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Reversal of refractory septic shock with drotrecogin alpha (activated)

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Abstract Objective: We previously reported that early continuous veno-venous hemodiafiltration (CVVHDF) enables rapid identification of a subgroup of patients with “refractory” septic shock and a 100% risk of death. The objective of this study was to investigate whether early administration of drotrecogin alpha (activated) (DrotAA) to this selected subgroup of septic patients at extremely high risk of death would significantly improve prognosis.

Method: Prospective observational study in a medical intensive-care unit of a University Hospital. Twenty-three patients with refractory septic shock were included. “Refractory” shock was defined as persistent circulatory failure despite adequate circulatory support, associated with persisting lactic acidosis despite early CVVHDF. Response to CVVHDF

was assessed after 6 h of this continuous procedure. Patients selected by this strategy received DrotAA infusion for four days. **Results:** The 28-day mortality rate of the 23 patients was 39%. No difference was observed at inclusion between survivors and nonsurvivors. In patients who finally survived, 12 h of DrotAA infusion was associated with a significant decrease in lactic acidosis and in norepinephrine dose. **Conclusion:** DrotAA therapy was associated with unexpectedly high 28-day survival in patients with “refractory” septic shock.

Keywords Sepsis · Septic shock · Circulatory failure · Multiple organ failure · Lactic acidosis · Hemodiafiltration · Drotrecogin alpha

Introduction

Despite ongoing improvement in supportive care and antimicrobial therapy, severe sepsis remains a major cause of mortality in intensive-care units (ICUs). Recently, drotrecogin alpha (activated) (DrotAA), a recombinant form of human activated protein C, has been shown to reduce the mortality of severe sepsis [1]. Following this pivotal trial (PROWESS), DrotAA was approved in Europe for treatment of patients with severe sepsis and at least two failing organ systems. A subsequent study, the ENHANCE trial, has provided supportive evidence for the

favorable benefit/risk ratio observed in PROWESS, and has suggested that DrotAA might be most effective when therapy is initiated as early as possible [2].

However, the benefit/risk ratio of the drug has been questioned, and a confirmatory trial has been called for [3]. In view of the frequency of severe sepsis observed in ICUs, and the cost of an individual treatment, early and routine use of DrotAA would pose a serious economic problem. More importantly, the ADDRESS trial has suggested the ineffectiveness of DrotAA in septic patients with a “low risk of death” [4]. This suggests that this drug should be restricted to patients “at high risk of death”,

although early identification of such patients is not straightforward [5].

Our previous study on early continuous veno-venous hemodiafiltration (CVVHDF) offered one approach to this important question by rapid identification of a subgroup of patients with “refractory” septic shock and a 100% risk of death [6]. Thus, the objective of this study was to investigate whether early administration of DrotAA to this selected subgroup of septic patients would significantly improve prognosis. A positive result might also reinforce the perceived efficacy of this treatment, which is challenged [7].

Patients and method

Between January 2005 and December 2008, all consecutive patients presenting “refractory” septic shock were prospectively included. We previously defined “refractory” septic shock as follows [6]:

- 1 sepsis, as previously defined [8];
- 2 worsening circulatory failure, resulting in increasing need for vasoactive support despite aggressive fluid resuscitation; and
- 3 increasing metabolic (mainly lactic) acidosis despite 6 h of CVVHDF.

Patients meeting the inclusion criteria but with rapidly fatal underlying medical conditions (McCabe score = 2) were not included.

Our early CVVHDF protocol has been accepted as a routine procedure by the Ethics Committee of the “Société de Réanimation de Langue Française”.

Severity indices

In all patients, the simplified acute physiology score [9] was calculated. The degree of organ dysfunction was also evaluated at inclusion by the SOFA score [10]. The severity of the patient’s underlying medical condition was stratified with the McCabe score [11] as nonfatal (score 0) or ultimately fatal (score 1). We also noted the presence or absence of a condition known to be associated with immunodepression as defined by AIDS, long-term corticosteroid treatment, and recent use of nonsteroidal anti-inflammatory drugs.

Hemodynamic monitoring and initial management of circulatory failure

Arterial pressure was monitored by use of an indwelling radial artery catheter. All patients had hypotension, defined as systolic arterial pressure (SAP) lower than

90 mmHg. Hypotension was present at admission (primary shock) or occurred during the stay in the unit (secondary shock). Fluid resuscitation was guided by transesophageal echocardiographic examination of the superior vena cava, as previously described [6, 12]. Continuous infusion of norepinephrine was started at a dosage of $0.1 \mu\text{g kg}^{-1} \text{min}^{-1}$, and progressively increased, until a systolic radial pressure >90 mmHg was obtained. Bedside echocardiography was used to measure cardiac index by the Doppler technique, and left ventricular ejection fraction [6, 12]. Dobutamine was added at a dose of $5 \mu\text{g kg}^{-1} \text{min}^{-1}$ when left ventricular ejection fraction was lower than 45% on transesophageal bedside echocardiography [6, 12, 13]. When circulatory improvement was judged to be insufficient with this combination (i.e., persistent and severe left ventricular systolic dysfunction by echocardiography), dobutamine was replaced by epinephrine infusion at $0.5\text{--}2 \mu\text{g kg}^{-1} \text{min}^{-1}$ [12, 13].

Laboratory data monitoring

From admission, blood gases, blood lactate, serum urea, and serum creatinine were recorded every 6 h.

Antibiotic therapy, surgical procedure

Empirical antibiotic therapy was started following diagnosis of sepsis, depending on its suspected origin (community or hospital-acquired) and source. As soon as possible, antibiotics were adapted to the culture findings, after consultation with a microbiologist. For culture-negative septic shock, antibiotics were consistent with broadly accepted guidelines.

All patients exhibiting septic shock of surgical origin had an efficient surgical procedure before inclusion.

Corticosteroid therapy

Low-dose steroids [14] were administered to all patients, as recommended by current guidelines [15], except to the last patient included.

Continuous veno-venous hemodiafiltration

CVVHDF with a polyacrylonitrile hemofilter (AN 69, cutoff point 40 kDa; Hospal, Lyon, France) was started after 6 h of aggressive circulatory support, if there was increasing metabolic acidosis and increased need for vasopressor drugs, as described in our previous report [6]. During the procedure, ultrafiltrate was totally replaced by bicarbonate-buffered hemofiltration fluid (Hemosol B0; Hospal). Hemofiltration ($2,000 \text{ mL h}^{-1}$) was associated

with dialysis (1,000 mL h⁻¹) permitting a total exchange rate of 3,000 mL h⁻¹. The anticoagulant was intravenous heparin, with an initial bolus of 2,000–3,000 IU, followed by 300 IU/kg to maintain the patient's activated clotting time at 60–70 s.

Drotrecogin alpha (activated)

Infusion of DrotAA (Xigris; Eli Lilly, Indianapolis, IL, USA) was started after 6 h of CVVHDF (12 h from admission) in patients in whom metabolic acidosis continued to increase. We used a dosage of 24 µg kg of body weight per hour for 96 h. The molecular weight of DrotAA is 55 kDa. CVVHDF was pursued during infusion.

Statistical analysis

Statistical calculations were performed using the Statgraphics plus package (Manugistics, Rockville, USA). Data are expressed as mean ± 1 standard deviation. Between-group comparisons were performed using the Mann–Whitney *U* test for continuous variables, or a chi-squared test, with Yates correction when required, for categorical variables. A *p* value <0.05 was considered as statistically significant.

Results

Between January 2005 and December 2008, 61 patients with severe septic shock were treated in our ICU. Thirty-six patients improved on CVVHDF. These 36 patients did not receive DrotAA, and the 28-day mortality rate of this subgroup was 25%. Twenty-five patients met the inclusion criteria of “refractory” shock and were thus eligible for the study. However, two patients with severe thrombocytopenia (platelet count <30,000), a contraindication to DrotAA administration, were excluded, and thus the study population comprised 23 patients (20 men, 3 women; mean age 63 ± 14 years). The main characteristics of the patients are presented in Table 1. All patients were mechanically ventilated for acute lung injury or acute respiratory distress syndrome. Our respiratory strategy has been extensively described elsewhere [16]. Additionally, all patients exhibited an acute renal injury, as defined by an urinary output below 30 mL h⁻¹ before implementation of CVVHDF [17].

Etiological features of septic shock are presented in Table 1. Infection was microbiologically documented in 17 (74%) patients from a positive blood culture and/or from the site of infection. All patients received broad-spectrum antibiotics, starting a mean of 2 ± 2.2 h after

Table 1 Epidemiological data of the 23 patients

| | |
|-----------------------------------|----------------|
| Age | 63 ± 14 |
| SAPS II | 71 ± 12 |
| SOFA | 16 ± 2 |
| McCabe = 0/1 (<i>n</i>) | 15/8 |
| Immunodepression, <i>n</i> (%) | 4 (17) |
| Primary/secondary shock, <i>n</i> | 20/3 |
| Low-dose steroids, <i>n</i> (%) | 22 (96) |
| Origin | |
| Community-acquired (<i>n</i>) | 20 |
| Hospital-acquired (<i>n</i>) | 3 |
| Site of infection (<i>n</i>) | |
| Pneumonia | 17 |
| Intra-abdominal | 3 |
| Surgical | 3 |
| Nonsurgical | – |
| Urinary tract | 2 ^a |
| Cellulitis | 1 |
| Microorganisms (<i>n</i>) | |
| G + cocci | 10 |
| G – cocci | 7 |
| Unidentified | 6 |

G + cocci, cocci Gram +; G – cocci, Cocci gram –

^a One patient was surgically managed

arrival at hospital. In patients in whom the microbial agent was identified, empirical antibiotics were appropriate in all cases. Hemodynamic data, and acid–base status, renal function, and respiratory data are presented in Table 2.

Fourteen patients finally survived, and so the 28-day mortality rate was 39%. All survivors had 96 h of DrotAA infusion. Among non-survivors, six died earlier, and only three had the complete treatment of 96 h of DrotAA infusion. As shown in Table 3, no difference was observed between patients who survived and patients who died. Figure 1 reports change in base deficit, lactate and pH during the first 24 h following the start of septic shock in living and deceased patients. As shown, all patients had persistent severe metabolic acidosis after 12 h which was markedly improved after 12 h of DrotAA infusion in patients who survived. Norepinephrine dose decreased from 1.22 ± 0.55 to 0.45 ± 0.10 µg kg⁻¹ min⁻¹ in surviving patients after 12 h of DrotAA infusion. At the same time, it increased from 1.46 ± 0.31 to 3 ± 0.72 µg kg⁻¹ min⁻¹ in deceased patients.

Finally, we did not observe any complication related to DrotAA treatment.

Discussion

The benefit/risk ratio of DrotAA has recently been questioned, and a confirmatory trial has been called for [3]. The ADDRESS trial has suggested the ineffectiveness of DrotAA in septic patients with a “low risk of death” [4].

Table 2 Clinical characteristics of the 23 patients at inclusion (just before DrotAA), except for renal function, which was assessed just before CVVHDF

| | |
|--|-------------|
| Circulatory function | |
| HR (beats min ⁻¹) | 117 ± 19 |
| SAP (mmHg) | 92 ± 21 |
| DAP (mmHg) | 52 ± 9 |
| CI (l min ⁻¹ m ⁻²) | 3.79 ± 1.08 |
| LVEF (%) | 52 ± 14 |
| Fluid administration H0–H6 (mL kg ⁻¹) | 41 ± 12 |
| Catecholamine dose (µg kg ⁻¹ min ⁻¹) ^a | 1.48 ± 1.07 |
| Epinephrine, <i>n</i> (%) | 4 (17) |
| Norepinephrine, <i>n</i> (%) | 19 (83) |
| Dobutamine, <i>n</i> (%) | 5 (22) |
| Acid–base status | |
| pH | 7.19 ± 0.08 |
| Lactate (mmol L ⁻¹) | 5 ± 2.7 |
| Base deficit (mmol L ⁻¹) | 9 ± 5.3 |
| Renal function | |
| Urinary output (mL h ⁻¹) | 13 ± 12 |
| Plasma urea (mmol L ⁻¹) | 13 ± 7.6 |
| Serum creatinine (µmol L ⁻¹) | 199 ± 93 |
| K ⁺ (mmol L ⁻¹) | 4.5 ± 0.8 |
| PO ₄ ⁻ (mmol L ⁻¹) | 1.4 ± 0.6 |
| Respiratory status | |
| PaO ₂ /FiO ₂ (mmHg) | 140 ± 77 |
| PaCO ₂ (mmHg) | 50 ± 13 |

HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; CI, cardiac index; LVEF, left ventricular ejection fraction

^a The dose of catecholamine given applies to norepinephrine or epinephrine or both together. It does not apply to dobutamine, which was used in combination with norepinephrine at a single dose of 5 µg kg⁻¹ min⁻¹

Table 3 Characteristics of survivors and nonsurvivors before DrotAA

| | Survivors (<i>n</i> = 14) | Nonsurvivors (<i>n</i> = 9) |
|---|-------------------------------|---------------------------------|
| Age | 63 ± 17 | 61 ± 6 |
| SAPS II | 70 ± 13 | 72 ± 12 |
| SOFA | 15 ± 2 | 16 ± 1 |
| NE (µg kg ⁻¹ min ⁻¹) | 1.22 ± 0.55 | 1.46 ± 0.31 |
| Base deficit (mmol L ⁻¹) | 9 ± 3.4 | 9 ± 4.1 |
| Lactate (mmol L ⁻¹) | 5.3 ± 0.1 | 5.4 ± 1 |
| pH | 7.19 ± 0.08 | 7.20 ± 0.08 |
| Platelets (mm ⁻³) | 160 ± 7.5 10 ³ | 188 ± 150 10 ³ |
| Fibrinogen (g L ⁻¹) | 7.3 ± 3.5 | 6.4 ± 3.6 |
| PaO ₂ /FiO ₂ (mmHg) | 148 ± 82 | 135 ± 71 |

NE, norepinephrine dose

This suggests that this drug should be restricted to patients “at high risk of death”, although early identification of such patients is not straightforward [5]. The PROWESS study reported a beneficial effect of DrotAA on prognosis, suggesting a potential marked effect of this drug in a subgroup of patients at a high risk of death [1]. Using the PROWESS data, Ely et al. [18] have reported that DrotAA is effective in patients with an APACHE II score

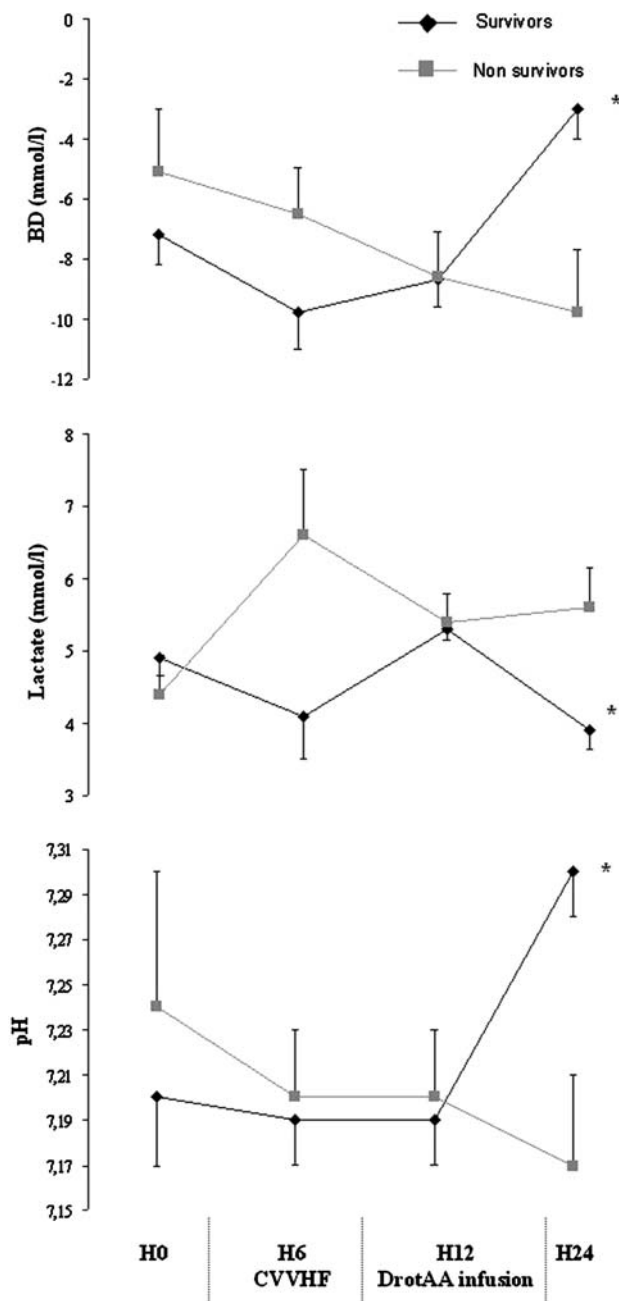


Fig. 1 Base deficit (BD), serum lactate concentration, and pH in survivors and nonsurvivors at admission (H0), at initiation of continuous veno-venous hemofiltration (H6 CVVHF), after 6 h of CVVHF just before DrotAA infusion (H12 DrotAA infusion), and after 12 h of DrotAA infusion (H24). * *p* < 0.05

>25, a SOFA score >11, and, particularly, in patients with a very high risk of death, calculated as 60–100%. In these patients, mortality in the control group was 78%, whereas mortality in the DrotAA group was 53% [18]. However, calculation of the risk of death was complicated, and involved building a logistic regression model including APACHE II score, age, logarithm of interleukin

six in the serum, dependency status, comorbidity status, and presence or not of urosepsis [18].

By definition, patients exhibiting “refractory” septic shock will have a 100% mortality rate when managed with current guidelines [6]. Thus, a practical problem for clinicians designing an innovative trial in sepsis with a new drug is to predict the “refractory” kind of septic shock rapidly and with high accuracy, so this new drug can be used for several hours. It has been suggested that early CVVHDF is beneficial in severe sepsis [19, 20]. Using CVVHDF in previous work we demonstrated that this “refractory” condition can be predicted in septic patients in less than 12 h with 100% sensitivity [6]. Our results have been confirmed by those of Cornejo et al. [21]. Thus, by first describing a powerful screening procedure, we can then use it to select a group of septic patients with a potentially very high mortality rate. In this study, 23 patients screened by this method were treated early with DrotAA, started within 12 h of admission. This timing is crucial because the efficacy of DrotAA is strongly associated with the interval between occurrence of shock and beginning of infusion [22]. Interestingly, in patients who survived, 12 h of DrotAA infusion was enough to markedly reduce serum lactate, base deficit, and norepinephrine dose, and to increase pH. In a retrospective study, Monnet et al. [23] have also reported a decrease in norepinephrine dose following 24-h DrotAA infusion.

In our previous paper [6], we reported on a series of 20 patients with “refractory” septic shock and 100% mortality rate. In this previous group, mean age was 58 ± 16 years and average SAPS II was 72 ± 21 . The SOFA score was not published, but, instead, we reported a LOD score [24] of 14.6 ± 3.2 . Average pH at admission was 7.11 ± 0.13 , with a base deficit of 13 ± 5 mmol L⁻¹

and a lactate level of 5.8 ± 3.2 mmol L⁻¹ [6]. In this study, DrotAA infusion in a very comparable group of patients, carrying thus potentially a 100% risk of death, was associated with an unexpectedly low mortality of 39%, whereas the SAPSII score of this population was 71 and the SOFA score at inclusion was 16. By comparison, mortality rates higher than 70% were reported in septic patients with four organ failures [25–27]. The CUB-Rea Network registered 8,251 patients hospitalized between 1993 and 2000 for an episode of septic shock and reported a 60% mortality rate for an average SAPS II of 58 [28]. In the EPISEPSIS study, which included 546 patients with severe sepsis, the average SAPS II and SOFA in patients who died were 60 and 12, respectively, as compared with only 42 and 7 in patients who recovered [29]. The particularly poor prognosis of refractory septic shock has led some authors to suggest that aggressive vasoactive support may be futile in this setting [30]. In this report, septic shock initially treated by dopamine, and requiring subsequent norepinephrine infusion had a 85% mortality rate [30]. In another report, septic patients exhibiting at least three organ failures, as in our patients, had a mortality rate of 92% [31].

Some limitations of this study should be acknowledged. First, improvement in survival in the ICU over time is observed in most studies when controlling for initial severity, and our results may in part reflect this tendency. Second, we have presented herein an observational study with no control group, and this might reduce the impact of our results.

In conclusion, in patients with “refractory” septic shock, our study showed that early use of DrotAA, combined with adequate vasopressor support and early CVVHDF, was associated with unexpectedly high survival.

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