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Mineralocorticoid deficiency in hemorrhagic shock

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Abstract

Background—In the critically ill, mineralocorticoid deficiency (MD) is associated with greater disease severity, the development of acute renal insufficiency, and increased mortality. We hypothesized that severely injured trauma patients presenting with hemorrhagic shock would demonstrate a high degree of MD. We also hypothesized that MD in these patients would be associated with increased length of stay, hypotension, fluid requirements, and acute kidney injury (AKI).

Materials and methods—Thirty-two trauma patients in hemorrhagic shock on admission to the trauma bay (SBP <90 mm Hg × 2) were enrolled. Blood samples were obtained on ICU admission and 8, 16, 24, and 48 hours later. Plasma aldosterone (PA) and renin (PR) were assayed by radioimmunoassay. MD was defined as a ratio of PA/PR > 2. Demographic data, injury severity score, ICU and hospital length of stay, fluid requirements, mean arterial pressure, serum sodium, hypotension, and risk for AKI were compared for patients with and without MD.

Results—At ICU admission, 48% of patients met criteria for MD. Patients with MD were significantly more likely to experience hypotension (MAP < 60 mm Hg) during the study period. MD patients required significantly more units of blood in 48 h than non-MD patients (13 [7–22] versus 5 [2–7], $P = 0.015$) and had increased crystalloid requirements (18L [14–23] versus 9L [6–10], $P < 0.001$). MD patients were at higher risk for AKI according to RIFLE and AKIN criteria.

Conclusions—MD is a common entity in trauma patients presenting in hemorrhagic shock. Patients with MD required a more aggressive resuscitative effort, were more likely to experience hypotension, and had a higher risk of AKI than non-MD patients. Future studies are needed to fully understand the impact of MD following trauma and the potential role for hormonal replacement therapy.

Keywords

Mineralocorticoid deficiency; Hyperreninemic hypoaldosteronism; Hemorrhagic shock; Trauma

1. Introduction

Trauma is the leading cause of death in people under the age of 40 in the United States with hemorrhagic shock accounting for 30%–40% of all trauma mortality [1]. Over the last several decades, there has been a 15%–25% reduction in immediate death due to hemorrhage, but such severely injured patients still face a high degree of postinjury morbidity and mortality [2]. A better understanding of the physiologic changes induced by hemorrhagic shock is important in managing these patients and may lead to a decrease in morbidity [3]. In particular, the activation of the renin-angiotensin-aldosterone system and hypothalamic-pituitary-adrenal axis represent major homeostatic responses to shock, and dysregulation is associated with cardiovascular collapse and poor outcome [4].

Dysfunction of both the hypothalamic-pituitary-adrenal axis and the renin-angiotensin-aldosterone system has been noted in septic patients, and a similar pattern of endocrinopathy may be important in trauma [5–8]. In particular, mineralocorticoid deficiency (MD) presenting as hyperreninemic hypoaldosteronism may contribute to the increased morbidity observed in septic patients. Mineralocorticoid deficiency in these patients is associated with greater inflammatory markers, increased renal failure, prolonged ICU stays, and higher mortality rates [9–14].

Mineralocorticoid deficiency may also occur in the setting of profound blood loss. In animal models, hemorrhage has been shown to cause glucocorticoid insufficiency and necrosis of the entire adrenal gland [15]. Given these findings, MD may be frequent after hemorrhagic shock, but to date clinical studies investigating MD following trauma are lacking.

This prospective observational clinical study investigates the prevalence and impact of MD following hemorrhagic shock. We hypothesized that severely injured trauma patients would exhibit a high degree of MD. We also hypothesized that MD in such patients would be associated with greater ICU length of stay, hospital length of stay, hypotension, and fluid requirements, and a greater risk for acute renal injury.

2. Materials and methods

2.1. Patients

We conducted a prospective observational study for 6 mo at our urban level I trauma center following approval by the Institutional Review Board of the University of Pennsylvania. Patients who presented to the trauma bay with shock (SBP <90 mm Hg $\times$ 2) due to blood loss were identified and screened at ICU admission. Exclusion criteria included age <18 y, pregnancy, current or recent (within 3 mo) history of corticosteroid use, and chronic renal failure or dialysis dependency. Patients admitted with concurrent traumatic brain injuries requiring neurosurgical intervention were also excluded, as were patients who expired within 24 h of admission. All enrolled patients underwent surgery and hemorrhage control

prior to ICU admission. Informed consent and HIPAA authorization were obtained from the next of kin. Data collected for each patient included demographics, injury severity score (ISS), ICU length of stay, and hospital length of stay. Venous lactate was measured on admission to the trauma bay. In addition, blood and crystalloid requirements, mean arterial pressure (MAP), serum sodium levels, and plasma creatinine values were recorded at each ICU blood draw. Hypotension was defined as a MAP measurement of ≤ 60 mm Hg [16].

2.2. Samples and assays

Blood samples were obtained from patients at ICU admission and at 8, 16, 24, and 48 h after ICU admission. Samples were collected in the supine position with standard EDTA plasma vacutainers, centrifuged at 1000 rpm for 10 min, followed by plasma separation and immediate freezing at -80°C until assay.

Radioimmune assay was used to measure plasma aldosterone (PA; Siemens, Los Angeles, CA) and direct plasma renin (PR; Beckman Coulter, Brea, CA) *post hoc* in duplicate at the Translational Core Research Facility at the University of Pennsylvania. Samples were processed in a masked fashion.

2.3. Calculation of PA/PR ratio

Plasma aldosterone (pg/mL) and direct plasma renin (pg/mL) values were used to calculate the plasma aldosterone/plasma renin ratio (PA/PR) [17]. As in prior studies, MD was defined as a PA/PR ratio of less than 2 [14].

2.4. Acute kidney injury

Serum creatinine was measured as part of routine clinical lab panels, and discharge creatinine was used as a baseline reference value. Risk of acute kidney injury was determined according to RIFLE criteria (1.5 times elevation in baseline creatinine) or AKIN criteria (absolute increase of ≥ 0.3 mg/dL over baseline creatinine) [18,19].

2.5. Statistical analysis

Statistical analyses were performed using Stata (Stata Corporation, College Station, TX). Mann-Whitney and Student *t*-tests were used to compare MD and non-MD patients for ICU length of stay, hospital length of stay, blood and crystalloid requirements, MAP, and serum sodium levels. Fisher exact test was used to compare the incidence of risk for acute renal injury and hypotension in MD and non-MD patients. Statistical significance was determined at a 2-tailed *P* value <0.05 .

3. Results

3.1. Demographics

Thirty-two trauma patients in hemorrhagic shock were enrolled, with a mean ($\pm$ SD) age of 36 ± 13 y, a mean ISS of 30 ± 14 , and median venous lactate of 4.9 mmol/L (3.4–9.0) (Table 1). All patients included in this study underwent rapidsequence intubation using etomidate. During the first 48 h after ICU admission, all but five patients received more than 5 units of blood, with a median value of 12 units (6–18) for the entire cohort. The median 48-h

crystalloid requirement for all patients was 14.9 L (10.8–20.7) (Table 1). Although median MAP values were similar in MD and non-MD patients, patients with MD were significantly more likely to experience episodes of hypotension (MAP $\leq$ 60 mm Hg) during the study period (10 *versus* 1, $P < 0.049$).

3.2. Mineralocorticoid deficiency

During the observation period, 8 patients (25%) were MD at all time points, 17 patients (53%) met MD criteria at least once, and 7 patients (22%) were never MD. At ICU admission, 13 patients (48%) met criteria for MD, as did 9 (59%) at 8 h, 18 (69%) at 16 h, 18 (58%) at 24 h, and 18 (62%) at 48 h (Table 2). Demographic variables were similar in MD and non-MD patients. Plasma aldosterone was within normal limits and similar between MD and non-MD patients, while plasma renin was markedly elevated only in MD patients ($P < 0.0033$) (Table 2).

3.3. Outcomes

MD did not correlate significantly with ICU length of stay. There was a trend toward increased hospital length of stay for patients who exhibited MD at least once during the study period, 23 d (15–33) *versus* 18 d (6–23), but this did not reach statistical significance ($P = 0.138$). MD patients required significantly more units of blood in 48 h than non-MD patients: 13 (7–22) *versus* 5 (2–7), $P = 0.015$. Crystalloid requirements were also significantly increased in MD patients: 18L (14–23) *versus* 9L (6–10), $P < 0.001$. Serum sodium levels were similar between groups (Table 3). A separate analysis of patients who were MD at all time points *versus* individuals who met MD criteria at least once during the study period did not show a significant difference for any outcome tested.

3.4. Acute kidney injury

The risk for acute kidney injury was elevated in patients who were MD at any time point compared to non-MD patients according to RIFLE criteria (18/25 [72%] *versus* 2/7 [29%], $P = 0.073$), although the results did not reach statistical significance (Table 4). There was a statistically significant increase in the risk for acute kidney injury in MD patients compared to non-MD patients according to AKIN criteria (21/25 [84%] *versus* 3/7 [43%], $P = 0.047$).

4. Discussion

In this first prospective clinical study of MD in trauma patients, we found that MD occurs frequently following hemorrhagic shock and is associated with the need for a more aggressive resuscitation post injury. Patients who experienced MD were found to have a significantly higher blood transfusion and crystalloid requirement than non-MD patients. In addition, patients who developed MD were at an increased risk for acute renal injury.

Specifically, in our cohort of severely injured trauma patients, the prevalence of MD ranged from 13 patients (48%) to 18 (69%) during the first 48 h of their hospitalization, with an overall prevalence of 78%. Interestingly, the prevalence of MD in our study is higher than the rates reported for MD in other types of shock (22%–64%) and may reflect the severe state of shock experienced by our patients [20]. On trauma bay admission, all patients

included in this study were hypotensive (SBP <90mm Hg $\times$ 2) with a median lactate of 4.9mmol/L (3.4–9.0).

Although aldosterone levels were within normal limits and similar in both MD and non-MD patients in this study, renin levels were markedly increased only in MD patients. In the setting of stress and trauma, a normal level of aldosterone in conjunction with an elevated renin level is inappropriate and represents a relative deficiency of aldosterone [17]. The development of relative mineralocorticoid insufficiency has been previously described in other critically ill patient populations, most notably those in septic shock. Moreover, given its high degree of mineralocorticoid activity, hydrocortisone is the steroid preferentially used to treat refractory septic shock [17].

In our patients, MD occurred within hours of the traumatic event. The timing of MD onset is important in evaluating the possible mechanism for MD. One proposed cause of MD is enhanced 17 α -hydroxylase expression, which is seen after chronic stress in rats and in cultured bovine zona glomerulosa cells chronically exposed to ACTH [21,22]. The rapid development of MD in our patients, however, is more consistent with an alternative theory of MD and is likely the result of damage to the zona glomerulosa. In animal studies, mild hemorrhage and hypotension resulted in adrenal necrosis within 4 h and was associated with a significant decrease in serum glucocorticoid levels [16]. Hypotension and hypoxia may also contribute to the development of MD through release of ROS, cytokines, and dopamin—all of which inhibit aldosterone synthase [23–25].

Another possible cause of MD in the current study is the use of etomidate [26]. All patients in this study required rapid sequence intubation and were treated with a single dose of etomidate in the trauma bay. Therapeutic levels of etomidate inhibit 11 β -hydroxylase, an enzyme that is required for aldosterone synthesis [27]. The use of etomidate in the critically injured clearly warrants further investigation, but is not likely to be the sole factor responsible for the high prevalence of MD observed in this study.

Importantly, we found that the development of MD was associated with the need for a more aggressive resuscitation effort compared to non-MD patients, despite similar ISS. Over the 48-h study period, MD patients required significantly more units of blood product than non-MD patients: 13 (7–22) *versus* 5 (2–7), $P = 0.015$. Crystalloid requirements were also significantly increased in MD patients: 18 L (14–23) *versus* 9 L (6–10), $P < 0.001$. Given the morbidity and mortality associated with increased blood transfusions independent of injury severity, the greater need for transfusion in MD patients is concerning and warrants further investigation [28].

The association between MD and increased crystalloid requirements is also interesting. While fluid loading can suppress aldosterone, renin levels are also suppressed [29]. Thus the PA/PR ratio should not be greatly affected by blood or crystalloid infusion. Similarly, increased sodium can suppress aldosterone secretion, although the effect on the PA/PR ratio is minimal. In a study investigating sodium loading on the PA/PR ratio in normotensive adults, only a 5% reduction in the PA/PR ratio was found after 3 d of high-dose sodium loading [30]. In our patients, serum sodium values were within normal limits at each time

point. Similarly, potassium values were followed closely and repleted as needed to keep values greater than 3.5 mEq/L. Thus, dilutional hypokalemia leading to selective suppression of aldosterone is not likely.

Hypotension (MAP $\leq$ 60mmHg) was also significantly more common in MD than non-MD patients during the study period (10 episodes *versus* 1 episode, $P < 0.049$). MAP is frequently used as a predictor of end-organ perfusion in critical illness, with a loss of autoregulation of flow occurring at a MAP < 60 mm Hg [16,31]. Because aldosterone increases blood pressure through sodium and water retention in the kidney as well as a rapid nongenomic vasoconstrictive effect, loss of these responses can cause hypotension in MD [32]. Treating MD may reduce hypotensive episodes and may also decrease the need for excess blood transfusions and crystalloid in these patients. Currently, adrenal insufficiency in septic shock is treated primarily with hydrocortisone [17]. In addition to excellent glucocorticoid activity, hydrocortisone possesses a relatively high degree of mineralocorticoid activity. It has been suggested that the vasoactive benefits associated with hydrocortisone use in septic shock are secondary to its mineralocorticoid activity [33]. Directly targeting mineralocorticoid deficiency may also be beneficial. Adding fludrocortisone to hydrocortisone therapy in septic patients has been associated with a decrease in the need for vasopressor support [34]. The use of mineralocorticoid supplementation or replacement in trauma patients, however, has not been investigated. Further inquiry into the causes and consequences of MD in trauma patients will be needed before specific interventions can be recommended.

Mineralocorticoid deficiency has been proposed as a cause of renal failure in critically ill medical patients, with a greater need for renal replacement demonstrated in MD patients [12]. The assessment of acute renal injury in trauma patients, however, is challenging. Both the Risk, Injury, Failure, Loss, End-stage renal failure (RIFLE) and Acute Kidney Injury Network (AKIN) criteria have been validated as a means of assessing acute renal injury [17,18,35]. Both, however, require a baseline creatinine value. Because baseline creatinine values were not available for our patients, we used the discharge creatinine as a proxy for baseline function. MD patients had significantly increased renal dysfunction compared to non-MD using AKIN criteria and approached significance using RIFLE criteria (Table 4). None of our patients, however, required renal replacement therapy. A larger study would help to assess if the increased risk of renal injury seen in MD trauma patients contributes to the development of renal failure.

The present study has several limitations. The effect of MD on mortality could not be tested as patients who expired during the first 24 h were excluded and no other deaths occurred. In addition, the sample size was small and the high prevalence of MD limited the power of the study to detect outcome differences between groups. Although we included only patients in hemorrhagic shock, study of a broader range of trauma patients could be helpful in assessing the impact of MD on outcomes. Although the time of day and position can affect aldosterone measurements in healthy patients, it is unclear if these variables remain important in the critically ill [36,37]. Nonetheless, although all blood samples were collected in the supine position, the timing of blood draws could not be standardized. Finally, given the observational nature of this study, the treatment of MD could not be evaluated.

In conclusion, we report that MD is a common entity in trauma patients presenting with hemorrhagic shock. Patients with MD were more likely to experience hypotensive episodes during the initial 48 h post injury and required a more aggressive transfusion and crystalloid resuscitation effort. Future studies with larger sample sizes should be undertaken in order to fully understand the impact of MD following trauma and the potential role of hormonal replacement therapy.

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Table 1

Demographics and outcomes

	MD (n = 25)	non-MD (n = 7)	P
Age, y	34 ± 11	41 ± 19	0.21
Gender, male	23 (92%)	7 (100%)	>.999
ISS	30 ± 14	32 ± 22	0.771
Mechanism			
Penetrating	22 (81%)	6 (86%)	>.999
Blunt	5 (19%)	1 (17%)	>.999
MAP, mm Hg [*]	77 (68–82)	74 (72–81)	0.964
Trauma bay lactate, mmol/L	5.3 (3.7–9.75)	3.4 (2.5–6.25)	0.16
Hypotensive episodes [†]	n = 10	n = 1	0.049
ICU LOS	11 (3–21)	10 (2.5–19)	0.732
Hospital LOS	23 (15–33)	18 (6–22.5)	0.138
Blood, total units [†]	13 (7–22)	5 (2–7)	0.015
Crystalloid, total L [†]	18 (14–23)	9 (6–10)	<0.001

LOS = length of stay; MD = mineralocorticoid deficient.

Reported as mean ± SD, n (%), or median (IQ range).

^{*} Combined MAP measurements for all time points.

[†] During the 48-h study period.

Table 2

Plasma aldosterone, plasma renin, and mineralocorticoid deficiency.

	ICU	8 h	16 h	24 h	48 h	P
PA/PR 2 (n)	14	9	8	13	11	
PA/PR <2 (n)	13	13	18	18	18	
Prevalence of MD	48%	59%	69%	58%	62%	
PA pg/mL ref (10–105)*						
MD	52 (30–65)	95 (44–140)	44 (27–98)	54 (36–97)	36 (18–48)	>0.9 [†]
Non-MD	50 (36–68)	72 (44–119)	70 (42–117)	43 (23–126)	44 (22–74)	
PR pg/mL ref (3–28)*						
MD	78 (62–170)	96 (64–185)	80 (36–221)	190 (54–311)	33 (20–119)	<0.0033 [†]
Non-MD	8.8 (4–10)	9.7 (4–10)	8.8 (5–14)	9.5 (5–14)	6.2 (5–14)	

PA = plasma aldosterone; PR = plasma renin; MD = mineralocorticoid deficient.

Reported as median (IQ range).

* Supine.

[†] For each time point between MD and non-MD groups.

Table 3

Laboratory values.

	TB	ICU	24 h	48 h	P
Sodium mEq/L					
MD	141 (139–142)	141 (138–143)	140 (136–144)	139 (138–143)	>0.8*
Non-MD	138 (138–142)	138 (138–144)	138 (136–144)	138 (137–140)	
BUN mg/dL					
MD	13 (10–15)	11 (9–14)	14 (11–16)	13 (8–17)	>0.9*
Non-MD	14 (13–16)	13 (9–16)	10 (8–15)	9 (9–15)	
Creatinine mg/dL					
MD	1.3 (1.1–1.6)	1.2 (0.9–1.3)	1.2 (1–1.7)	1.1 (0.8–1.3)	>0.9*
Non-MD	1.3 (1.1–1.4)	0.99 (0.8–1.5)	1.0 (0.9–1.2)	0.92 (0.9–1.1)	

BUN = blood urea nitrogen; MD = mineralocorticoid deficient; TB = trauma bay.

Reported as median (IQ range).

* For each time point between MD and non-MD groups.

Table 4

Mineralocorticoid deficiency and renal function.

	MD <i>(n = 25)</i>	non-MD <i>(n = 7)</i>	<i>P</i>
Met RIFLE criteria	18 (72%)	2 (29%)	0.073
Met AKIN criteria	21 (84%)	3 (43%)	0.047
Renal replacement therapy	0 (0%)	0 (0%)	>.999

AKIN = Acute Kidney Injury Network; MD = mineralocorticoid deficient; RIFLE = Risk, Injury, Failure, Loss, End-stage.