Administration of Recombinant Erythropoietin Determines Increase of Peripheral Resistances in Patients with Hypovolemic Shock

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Table 1. Clinical findings from the selected patients

Patient	Age	Sex	Hypotensive time before treatment with rHuEPO, h	Diagnosis	Outcome
12					

Dear Sir,

Most mammalian cells secrete and respond to a wide range of growth factors (GFs), and the hypothesis that GFs can modify the endocrine action of the endothelial cells and control the vascular tone is very interesting. Cytokines such as interleukin-(IL)-1, IL-2, tumor necrosis factor (TNF) and interferon, seem to be able to increase the secretion of nitric oxide, a powerful vasodilator agent, by the endothelial cells [1-4]. The vasoactive action of IL-1 and IL-2 has already been shown to determine a marked hypotension [2, 5], whereas platelet-activating factor (PAF) determines both a systemic hypotension and a pulmonary hypertension [6]. Endothelin-1, a vasoactive agent controlling smooth muscle cells proliferation and contractility, has potent vasoconstrictive properties [7]. A similar vasoactive effect was also supposed for erythropoietin (EPO), a hormone known for the regulatory action it performs on the erythropoiesis process.

Through the clearance of xenon-133, a vasopressive activity of the hormone (rHuEPO) was shown [8], while rHuEPO administration inhibits the cutaneous vasodilation induced by acetylcholine [9]. In rats with hemorrhagic shock we demonstrated the administration of rHuEPO would prolong the survival time and increase the percentage of the survived animals as well as the mean arterial blood pressure compared to controls [10]. The purpose of the present study was to examine the hemodynamic effect of rHuEPO administration in patients with severe shock. Our study was carried out on 2 patients with severe shock admitted to our

Intensive Care Unit according to the following criteria: severe hypotension (PAS < 60 mm Hg), abso-

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lute inotropic and vasopressor drugs dependence (a severe decrease of blood pressure would occur when drugs were discontinued) (table 1). Informed written consent was obtained from their relatives.

rHuEPO (10,000 U i.v.) was administered every 4 h to the 2 patients. They also received a standard treatment for shock, i.e., dopamine, dobutamine, normosol, emagel, and this treatment was held constant during the EPO dosing period. Metabolic acidosis, when present, was treated with bicarbonates to keep pH at 7.3. All patients were on mechanical ventilator assistance.

Hemodynamic evaluation was performed using a computer-assisted system (Oximetric 3, Abbott) able to monitor oxygen saturation continuously through reflection spectrophotometry by the use of a catheter placed in the pulmonary artery. This system is able to determine a complete hemodynamic evaluation of the cardiac output by

polytraumatized survival

hypovolemic

shock

esophageal exitus

varix rupture at 24th

shock hour

thermodilution. Every 4 h we recorded central venous pressure, pulmonary wedge pressure, average pulmonary arterial pressure, average cardiac index, systemic and pulmonary vascular resistances, oxygen saturation, heart rate, systolic arterial pressure and diastolic arterial pressure.

EPO administration determined the rise of pulmonary and systemic resistances. In patient I, who survived, the increase of peripheral resistances was parallel to the increase of the cardiac index, initially below the baseline value. SO₂ also showed a progressive increase. In the second patient, who died 24 h after the treatment, a progressive increase of the resistances with a reduction of the cardiac index, high at the beginning, was recorded (tables 2, 3).

The lack of knowledge on the intimate physiopathology of shock is undoubtedly responsible for the high mortality rate we have in this syndrome and well relates to the effort

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Table 2. Hemodynamic evaluation of patient I during rHuEPO administration (the fifth was not administered because the blood pressure was > 110)

Table 3. Hemodynamic evaluation of patient II during treatment with rHuEPO

Administration

10 12 16

8.95 4.70 1,175 65 95 40 100 72 7.30

CVP, mm Hg PCWP, mm Hg MPA, mm Hg MCO, l/min MCI, l/min/m² SVR, dyn s cm⁻⁵
PVR, dyn s cm⁻⁵ HR, beats/min PAD, mm Hg PAS, mm Hg SvO₂, % PH
pCO₂, Torr HCO₃, mmol/l O₂, %

7 9

11

14 5.97 3.90

11

15 4.90 4.90 3.60 3.90

510 810 1,084

36 50 45

125 120 113

ND 40 50

60 80 90

50 57 65

7.31 7.32 7.39

36.1 37.3 35.1 35.4 19.3 20.2 20.3 22.1 83.5 86.7 90.1 93.4

Measurements

CVP, mm Hg PCWP, mm Hg MPA, mm Hg MCO, l/min MCI, l/min/m² SVR, dyn s cm⁻⁵
PVR, dyn s cm⁻⁵ HR, beats/min PAD, mm Hg PAS, mm Hg SvO₂, % PH

pCO₂, Torr HCO₃, mmol/l O₂, %

basal 4th h 8th h 12thh 16thh

1st 2nd 3rd 4th 5th

CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; MPA, mean pulmonary artery pressure; MCO, mean cardiac output; MCI, mean cardiac index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; HR, heart rate; PAD, diastolic arterial pressure; PAS, systolic arterial pressure; SvO₂ > 2, oxygen saturation. Abbreviations as in table 2.

in searching alternative therapies to the ino-tropic and vasopressor drugs usually used in this syndrome. Recently the role GFs and cytokines play in shock has been studied too. Indeed there is recent evidence that an increase of plasmatic TNF and PAF occurs in shock, and such substances are able to determine many of the symptoms present in shock. Moreover, recent studies have provided that PAF antagonists play protective actions in several types of experimental shocks [11, 12].

Our studies suggest that EPO also is able to induce hemodynamic variations in patients with severe shock. The main response in our patients treated with EPO appears to be the increase of the vascular resistance, although survival seems to be closely related to the ability of the heart to adjust itself to the postload increase. The small sample size does not allow us to hypothesize the possibility of using EPO to treat severely shocked patients. Our findings, however, seem to suggest a deeper study on the hemodynamic events which follow the administration of the hormone.

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432

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