ORIGINAL ARTICLE

Observational Study

Timing, method and discontinuation of hydrocortisone administration for septic shock patients

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Abstract

AIM
To characterize the prescribing patterns for hydrocortisone for patients with septic shock and perform an exploratory analysis in order to identify the variables associated with better outcomes.

METHODS
This prospective cohort study included 59 patients with septic shock who received stress-dose hydrocortisone.

It was performed at 2 critical care units in academic hospitals from June 1st, 2015, to July 31st, 2016. Demographic data, comorbidities, medical management details, adverse effects related to corticosteroids, and outcomes were collected after the critical care physician indicated initiation of hydrocortisone. Univariate comparison between continuous and bolus administration of hydrocortisone was performed, including multivariate analysis, as well as Kaplan-Meier analysis to compare the proportion of shock reversal at 7 d after presentation. Receiver operating characteristic (ROC) curves determined the best cut-off criteria for initiation of hydrocortisone associated with the highest probability of shock reversal. We addressed the effects of the taper strategy for discontinuation of hydrocortisone, noting risk of shock relapse and adverse effects.

RESULTS
All-cause 30-d mortality was 42%. Hydrocortisone was administered as a continuous infusion in 54.2% of patients; time to reversal of shock was 49 h longer in patients who were given a bolus administration [59 h (range, 47.5-90.5) *vs* 108 h (range, 63.2-189); *P* = 0.001]. The maximal dose of norepinephrine after initiation of hydrocortisone was lower in patients on continuous infusion [0.19 µg/kg per minute (range, 0.11-0.28 µg)] compared with patients who were given bolus [0.34 µg/kg per minute (range, 0.16-0.49); *P* = 0.004]. Kaplan-Meier analysis revealed a higher proportion of shock reversal at 7 d in patients with continuous infusion compared to those given bolus (83% *vs* 63%; *P* = 0.004). There was a good correlation between time to initiation of hydrocortisone and time to reversal of shock (*r* = 0.80; *P* < 0.0001); ROC curve analysis revealed that the best criteria for prediction of shock reversal was a time to initiation of hydrocortisone of ≤ 13 h after administration of norepinephrine, with an area under the curve of 0.81 (*P* < 0.001). The maximal dose of norepinephrine at initiation of hydrocortisone with the highest association with shock reversal was ≤ 0.28 µg/kg per minute, with an area under the curve of 0.75 (*P* = 0.0002). On a logistic regression model, hydrocortisone taper was not associated with a lower risk of shock relapse (RR = 1.29; *P* = 0.17) but was related to a higher probability of hyperglycemia [odds ratio (OR), 5.3; *P* = 0.04] and hypokalemia (OR = 10.6; *P* = 0.01).

CONCLUSION
Continuous infusion of hydrocortisone could hasten the resolution of septic shock compared to bolus administration. Earlier initiation corresponds with a higher probability of shock reversal. Tapering strategy is unnecessary.

Key words: Corticosteroids; Hydrocortisone; Timing; Administration; Discontinuation; Septic shock

Core tip: Until now, the indications, timing, administration, and discontinuation of hydrocortisone for septic shock patients have been widely variable. Our study found that continuous infusion was the most effective method compared to bolus administration; we also identified a time from vasopressor administration of ≤ 13 h and/or a norepinephrine dose of ≤ 0.28 µg/kg per minute as the best clinical criteria for initiation of hydrocortisone. We found no benefit from the tapering strategy, which was only associated with a higher incidence of hyperglycemia and hypokalemia.

INTRODUCTION
Since William Schumer stated in the mid-1970s that early administration of adjunctive steroids could be helpful in the management of patients with septic shock[1], investigators have developed experimental animal and human trials to study the role of corticosteroid therapy; however, this benefit remains controversial[2,3]. The controversy may exist because the studies have varied in their design, steroid preparation, dose, strategy of administration (intermittent bolus or continuous infusion), length of therapy, time of initiation, and patterns of discontinuation[4].

Corticosteroids had been shown to be associated with a faster reversal of shock compared to placebo[5-9]. For that reason, the 2012 Surviving Sepsis Campaign Guidelines recommended administration of hydrocortisone (200 mg/d) if hemodynamic stability is not achievable after fluid resuscitation and vasopressor therapy[2]. Nevertheless, the patterns in clinical practice remain widely heterogeneous because of differing interpretations of the definition of poor responsiveness of shock to fluid and vasopressor therapy, discrepancy between clinicians' interpretation of guidelines, discrepancy in clinical practice, and unfamiliarity with existing evidence[10].

The aim of this observational study was to characterize the use of hydrocortisone in septic shock patients in order to identify the most effective method of administration and withdrawal, and to find the best clinical criteria for initiation of corticosteroid therapy to increase the probability of shock reversal.

MATERIALS AND METHODS
Setting
This was a prospective cohort study conducted in 2 medical/surgical intensive care units at tertiary academic hospitals from June 1st, 2015, through July 31st, 2016. All patients recruited in Instituto Jalisciense de Cancerología had oncologic disease; there were no

oncologic patients recruited at Hospital Civil Fray Antonio Alcalde. Inclusion criteria for patients were a diagnosis of septic shock, defined as sepsis induced hypotension persisting despite adequate fluid resuscitation[2], for which the attending intensivist determined the need for adjunct hydrocortisone therapy at a stress dose (no more than 200 mg/d), regardless of the timing and method of administration. Shock reversal was considered when the arterial pressure remained stable (SAP > 90 mmHg or MAP > 70 mmHg without requirement of new vasopressor infusion) for more than 24 h. Relapse was defined as recurrence of septic shock, requiring norepinephrine resumption within first 7-d after reversal. Patients with a previous diagnosis of adrenal insufficiency, who received hydrocortisone at a dose more than 200 mg/d, and who died within the first 48 h after intensive care unit (ICU) admission were excluded. The scientific and ethics committees at Instituto Jalisciense de Cancerología (INV-01/16) and Hospital Civil Fray Antonio Alcalde (HCG/CEI-0321/16) approved this investigation.

Data collection
After patients with septic shock were deemed candidates for initiation of hydrocortisone, informed consent was obtained from patient or their next of kin, and data were prospectively collected. Recorded information included demographic data, comorbidities, maximal dose (calculated to ideal body weight) and length of vasopressor requirement, timing, method of administration and discontinuation of hydrocortisone, adverse effects of corticosteroids, ICU length of stay, time to death, and 30-d mortality. The Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ) score and the Sequential Organ Failure Assessment score were calculated within the first day of ICU admission.

Statistical analysis
Continuous variables were reported as the mean [standard deviation (SD)] if they were normally distributed, or the median [interquartile range (IQR)] if they were not normally distributed, according to the Shapiro-Wilk test. A Mann-Whitney or *t*-test was used for comparison between groups as appropriate. We used a two-way mixed ANOVA test for comparison between pre- and post- hydrocortisone maximal doses of norepinephrine. Categorical variables were expressed as the number of measurements (%) and were compared by χ^2 test. We constructed receiver-operating characteristic (ROC) curves for time to initiation of hydrocortisone and dosage of norepinephrine at initiation of hydrocortisone to determine the ability for prediction of shock reversal; optimal cut-off values were obtained with the greatest sum of sensitivity and specificity using the Youden index[11]. The relationship between time to initiation of hydrocortisone and total duration of shock was estimated with the Spearman correlation coefficient test. We performed a Kaplan-Meier analysis to compare the shock reversal rate at 7 d between continuous and bolus administration.

Multivariate logistic regression was performed to identify factors associated with shock reversal and adverse effects. Calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test, considered as adequate if $P > 0.05$[12]. Based on vasopressor dosages in a previous study of septic shock patients with our same settings[13], we determined that 26 patients with continuous infusion and 26 with bolus administration of hydrocortisone would be needed to detect a difference of 0.10 μg/kg per minute in norepinephrine maximal dosage from 12 h after initiation of corticosteroid with a 90% statistical power and type Ⅰ error of 5%. For all tests, *P*-values were two-sided, and a value lower than 0.05 was considered statistically significant. We used MedCalc (Ver 16.4.3, Ostend, Belgium) for calculating sample size and for the statistical analysis.

The statistical methods of this study were reviewed by Miguel A. Ibarra-Estrada, clinical investigator and biomedical statistics analysis expert from Critical Care Unit, Instituto Jalisciense de Cancerología, Guadalajara Jalisco 44280, Mexico; Critical Care Unit, Hospital General Regional #180, Instituto Mexicano del Seguro Social, Tlajomulco de Zúñiga Jalisco 45655, Mexico.

RESULTS
Throughout the study period, 826 patients were admitted to both ICUs, of which 66 (7.9%) had a diagnosis of septic shock; 59 patients met the inclusion criteria because 7 subjects died within the first 48 h (Figure S1, supplementary material). The median age was 57 years (IQR, 38-65), 26 patients (44.1%) were men, 25 patients (42.4%) were oncologic, and 42 patients (71.2%) were surgical patients. The most common source of infection was pneumonia, which presented in 26 patients (44.1%). The mean APACHE Ⅱ score was 21.5 (SD ± 5.8). Hydrocortisone was administered as a continuous infusion in 54.2% of patients; the median dose of norepinephrine at initiation of hydrocortisone was 0.3 μg/kg per minute (IQR, 0.18-0.39), there were no systemic steroids administered other than hydrocortisone, time from norepinephrine to initiation of hydrocortisone was 12 h (IQR, 6-27), and length of vasopressor requirement was 83 h (IQR, 49-120). Among survivors, hydrocortisone was tapered in 23 patients (53.5%). Overall 30-d mortality was 42.4%.

Method of administration
There were no significant differences in demographic and baseline clinical characteristics between patients in the continuous infusion and bolus groups (Table 1). We found no differences in these characteristics between recruitment centers (Table S1, supplementary material). Patients in the bolus group received hydrocortisone 6 h later than patients with continuous infusion (*P* = 0.01), and time to shock reversal was 49 h longer (*P* = 0.001). Concerning adverse affects, bolus administration was significantly associated with higher incidence of new

Table 1 Univariate analysis of demographic, clinical characteristics and outcomes of the study population according to method of administration of hydrocortisone

Characteristics	Continuous infusion (*n* = 32)	IV bolus (*n* = 32)	*P* value
Age, median (IQR)	50 (37-64)	61 (39-70)	0.19
Male gender, *n* (%)	12 (37.5)	14 (51.9)	0.27
Oncologic disease, *n* (%)	15 (46.9)	10 (37)	0.45
Surgical patients, *n* (%)	25 (78.1)	17 (63)	0.2
Infection source, *n* (%)			
Pneumonia	13 (40.6)	13 (48.1)	0.56
Ventilator associated	7 (21.8)	6 (22.2)	0.87
Health care associated	3 (9.3)	4 (12.5)	0.66
Community acquired	3 (9.3)	3 (11.1)	0.52
Abdomen	14 (43.7)	10 (37)	0.6
Soft tissue	4 (12.5)	1 (3.7)	0.23
Urinary tract	1 (3.1)	2 (7.4)	0.45
Other	0 (0)	1 (3.7)	0.27
Diabetes, *n* (%)	8 (25)	4 (14.8)	0.33
Acute kidney injury, *n* (%)	14 (43.7)	17 (63)	0.14
Baseline creatinine, mg/dL, median (IQR)	0.8 (0.7-1.4)	1.1 (0.7-1.5)	0.32
ARDS, *n* (%)	10 (31.2)	11 (40.7)	0.45
APACHE II score (SD)	21 ± 6	21.7 ± 5.6	0.76
SOFA score (SD)	10 ± 2.9	11 ± 2.7	0.16
Vasopressin use, *n* (%)	12 (37.5)	4 (14.8)	0.5
Maximum NE dose (mcg/kg per minute), median (IQR)	0.25 (0.17-0.36)	0.33 (0.20-0.39)	0.55
Hydrocortisone dose (mg/kg per day), median (IQR)	2.63 ± 0.27	2.75 ± 0.31	0.13
NE to hydrocortisone (h), median (IQR)	8 (4-19.5)	14 (8-31.5)	0.01
Time to shock reversal (h), median (IQR)	59 (47.5-90.5)	108 (63.2-189)	0.001
Shock relapse, *n* (%)	4 (18.2)	7 (38.9)	0.14
Hydrocortisone tapered, *n* (%)	10 (41.7)	13 (68.4)	0.08
Diuretic use, *n* (%)	19 (59.4)	11 (40.7)	0.15
New onset hypernatremia, *n* (%)	17 (53.1)	18 (66.7)	0.29
New onset hypokalemia, *n* (%)	12 (37.5)	18 (66.7)	0.02
New onset hyperglycemia, *n* (%)	19 (59.4)	23 (85.2)	0.03
Superinfection, *n* (%)	3 (9.4)	5 (18.5)	0.31
Wound dehiscence, *n* (%)	3 (9.4)	2 (7.4)	0.78
UGIB, *n* (%)	1 (3.1)	0 (0)	0.35
ICU-AW, *n* (%)	8 (25)	9 (33.3)	0.48
Vasopressor-free days, median (IQR)	3 (2-5)	2 (0-3.7)	0.12
ICU LOS, median (IQR)	8.5 (6-13)	9 (5-13)	0.81
30-d mortality, *n* (%)	10 (31.2)	15 (55.6)	0.06

APACHE II: Acute physiology and chronic health evaluation; ARDS: Acute respiratory distress syndrome; ICU-AW: Intensive care unit acquired weakness; ICU LOS: Intensive care unit length of stay; IQR: Interquartile range; NE: Norepinephrine; SOFA: Sequential Organ Failure Assessment; UGIB: Upper gastrointestinal bleeding.

onset hyperglycemia, with a relative risk (RR) of 2.7 (*P* = 0.03); hypokalemia was also more common with bolus administration, with a RR of 1.8 (*P* = 0.03). There was a trend to higher mortality in the bolus group, but this was not statistically significant (RR = 1.5; *P* = 0.06).

Regarding efficacy, continuous infusion was associated with a lower norepinephrine maximal dose requirement, from 12 h after hydrocortisone initiation. At two-way mixed ANOVA test, the maximal dose of norepinephrine for patients with continuous infusion after initiation of hydrocortisone was 0.19 μg/kg per minute, compared to 0.34 μg/kg per minute for patients on bolus administration, with a significant interaction between groups (*P* = 0.04; Figure 1). At Kaplan-Meier analysis, continuous infusion was also significantly associated with a higher proportion of shock reversal at 7 d after presentation of shock (83% *vs* 63%; *P* = 0.004; Figure 2); this difference remained significant after adjustment for vasopressin use with Cox proportional hazards regression (*P*

= 0.02).

At survival analysis, there was a trend to higher survival in patients on continuous infusion, with a hazard ratio for death of 0.47; however, this was not significant after adjustment for time to initiation of hydrocortisone (*P* = 0.06).

Initiation
We found a significant correlation between time to initiation of hydrocortisone and time to shock reversal, with a Spearman correlation coefficient of 0.80 (*P* ⩽ 0.001; Figure 3). Moreover, we built a ROC curve for this variable and obtained the best cut-off at ⩽ 13 h, with a significant area under the curve (AUC) at 0.81 (*P* ⩽ 0.0001), obtaining a sensitivity of 70% and specificity of 88% for prediction of shock reversal (Figure 4). Taking the dose of norepinephrine as a potential criterion for prompting initiation of hydrocortisone, ROC curve analysis revealed the best cut-off at ⩽ 0.28 μg/kg per minute,

Table 2 Univariate and multivariate logistic regression analysis for relevant factors associated with new-onset hyperglycemia

Variable	Univariate		P value	Multivariate	P value
	NO-H (*n* = 42)	No NO-H (*n* = 17)		Adjusted OR (95%CI)	
Bolus hydrocortisone, *n* (%)	19 (45.2)	13 (76.5)	0.04	3.2 (0.5-26.5)	0.99
Hydrocortisone taper, *n* (%)	20 (64.5)	3 (27.3)	0.03	5.3 (1.8-34.5)	0.04
Diabetes, *n* (%)	11 (26.2)	1 (5.9)	0.08	6.2 (0.4-79.0)	0.95

Goodness-of-fit (Hosmer-Lemeshow). χ^2 = 0.019, *P* = 1.00; AUC, 0.88 (0.75-0.96), *P* = 0.0001. NO-H: New-onset hyperglycemia; OR: Odds ratio.
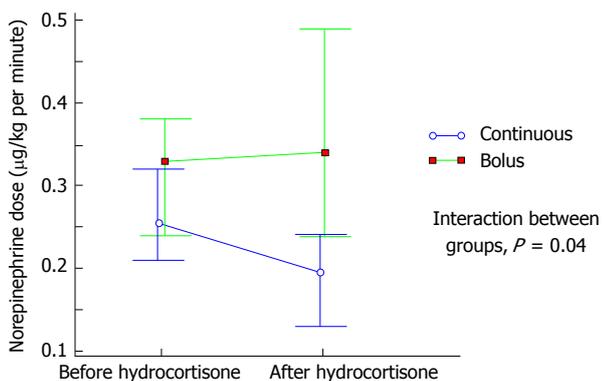

Figure 1 Change in maximal norepinephrine dose from 12 h after initiation of hydrocortisone. Comparison between continuous and bolus administration groups, with two-way mixed ANOVA test, *P* = 0.04.
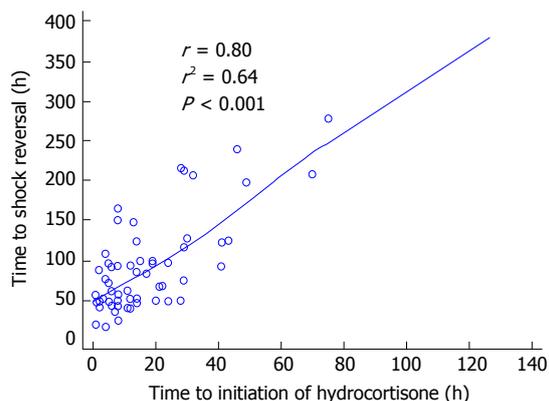

Figure 3 Correlation between time to initiation of hydrocortisone and total time to shock reversal. Spearman correlation coefficient 0.80, *P* < 0.001.
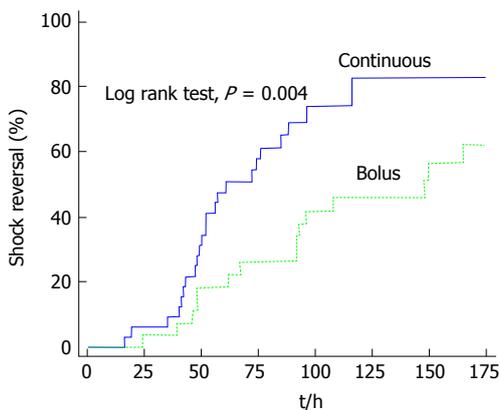

Figure 2 Kaplan-Meier analysis comparing the rate of septic shock reversal, according to administration of hydrocortisone. At 7 d (168 h), 83% of continuous infusion patients were vasopressor-free compared to 63% of patients who were in the bolus administration group, *P* = 0.004.
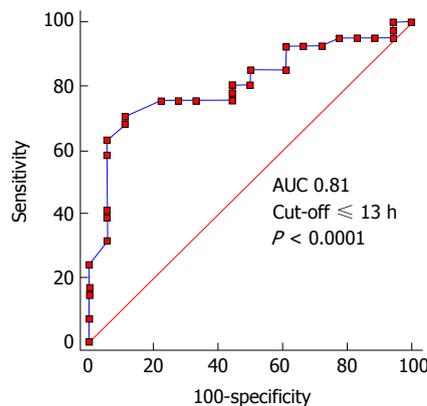

Figure 4 Receiver operating characteristic curve analysis of time to initiation of hydrocortisone for prediction of shock reversal. AUC, 0.81, *P* < 0.0001. Cut-off obtained with Youden index. AUC: Area under the curve.

with an AUC of 0.75 (*P* = 0.0002), a sensitivity of 65%, and a specificity of 88% for shock reversal.

Discontinuation and adverse effects

As expected for patients with shock reversal, length of hydrocortisone administration was significantly longer for patients with the tapering strategy than for patients with sudden discontinuation [121 h (IQR, 81-245) *vs* 50 h (IQR, 44-101); *P* = 0.001]. Taper strategy was independently associated with a higher risk of hyperglycemia (RR = 3.2; *P* = 0.042), and hypokalemia (RR = 2.8; *P* = 0.005). Because bolus administration was also independently associated with higher risk of

hyperglycemia and hypokalemia at univariate analysis, we performed logistic regression models adjusting for potential confounding variables; only the taper strategy maintained statistical significance for higher risk of hyperglycemia (Table 2) and had the highest OR for hypokalemia (Table 3).

Hydrocortisone taper was not associated with a lower risk of shock relapse (RR = 1.29; *P* = 0.17).

Shock reversal

In order to identify the variables associated with a higher probability of shock reversal, we performed a logistic regression model, adjusting for relevant covariables. As shown in Table 4, only the initiation of hydrocortisone ≤

Table 3 Univariate and multivariate logistic regression analysis for relevant factors associated with new-onset hypokalemia

Variable	Univariate		P value	Multivariate	P value
	NO-HK (*n* = 30)	No NO-HK (*n* = 29)		Adjusted OR (95%CI)	
Bolus hydrocortisone, *n* (%)	12 (40)	20 (69)	0.02	8.5 (1.2-59.9)	0.03
Hydrocortisone taper, *n* (%)	17 (77.3)	6 (30)	0.002	10.6 (1.5-73.3)	0.01
AKI, *n* (%)	13 (43.3)	18 (62.1)	0.08	0.1 (0.01-0.8)	0.03
Diuretic use, *n* (%)	20 (66.7)	10 (34.5)	0.01	6.3 (0.95-42.0)	0.05

Goodness-of-fit (Hosmer-Lemeshow). χ^2 = 5.52, *P* = 0.59; AUC, 0.88 (0.74-0.95), *P* = 0.0001. AKI: Acute kidney injury; HK: Hypokalemia; OR: Odds ratio.

Table 4 Univariate and multivariate logistic regression analysis for relevant factors associated with shock reversal

Variable	Univariate		P value	Multivariate	P value
	Shock reversal (*n* = 30)	No-reversal (*n* = 29)		Adjusted OR (95%CI)	
Age (yr), SD	53 ± 16.3	50 ± 16.3	0.46		
Male gender, *n* (%)	15 (36.6)	11 (61.1)	0.08	1.4 (0.21-10.1)	0.68
Medical disease, *n* (%)	11 (26.8)	6 (33.3)	0.61		
Oncologic disease, *n* (%)	20 (48.8)	5 (27.8)	0.13	1.0 (0.18-6.3)	0.92
AKI, *n* (%)	17 (41.5)	14 (77.8)	0.01	0.3 (0.05-2.0)	0.23
ARDS, *n* (%)	12 (29.3)	9 (50)	0.12	2.7 (0.4-16.9)	0.27
Superinfection, *n* (%)	5 (12.2)	3 (16.7)	0.68		
APACHE Ⅱ score (SD)	20 ± 5.4	23 ± 6.4	0.16	1.1 (0.9-1.3)	0.18
SOFA score (SD)	10 ± 3.0	10 ± 2.4	0.69		
Vasopressin use, *n* (%)	10 (24.4)	6 (33.3)	0.48	2.5 (0.4-15.4)	0.31
Early hydrocortisone (≤ 13 h from NE), *n* (%)	28 (68.3)	2 (11.1)	0.0001	13.8 (1.4-129)	0.02
NE dose at hydrocortisone initiation ≤ 0.28 μg/kg per minute, *n* (%)	28 (68.3)	2 (11.1)	0.0001	32.4 (2.7-382)	0.005

Goodness-of-fit (Hosmer-Lemeshow). χ^2 = 7.01, *P* = 0.53; AUC, 0.91 (0.80-0.96), *P* ≤ 0.0001. AKI: Acute kidney injury: APACHE Ⅱ: Acute physiology and chronic health evaluation; ARDS: Acute respiratory distress syndrome; NE: Norepinephrine; SOFA: Sequential organ failure assessment.

13 h from vasopressor administration and initiation of norepinephrine at a dose ≤ 28 μg/kg per minute were statistically significant.

DISCUSSION

The main finding in our study is that, compared to bolus strategy, the administration of hydrocortisone by continuous infusion may lead to a faster reversal of shock and is associated with a higher proportion of vasopressor-free patients at 7 d. Furthermore, we identified optimal cut-off criteria for initiation of hydrocortisone, either based on the time from initiation of vasopressor, or the current maximal dose of norepinephrine. This study also suggests there is no benefit of the tapering strategy because it does not lower the risk of shock relapse but is only associated with a higher incidence of adverse effects.

The current Surviving Sepsis Campaign Guidelines[2] suggest using continuous infusion, rather than a repetitive bolus of hydrocortisone. This recommendation is only based on the results of an observational study in which bolus hydrocortisone was associated with increased blood glucose levels and more variable peak values compared to continuous infusion[14]. This assumption was confirmed by univariate analysis in our study, and the findings strengthen this recommendation's effectiveness because the vasopressor requirement was 2 d shorter for patients on continuous infusion.

Most current studies, including meta-analyses, only focus on the association between corticosteroids and mortality in septic shock patients[6-10,15-20]; therefore, information related to the hemodynamic effects of both methods of administration is limited. In a recent Chinese study of septic shock patients, the continuous infusion strategy was correlated with a slight improvement in mean arterial pressure but only at 6 h after corticosteroid treatment, and the response was not sustained[21]. To our knowledge, this is the first study comparing both methods in which continuous infusion was found to hasten shock reversal. A possible explanation is the noted high variability in glucocorticoid sensitivity among septic shock patients with severe disease, as measured by suppression of inflammatory cytokine production[22]. Moreover, it has been found that a common genetic variation in the promoter of NF-ĸB1 (insertion-deletion polymorphism - 94ins/delATTG) is, in fact, associated with nonresponse and a 3-fold increase in risk of death in patients receiving hydrocortisone[23]. As these factors were not included in our study, the distribution of this potential bias in our population is unknown.

The primary change in practice reported after the publication of the Corticosteroid Therapy of Septic Shock study[9] and the updated Surviving Sepsis Campaign Guidelines was that physicians no longer used the cosyntropin stimulation test to identify which patients would benefit from corticosteroids[24]. However, since there are no specific criteria for definition of poorly responsive shock, a major discrepancy between clinicians' interpretation guidelines and clinical practice is the trigger for initiation of hydrocortisone. In a recent study[10], the most common

clinical threshold for prescribing corticosteroids was the presence of 2 or more vasopressors in 64% of patients. We believe that there should be a global agreement according to variables associated with the higher probability of shock reversal. Based on our results at ROC curve analysis and correlation with time to shock reversal, we suggest initiation of hydrocortisone at $\leqslant$ 13 h after vasopressor administration. This conclusion agrees with a recent study of severely shocked patients in which the early administration of hydrocortisone (< 9 h) was associated with a significantly lower total time of vasopressors and mortality[25].

In a retrospective review addressing norepinephrine as a trigger for initiation of corticosteroids, the dose was arbitrarily defined as non-weight-based low, moderate, or high[10]. Through a more objective approach, we found a dose of $\leqslant$ 0.28 μg/kg per minute to be the best predictor for shock reversal, a lower threshold than what has been used in most studies[9,25,26], reinforcing the recommendation of an earlier initiation of hydrocortisone also based on vasopressor dose[27,28].

Another interesting finding of this study is the apparent lack of benefits to the tapering strategy for discontinuation of hydrocortisone. The Surviving Sepsis Campaign Guidelines suggest tapering from steroids when they are no longer required; therefore, this strategy is the most commonly used (in up to 74% of patients), depending on the duration of hydrocortisone therapy[10]. Unfortunately, there has been no comparative study between tapering and abrupt cessation, and the main argument for this suggestion is a small crossover study in which shock relapse occurred in 30% of patients with sudden discontinuation[29]; however, the study was underpowered to reach that conclusion, because the data arose from a subgroup analysis of 20 patients. Therefore, tapering has a 2D recommendation (the weakest possible) on the GRADE system. Furthermore, there have been other randomized controlled studies in which corticosteroids were abruptly discontinued without reported increased risk of shock relapse[7,8]. In the current study, tapering was only associated with adverse effects; therefore, we suggest this should be avoided, especially for patients with ongoing hyperglycemia and/or hypokalemia.

The main strength of this study is that it was specifically designed to compare the efficacy between both methods of administration of hydrocortisone, according to vasopressor requirement, indirectly assessing their effects on immunomodulation and vasomotor tone improvement.

This study has some limitations; we did not address the effects of the use of some drugs known to affect adrenal function (*e.g.,* etomidate, antifungals, benzodiazepines, and opioids)[30]. Medical management for septic shock patients is always based on the current Surviving Sepsis Campaign Guidelines and are very similar at both hospitals; however, due to the observational and nonrandomized design of the study, we cannot ensure completely homogeneous treatment regarding other relevant variables associated with improving outcomes (*e.g.,* appropriateness and type of fluid resuscitation and correct and timely use of antibiotics). This study was powered to detect differences in short-term vasopressor requirements and to find the best cut-offs for initiation of hydrocortisone only; therefore, results concerning analysis between groups should be interpreted cautiously, and should be taken as hypothesis-generating data for the design of future clinical randomized controlled trials.

In conclusion, we found that continuous infusion of hydrocortisone could hasten resolution of septic shock compared with bolus administration, and that earlier initiation based on time and/or norepinephrine dose is related with a higher probability of shock reversal. The tapering strategy appears unnecessary and may be only related to additional adverse effects.

COMMENTS

Background
The latest Surviving Sepsis Campaign Guidelines recommend administration of low-dose hydrocortisone (200 mg/d) when hemodynamic stability is not achievable after fluid resuscitation and vasopressor therapy. Although the benefits of hydrocortisone are increasingly being recognized, several issues concerning its specific indications, clinical criteria for initiation, adequate method of administration, and strategy of discontinuation are unresolved, which leads to widely heterogeneous prescribing practices among critical care physicians. Studies addressing those issues are lacking.

Research frontiers
The reported prescribing patterns of hydrocortisone for patients with septic shock come from studies performed only in the United States and describe a wide variability of clinical practices. In Mexico, this kind of information is scarce.

Innovations and breakthroughs
Continuous infusion of hydrocortisone leads to faster resolution of shock than bolus administration. Initiation of hydrocortisone at $\leqslant$ 13 h after starting norepinephrine and/or a maximal dose of $\leqslant$ 28 μg/kg per minute is associated with a higher probability of shock reversal. There is no benefit from a tapering strategy because this was only shown to lead to additional adverse effects.

Applications
The results of the study add valuable information, which could contribute to the initiation of a widespread agreement regarding specific indications on the correct use of hydrocortisone in septic shock patients.

Peer-review
It is a well design study, though performed in a small group of patients.

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