How safe is the administration of hydrocortizone in patients with septic shock?

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Abstract

Introduction. *Although the administration of hydrocortisone in septic shock generates adverse effects, the risk of corticosteroid-induced hypernatremiamay be reduced by continuous administration of the drug.*

Materials and methods. *171 patients with septic shock were randomized into three study groups: group A (n = 58) – 200 mg/day of hydrocortisone hemisuccinate in four doses; group B (n = 59) – same dose of hydrocortisone hemisuccinate in continuous administration; group C (n = 54) – no hydrocortisone hemisuccinate. Mean serum sodium values, the number of hypernatremia episodes and variations in serum sodium (Navar) were investigated for seven days.*

Results. *Mean values were normal in group C (140.35 ± 7.390 mEq/L to 144.79 ± 8.338 mEq/L). High mean values appeared on day 4 in group A (147.21 ± 8.470 mEq/L to 149.37 ± 8.973 mEq/L on day 7) and on day 5 in group B (146.36 ± 8.272 mEq/L to 147.70 ± 8.865 mEq/L). Navar was 8.59 ± 5.960 mEq/L (-8 and 21 mEq/L) in group A, 6.63 ± 7.609 mEq/L (-17 and 23 mEq/L) in group B and 4.54 ± 7.455 mEq/L (-12 and 22 mEq/L) in group C. This variation is statistically significant when groups A and B are compared to group C (p = 0.012) and when only group A is compared to group C (p = 0.0019). The risk of hypernatremia after HHS was almost three times higher than that of patients who did not receive this drug (RR 2.82, 1.35<OR<5.90, p = 0.0041) and slightly higher when HHS was deliveredas a bolus (RR 3.08, 1.32<OR<7.25, p = 0.0071).*

Conclusions. *Continuous administration of HHS in septic shock is associated with a lower risk of hypernatremia than bolus administration.*

Key words: hydrocortisone, septic shock, hypernatremia

INTRODUCTION

Sepsis is a systemic condition determined by the exaggerated response of a host to infection, leading to multiple organ failure and death. The first definition criteria of sepsis were established in 1992 (1), labeling it a systemic inflammatory response induced by a confirmed or suspected infection and characterized by at least two of the following four criteria: fever (over 38°C) or hypothermia (under 36°C); tachycardia (heart rate over 90 beats/minute); tachypnea (respiratory rate over 20 breaths/minute) and leukocytosis (> 12,000 elements/mm^3) or leukopenia (< 4,000 elements/mm^3) or >10% immature leukocytes (bands). **Severe sepsis** is defined as sepsis accompanied by end-organ dysfunction andperipheral hypoperfusion. **Septic shock** is

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represented by sepsis accompanied by persistent arterial hypotension which does not respond to adequate administration of intravenous fluids.

Sepsis is considered to be the main cause of morbidity and mortality in the intensive care unit (ICU) (2). The incidence of sepsis and severe sepsis in the ICU varies between 20 and 80% in observational studies (3-7). Septic shock affects between 10 and 30% of the patients admitted to the ICU (3,5,8) and its incidence is currently on the rise (4).

The efficacy of cortisol administration in septic shock generates many controversial issues, among them being the difficulty in establishing a correct diagnosis of relative adrenal insufficiency in septic patients, the lack of influence of corticosteroid administration on mortality rates and the high risk of adverse effects associated with the use of these drugs. These aforementioned complications of corticosteroid use include immunosuppression, decreased leukocyte count, superinfection, hyperglycemia and fractious blood glucose levels, hypernatremia, hypokalemic metabolic acidosis, apoptosis at the level of the intestinal epithelium with an increased risk of gastro-intestinal complications, abnormal wound healing, acute psychosis and neuromyopathy leading to difficulties in weaning the patient off the ventilator (9). The extent of these complications varies according to the dosage, as well as the type and duration of corticosteroid administration. Septic patients with relative adrenal insufficiency are at increased risk of hyponatremia; this is indeed one of the criteria according to which this condition is diagnosed. Hypernatremia is often influenced by iatrogenic factors, such as the excessive use of isotonic solutions (normal saline), the administration of high quantities of sodium bicarbonate solutions to treat metabolic acidosis and extensive uncorrected fluid and electrolyte loss.

The objective of this study was to evaluate the safety of administering hydrocortisone in septic patients by investigating their serum sodium profile. To our knowledge, there are only a few studies which compare the influence of the mode of corticosteroid administration on hemodynamic parameters and treatment tolerance. We therefore based this study on the hypothesis that the continuous administration of corticosteroids may lower the risk of hypernatremia in patients with sepsis.

MATERIALS AND METHODS

This is a prospective, randomized, unicentric study which took place at a multidisciplinary intensive care unit (ICU) with 35 beds which host patients with medical and surgicalillnesses, as well as patients with multiple trauma. 181 of patients admitted to the ICU during a period of 5 years and 8 months met all the inclusion and exclusion criteria of this study and signed an informed consent form. 10 patients were then excluded due to incomplete data or withdrawal of their consent during the study. The remaining 171 patients were randomized into three study groups according to the type of treatment they received: group A (n = 58) treated with 200 mg/day of hydrocortisone hemisuccinate (HHS) divided into four doses, group B (n = 59) who received an equal dose of HHS via continuous administration and group C (n = 54) was not treated with HHS. This treatment was administered for the duration of seven consecutive days. Serum sodium values were investigated by comparing mean individual values, the number of hypernatremia episodes and the variations in serum sodium in a given patient (Na_{var}).

The following **inclusion criteria** were adopted:

1. Patients over 18 years of age whose legal representative(s) signed an informed consent form.

2. The presence of septic shock, defined according to the following criteria (1,10):

a. proof of infection **or** a high index of suspicion;

b. three or more of the following criteria: mechanical ventilation, heart rate over 90 beats/minute, the presence of fever or hypothermia (body temperature > 38°C or < 36°C), the presence of leukocytosis (> 12.000 leukocytes/mm^3) or leukopenia (< 4,000 leukocytes/mm^3);

c. sepsis-induced persistent arterial hypotension (diagnosed after the exclusion of all other potential causes of hypotension in patients with a systolic blood pressure < 90 mmHg or a decrease in systolic blood pressure by ≥ 40 mmHg or a mean arterial blood pressure ≤ 65 mmHg).

3. The necessity of noradrenaline administration to maintain a mean arterial blood pressure > 70 mmHg (despite adequate fluid resuscitation).

The following **exclusion criteria** were adopted: patients with preexistent adrenal pathology, patients who had received corticosteroids or immunosuppressants in the year before, HIV infection, acute myocardial infarction, pulmonary embolism, terminal cancer, chronic renal insufficiency necessitating hemodialysis, Child-Pugh Class C hepatic cirrhosis,

patients who were not expected to survive more than 24 hours, patients under 18 years of age.

The present study was approved by the hospital's Ethics Committee and informed consent was obtained from the patients' legal representatives after the diagnosis of septic shock was established, but before randomization. Patients were assigned to one of the three study groups by a computer, using the ratio 1:1:1 and a list of randomized numbers compiled by a person who was not involved in the study. Patients were recruited into the study in the first 24 hours after the onset of septic shock.

The following **parameters** were recorded:

1. **Demographic data**: age, sex, body weight, diagnosis at admission (according to which the patients were divided into a medical, surgical or trauma ICU group)

2. **The origin of sepsis**

3. **Hemodynamic parameters**:

• *standard, non-invasive monitoring*: heart rate, EKG tracing (leads DII or V_2), systolic and diastolic arterial blood pressure ($_SBP$, $_DBP$), hourly urine output;

• *invasive monitoring*: mean arterial blood pressure ($_MBP$), central venous pressure (CVP), cardiac index (CI), stroke volume (SV), stroke volume index (SVI), stroke volume variation (SVV), systemic vascular resistence index (SVRI), central venous oxygen saturation ($ScvO_2$).

4. **General parameters**: peripheral body temperature (°C)

5. **Respiratory parameters**: respiratory frequency, oxygen saturation of peripheral arterial blood (SpO_2), type of mechanical ventilation and its associated parameters, fraction of inspired oxygen (FiO_2)

6. **Parameters derived from the analysis of arterial blood gasses**: partial pressure of oxygen in peripheral arterial blood (paO_2), partial pressure of carbon dioxide in peripheral arterial blood ($paCO_2$), blood pH, serum bicarbonate, base excess (BE), difference between the alveolo-arterial oxygen gradient ($p(A-a)O_2$), serum lactate; we also calculated the paO_2/FiO_2 ratio.

7. **Biochemical parameters**: complete blood count, glycemia, electrolytes (sodium, potassium, chloride), common coagulation tests (apTT, INR, fibrinogen), transaminases, total bilirubin and its fractions, serum albumin, urea and creatinine.

8. **The daily administered dose of noradrenaline.**

According to their diagnosis upon admission to the ICU, the patients were divided into three categories: trauma (T), surgical cases (S) and medical cases (M). Haemodynamic monitorization of the patients was done by both invasive and non-invasive methods in all patients. Invasive monitoring was done using the Vigileo™ monitor (Edwards Lifesciences Corporation, Irvine, USA) and the FloTrac™ dedicated pressure sensor. This sensor was connected to a common arterial catheter which was inserted at the level of the radial artery. Single- or multilumen central venous catheters (Vygon Corporation, Ecouen, France) were used to monitor central venous pressure and were inserted into the superior vena cava via the internal jugular vein or the subclavian vein. Non-invasive and invasive parameters were recorded every hour, but only the „worst" values recorded every 24 hours were taken into account when introducing this information into a database or when calculating the gravity scores. The drug used in this study was hydrocortisone hemisuccinate commercialized in 100 mg-flasks (E.I.P.I.C.O. MED SRL – Romania: 100 mg powder and 2 mL benzyl-alcohol 0.9% as a reconstitution solution).

RESULTS

The mean age of the patients included in this study was 60.41 ± 19.36 years in group A, 59.02 ± 20.28 years in group B and 61.00 ± 18.54 years in group C. The following gender distribution was present: group A women/men – 16/42; group B women/men – 21/38; group C women/men – 22/32. Figure 1 shows the distribution of thepatients in these three groups according to their ICU admission category (T, S and M). There were no statistically significant differences in mean age, gender distribution, ICU admission category and gravity scores between the three groups, as demonstrated by Table 1.

Table II presents the variations in mean serum sodium values registered in the seven days during which the patients were observed. The results show an increase in serum sodium values in all three study groups, because $Na_{var} > 0$. Na_{var} is defined as the difference between the values of serum sodium on the last day and first day of monitorization (measured in mEq/L). The recorded Na_{var}values were 8.59 ± 5.960 mEq/L (with variations between -8 and 21 mEq/L) in group A, 6.63±7.609 mEq/L (with variations between -17 and 23 mEq/L) in group B and 4.54 ± 7.455 mEq/L (with variations between -12 and 22 mEq/L) in group C. These differences in Na_{var} values were statistically significant when groups A and B were compared to group C (i.e. hydrocortisone administration vs. control; p = 0.012)

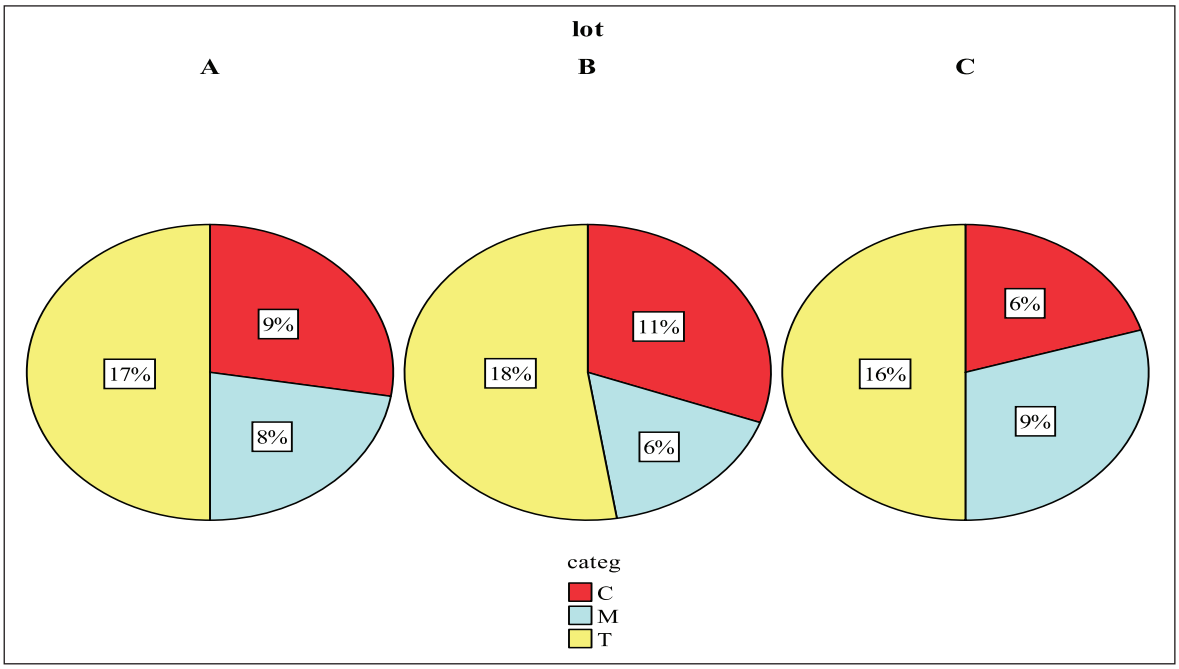

FIGURE 1. *The associative distribution of patients according to study group and diagnosis upon admission to the ICU (T – trauma, S – surgery and M – medical)*

TABLE 1. *The description of the study groups according to the following demographical parameters: age, sex, admissions category, gravity scores*

Parameter		Study group			p
		A (n = 58)	B (n = 59)	C (n = 54)	
Age (years)		60.41 ± 19.36	59.02 ± 20.28	61.00 ± 18.54	0.855
ICU Admissions Category	S	16	18	11	0.525
	M	13	10	16	
	T	29	31	27	
Gender	F	16	21	22	0.335
	M	42	38	32	
SOFA		12 ± 2.59	12 ± 2.12	11 ± 2.56	0.428
APACHE II		21.5 ± 9.9	24 ± 7.83	22.5 ± 9.65	0.82
SAPS II		51 ± 16.14	52 ± 16.57	51 ± 15	0.332

SOFA – Sequential Organ Failure Assessment Score
APACHE II – Acute Physiology and Chronic Health Evaluation II
SAPS II – Simplified Acute Physiology Score II

and when groups A and C were compared (i.e. bolus administration of hydrocortizone vs. control; p = 0.019).

Normal values of serum sodium were present throughout the duration of the study in group C, varying between 140.35 ± 7.390 mEq/L and 144.79 ± 8.338 mEq/L. Contrastingly, this parameter was abnormal in groups A and B. Continually rising values of serum sodium were registered in group A on days 4 (147.21 ± 8.470 mEq/L) through 7 (149.37 ± 8.973 mEq/L) and in group B on days 5 (146.36 ± 8.272 mEq/L) through 7 (147.70 ± 8.865 mEq/L).One can presume that hydrocortisone administration favors hypernatremia – serum sodium values are increased on days 4 and 7 in both group A and group B in comparison to group C (p = 0.038 and 0.035, respectively). Na_{var} is significantly higher in groups A and B compared to group C (p = 0.012). One can observe that hypernatremia progresses faster who hydrocortisone is administered as a bolus instead of being given in a continual fashion: hypernatremia appears on day 4 in group A vs. day 5 in group B. However, this difference was not statistically significant between the two groups (p > 0.05). A significant rise in serum sodium values is detected between days 4 and 7 when group A is compared to group C, but this rise is not statistically significant when group B is compared to group C (except on day 2).

Table 3 shows that the frequency of hypernatremia is almost constant in group C, but doubles itself during the study period in group A (13 episodes on day 1 vs. 31 episodes on days 4-7) and group B (12 episodes on day 1 vs. 25-27 episodes on days 3-7). These differences are statistically significant between groups A and C (p_{AC} < 0.05).

TABLE 2. *The variation of serum sodium levels (Na_{var}) in the three study groups during the seven days in which hydrocortisone hemisuccinate (HHS) was administered*

Serum sodium levels	STUDY GROUPS			P			
	Group A (n = 58)	Group B (n = 59)	Group C (n = 54)	A/B/C	A/B	A/C	B/C
Day 1	141.28 ± 6.542	141.53 ± 7.326	140.35 ± 7.390	0.656	0.846	0.484	0.399
Day 2	143.30 ± 7.338	144.08 ± 7.221	141.17 ± 6.952	0.088	0.566	0.120	0.031*
Day 3	145.27 ± 8.089	145.57 ± 7.527	143.12 ± 6.425	0.178	0.841	0.131	0.072
Day 4	147.21 ± 8.470	145.72 ± 7.923	143.24 ± 7.293	0.038*	0.351	0.012*	0.098
Day 5	147.73 ± 8.666	146.36 ± 8.272	144.00 ± 7.530	0.072	0.408	0.023*	0.136
Day 6	148.49 ± 8.317	147.06 ± 8.329	144.57 ± 7.525	0.053	0.387	0.015*	0.121
Day 7	149.37 ± 8.973	147.70 ± 8.865	144.79 ± 8.338	0.035*	0.348	0.010*	0.099
Na_{var}	8.59 ± 5.960 Min. -8 Max. 21	6.63 ± 7.609 Min. -17 Max. 23	4.54 ± 7.455 Min. -12 Max. 22	0.012*	0.124	0.0019*	0.1437
Na_{var} = the difference between the serum sodium values (expressed in mEq/L) on the first and last day of the study period							

(* = statistically significant differences in serum sodium values between study groups, $p < 0.05$)

TABLE 3. *The dynamic distribution of hypernatremia episodes in the three study groups during the seven days in which hydrocortisone hemisuccinate (HHS) was administered*

	STUDY GROUP			P			
Hypernatremia	Group A (n = 58)	Group B (n = 59)	Group C (n = 54)	A/B/C	A/B	A/C	B/C
Day 1	13	12	12	0.956	0.481	0.581	0.822
Day 2	16	17	9	0.146	0.241	0.128	0.179
Day 3	26	27	13	0.098	0.995	0.053	0.042*
Day 4	30	25	12	0.013*	0.566	0.002*	0.042*
Day 5	31	25	15	0.071	0.442	0.014*	0.228
Day 6	31	23	14	0.025*	0.276	0.005*	0.179
Day 7	31	25	13	0.021*	0.487	0.004*	0.074

(* = statistically signigicant differences in the daily frequency of hypernatremia in the three study groups, $p < 0.05$)

Table 4 analyses the risk of hypernatermia as a function of HHS administration pattern and route. The results suggest that the administration of HHS significantly favors the ocurrence of elevations in normal serum sodium levels ($p_{AB/C} < 0,05$; $p_{A/C} < 0,05$; $p_{B/C} < 0.05$), as the risk of hypernatremia is approximately three times greater in patients who received cortisol compared to those who were not treated with this drug (RR 2.82, 1.35<OR<5.90, p = 0.0041). This risk is greater in patients who received a bolus of HHS in comparison to those who have not (group A – RR 3.08, 1.32<OR<7.25 vs. group C – p = 0.0071; group B – RR 2.58, 1.12<OR<6.01 vs. group C, p = 0.0245). The mean risk of hypernatremia which can be atributed to HHS is 64.5%. This risk was greater in patients who received boluses of HHS (67.5%) in comparison to those in which HHS was administered continually (61.24%). If the administration of HHS as a bolus is compared with continuous administration, the risk of hypernatremia which can be attributed to HHS

TABLE 4. *The risk of hypernatremia as a function of hydrocortisone hemisuccinate (HHS) administration pattern and route*

Comparison between study groups	p	Estimated relative risk of hypernatremia after administration of HHS (OR; CI 95% OR)	The risk of hypernatremia due to the adminstration of HHS (%)
(A+B) vs. C	0.0041*	2.82 (1.35<OR<5.90)	64.5
A vs. C	0.0071*	3.08 (1.32<OR<7.25)	67.5
B vs. C	0.0245 *	2.58 (1.12<OR<6.01)	61.24
A vs. B	0.7705	1.20 (0.54<OR<2.65)	16.7

(* = statistically signigicant differences in the frequency of hypernatremia between the three study groups, $p < 0.05$)

is 16.7%, RR 1.20, 0.54<OR<2.65, p = 0.7705 (no statistical significance).

DISCUSSIONS

Although the use of corticosteroids in the treatment of severe infections has been a controversial subject for over 50 years (11,12), some aspects still have not been elucidated.

A normal adult secretes 15-25 mg of cortisol/day, reaching 200-350 mg/day in maximum stress (13). These data have led pharmacologists to classify corticosteroid doses into small (25-200 mg/day), stress-dose (200-300 mg/day), supraphysiological (300-1,000 mg/day) and extreme (>1,000 mg/day) (13). The ideal dose of corticosteroids in patients with sepsis should eliminate hyperinflammation without triggering immunosuppression or other adverse reactions (13). The emergence of the concept of relative adrenal insufficiency emerged influenced physicians to administer substitutive doses of cortisol (maximum 200 mg/day) for longer periods of time (7 days or until the remission of septic shock) (14-25). The use of higher doses is clearly contraindicated in septic shock.

Very few studies have correlated the mode of administration of HHS (bolus vs. continuous) with the drug's adverse effects. A study done by Keh et al. in 2003 (26) compared the continuous administration of low doses of cortisol to placebo and demonstrated the benefic effects of the drug on both haemodynamic parameters and proinflammatory mediators. Other experimental studies have shown that bolus administration leads to variations in the serum concentration of cortisole, with the subsequent inhibition of the cellular immune response (27). Loisa et al. (28) was the first to compare continuous and bolus administration of HHS with respect to glycemic control and septic shock remission. He concluded that continuous administration reduces the number of hyperglycemic episodes and facilitates their control using smaller and less-frequently adjusted doses of insulin. No haemodynamic differences between the two groups were noted. However, continuous administration may lead to a persistent inhibition of the hypothalamic-pituitary-corticoadrenal axis. Current data do not allow us to make a firm recommendation in this sense, although it seems to be better to administer HHS in a continuous manner when possible (29).

The current study has demonstrated that the administration of cortizol increases the risk of hypernatremia in patients with septic shock. When HHS is administered, the number of hypernatremic episodes is twice a great, the mean serum sodium levels rise above normal on the fourth (bolus), respectively on the fifth day of treatment (continuous administration) and the risk of hypernatremia is three times as high. The results of this study confirm the possible advantages demonstrated by continuous administration of HHS (group B) in comparison to bolus administration of similar doses (group A) in patients with septic shock: hypernatremia appears 24 later in the former group and the relative risk of hypernatremia is smaller (RR 2.58 vs. 3.08).

CONCLUSIONS

The present study confirms the hypothesis that patients with septic shock who receive hydrocortisone are at higher risk of developing hypernatremia, although this risk can be lowered by the administration of the drug in a continuous mode.

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