higher in the CI group (CI: 184 mg/dL vs BD: 174 mg/dL, $P < .01$). Additionally, the CI group had higher per hour insulin requirements in the 12-hour period prior to hydrocortisone therapy (CI: 12 U vs BD: 6.7 U, $P < .01$) and there was no difference in the number of patients receiving intravenous insulin at baseline. Half of the subjects had diabetes and most required ventilator support. Patients were in multiple ICUs with varying etiologies of shock, including sepsis, postcardiopulmonary bypass vasoplegia, and trauma. Norepinephrine and vasopressin were the most commonly used vasopressors. The use and types of nutritional support were similar between groups, as was the use of dextrose infusions. Additional baseline characteristics are available in Table 1.

Glucose Measurements and Insulin Requirements

There was a significantly higher mean insulin requirement in the CI group relative to BD group with no difference in mean glucose levels (Table 2). However, the change in insulin requirements from the 12 hours before and after hydrocortisone therapy was not different (BD: 23.7 [54.3] mg/dL, CI: 29.7

Table 1. Baseline Characteristics.

	CI, n = 52	BD, n = 52	*P* Value
Male gender, n (%)	31 (60)	26 (50)	.43
Age, mean (SD), years	62.6 (14.2)	63.2 (14.5)	.68
Mean length of hydrocortisone therapy, mean (SD), days	5.2 (4.8)	5 (4.3)	.81
Mean blood glucose 12-hour period prior, mean (SD), mg/dL	183.8 (94.4)	174.4 (150.0)	<.01
Mean insulin requirements 12-hour period prior, mean (SD), units	12.0 (12.8)	6.7 (7)	<.01
Route of insulin administration prior to hydrocortisone, n (%)			.71
Intravenous	14 (26.9)	11 (21.1)	
Subcutaneous	13 (25)	11 (21.1)	
No therapy	25 (48.1)	30 (57.7)	
Nutrition, n (%)			.82
None/NPO	35 (67.3)	32 (61.5)	
Enteral nutrition	17 (32.7)	15 (28.8)	
Total parenteral nutrition	0 (0)	5 (9.6)	
Renal replacement therapy, n (%)			.0661
Intermittent HD	1	5	
CRRT	11	14	
None	40	33	
Mechanical ventilation, n (%)	47 (90)	45 (87)	.762
Vasopressor, n (%)			.804
Dopamine	4 (8)	5 (10)	
Epinephrine	8 (15)	9 (17)	
Norepinephrine	48 (92)	51 (98)	
Phenylephrine	12 (23)	7 (13)	
Vasopressin	28 (54)	30 (58)	
Subjects with diabetes, n (%)	25 (48)	25 (48)	
ICU, n (%)			
MICU	28 (54)	28 (54)	
SICU	14 (27)	14 (27)	
CICU	6 (12)	6 (12)	
CVICU	4 (8)	4 (8)	

Abbreviations: BD, bolus dose; CI, continuous infusion; CICU, cardiac intensive care unit; CRRT, continuous renal replacement therapy; CVICU, cardiovascular intensive care unit; HD, hemodialysis; ICU, intensive care unit; MICU, medical intensive care unit; SD, standard deviation; SICU, surgical intensive care unit.

[79.8]; $P = .66$). The average glucose levels met appropriate targets and were less than 150 mg/dL after 24 hours (Figure 1). Insulin requirements decreased for both groups during the 72-hour study (Figure 2) period and there was no difference in glycemic variability (Table 2). Notably, there was no difference in time within goal BG range for the 72-hour study period or any interim time points (Table 3). Hypoglycemic events (defined as less than 70 mg/dL) were rare, and there was no difference in the rate between groups (BD: 1.1%, CI: 1.4%; $P = .5$). There was also no difference in the rate of readings greater than 220 mg/dL (BD: 6.7%, CI: 5.7%; $P = .27$). In addition, there was also no difference observed in the secondary end points of in-hospital mortality and ICU and hospital length of stay (Tables 2 and 4). Insulin requirements were divided into 3 groups: correctional subcutaneous, scheduled subcutaneous, or continuous intravenous infusion. At 72 hours, data were available for 48 subjects in the CI group and for 44 subjects in the BD group. There was no difference in the type of insulin required or the number of types of insulin required between groups (Tables 2).

Discussion

This study found no difference in BG measurements or glycemic variability in patients receiving CI hydrocortisone instead of BD hydrocortisone for shock. Research comparing the effects of CI versus BD hydrocortisone on glycemic control and variability is limited, and this study provides a comparison of the 2 modalities in clinical practice. The 2012 guideline recommendation to use CI was based on an observational study of 16 subjects with septic shock by Weber-Carstens et al.[9] The study used a crossover design to demonstrate a difference in the primary end point of mean peak BG level after a single BD of hydrocortisone compared to a CI (154 vs 128 mg/dL, $P < .01$). By contrast, our study utilized a retrospective study design to compare 2 groups receiving different modalities of hydrocortisone and provided a comparison using a more clinically relevant end point of mean glucose over a 72-hour period. Glucose

Table 2. Blood Glucose and Insulin Requirements During Hydrocortisone Therapy.

Outcome	CI, n = 52	BD, n = 52	*P* Value
Blood glucose (mg/dL) over 72 hours, mean (SD)	141.2 (47.1)	144.5 (53.6)	.23
Insulin requirements (U/h) over 72 hours, mean (SD)	7.8 (7.7)	5.5 (6.9)	<.0001
Blood glucose <70 mg/dL (n, episodes)	16	19	.5
BG variability, mean (SD)	25.6 (12.4)	25.9 (13.8)	.9074
Insulin Therapy Type at 72 Hours	**CI, n = 48**	**BD, n = 44**	***P* Value**
Correctional, n (%)	9 (19)	2 (5)	.0525
Scheduled subcutaneous, n (%)	24 (50)	17 (39)	.3003
IV insulin infusion, n (%)	22 (46)	14 (32)	.2026

Abbreviations: BD, bolus dose; CI, continuous infusion; IV, intravenous; SD, standard deviation.

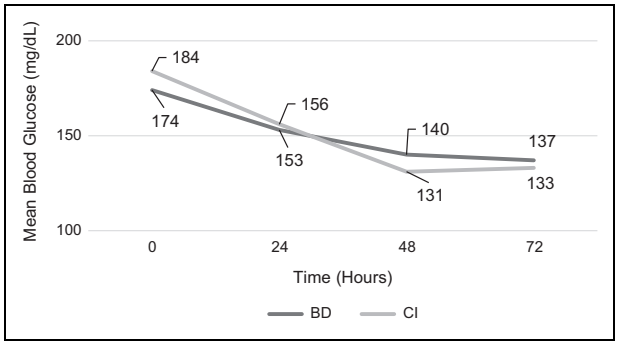

Figure 1. Mean blood glucose. *$P = .23$.

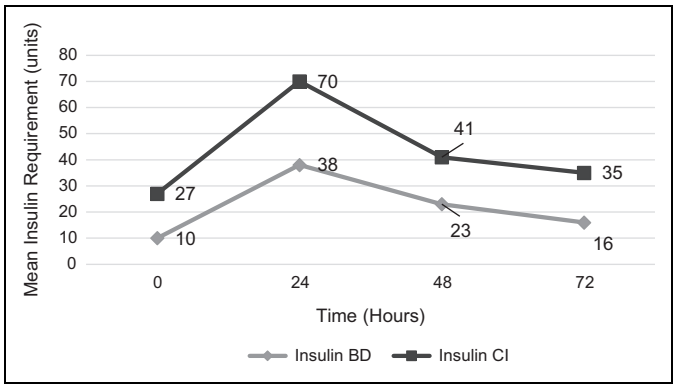

Figure 2. Mean insulin requirement. *$P = .0001$.

Table 3. Time in Blood Glucose Range 70 to 180 mg/dL.

Average Time in Range (hours), Mean (Standard Deviation)	CI, n = 52	BD, n = 52	*P* Value
0-24	18 (6)	18.4 (6.6)	.79
25-48	20.1 (7.2)	20.6 (5.9)	.75
49-72	21.4 (4.8)	21.68 (5.4)	.78
Total time: 0-72	19.8 (6.2)	20.02 (6.2)	.23

Abbreviations: BD, bolus dose; CI, continuous infusion; SD, standard deviation.

Table 4. Patient Outcomes.

Outcome	CI, n = 52	BD, n = 52	*P* Value
In-hospital mortality, n (%)	25 (48)	31 (60)	.3254
ICU length of stay, mean (SD)	13.3 (9.1)	12.8 (19.2)	.8656
Hospital length of stay, mean (SD)	21.9 (16.4)	20.2 (26.4)	.6941

Abbreviations: BD, bolus dose; CI, continuous infusion; ICU, intensive care unit; SD, standard deviation.

readings between the previous study and our study are similar. Mean glucose readings while on CI therapy in the previous study were 136 to 142 mg/dL following resumption of CI therapy, compared to 141 mg/dL in our study.[9] The BG readings on BD therapy were different between studies with a mean glucose of 144 mg/dL in our study relative to a mean peak glucose of 154 mg/dL in the previously published study, with mean glucose not reported. A large variation in insulin requirements was observed between studies, with the previously published study reporting a range in insulin use between 2.8 and 3.1 U/h during the 12-hour study period. By contrast, our insulin use was much higher with an average of 5.5 to 7.8 U/h. Use of insulin in clinical practice rather than use under controlled study conditions for a limited period of time is likely the reason for this observed difference.

BG Variability

Although glycemic variability was not a study end point in the work by Weber-Carstens et al, they reported no difference in intraindividual variability but more interindividual variability in BG levels after the BD as compared to the CI group (range, 132-178 mg/dL vs 114-141 mg/dL). Their observed wider range in BG between individuals makes it difficult to predict any one individual's BG response to hydrocortisone. The use of a larger sample size in our study allowed for better comparison between the 2 groups and reduced confounding variables. Finally, our target BG was less than 180 mg/dL, which better reflects current practice and guideline recommendations for BG targets, compared to the tight glycemic control seen in the prior study.[12] It is unknown whether the use of more modest BG control targets would have led to the same results in the prior study.

Loisa et al conducted a prospective, randomized study of 48 subjects to assess glucose profiles in patients with septic shock who received either 200 mg/d CI hydrocortisone (n = 22) or a 50 mg bolus every 6 hours for 5 days.[13] The primary end point was difference in mean BG with a target goal of 72 to 126 mg/dL. Of note, our study included patients with type 2 diabetes and matched groups, whereas the Loisa et al's study excluded patients with a history of diabetes. The overall mean BG of their study was lower in the CI group by 3.6 mg/dL ($P = .04$). Due to different BG targets, our overall mean BG (141.3 mg/dL vs 144.5 mg/dL) was higher than that found in the Loisa et al's study (115.2 mg/dL vs 111.6 mg/dL). However, we found a similar difference in overall mean BG between groups (3.2 mg/dL vs 3.6 mg/dL). In both studies, the clinical significance of these differences in BG is questionable. As expected for lower glucose targets, patients in the previous study had higher insulin requirements than those in our study.

At least 2 studies conducted after the release of the 2012 Surviving Sepsis Campaign guidelines incorporated the recommendation of CI hydrocortisone. Neither compared CI to BD; however, they both included hyperglycemia as a safety end point. The HYPRESS study compared 200 mg CI hydrocortisone to placebo to determine whether hydrocortisone prevents the progression of severe sepsis to septic shock. Hyperglycemia occurred more often in the hydrocortisone group compared to placebo (90.9% vs 81.5%, difference: 9.4%; 95% confidence interval: 2.4%-16%; $P = .009$).[10] The ADRENAL study compared 200 mg CI hydrocortisone to placebo to determine the impact of hydrocortisone on mortality in patients with septic

shock. Six episodes of hyperglycemia were noted in the CI group compared to 3 in the placebo group.[11]

Limitations

There were several limitations to our study. Due to the retrospective study design, data were limited to what was documented in the medical record. Only 52 subjects were included per group, which resulted in a failure to meet power to detect a 6% difference. Our study also had large variations in BG readings and insulin requirements relative to previously published data. This hindered the ability of our study to detect differences but is more reflective of clinical practice with higher BG targets (140-180 mg/dL) than previous studies which targeted lower values and controlled glucose under strict study conditions. Although the use of various types of nutritional support was similar between groups, the amount of dextrose administered could confound these results. Additionally, the larger baseline insulin requirements observed in the CI group created a selection bias to the study results, whereby patients with difficulties in glycemic control were selectively prescribed CI therapy. However, in interpreting these results, it demonstrates that selection of CI therapy may not be of benefit to patients with baseline hyperglycemia.

Conclusions

This study found no difference in mean BG with the use of CI hydrocortisone therapy relative to BD therapy for shock. However, given the sample size, the results need additional confirmation through larger trials. Patients receiving CI therapy had higher mean insulin requirements at baseline and during the study period. Given the lack of benefit related to glycemic control and potential complexities associated with CI therapy including need for additional intravenous lines, potential drug incompatibilities, and increased use of resources including infusion pumps and lines, it is reasonable for clinicians to safely use BD hydrocortisone in critically ill patients with shock.

Declaration of Conflicting Interests

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