Steroids 77 (2012) 1101–1106

Contents lists available at SciVerse ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

Counteraction of early circulatory derangement by administration of low dose steroid treatment at the onset of established endotoxemic shock is not directly mediated by TNF-α and IL-6

Ewa Söderberg [a,*], Miklós Lipcsey [a], Jan Sjölin [b], Anders Larsson [c], Mats B. Eriksson [a]

[a] Section of Anaesthesiology & Intensive Care, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden
[b] Section of Infectious Diseases, Department of Medical Sciences, Uppsala University, Uppsala, Sweden
[c] Section of Clinical Chemistry, Department of Medical Sciences, Uppsala University, Uppsala, Sweden

ARTICLE INFO

Article history:
Received 15 February 2012
Received in revised form 30 May 2012
Accepted 5 June 2012
Available online 15 June 2012

Keywords:
Animal models
Circulatory failure
Cytokines
Endotoxin
Hydrocortisone
Septic shock

ABSTRACT

Background: Once a septic condition is progressing, administration of steroids in the pro-inflammatory phase of septic shock ought to yield maximal effect on the subsequent, devastating inflammatory response. Recently, a retrospective study showed that early initiation of corticosteroid therapy improved survival in septic shock. We aimed to prospectively evaluate effects of early administrated hydrocortisone therapy on physiologic variables in a porcine model of septic shock.
Experiment: Eight anesthetized pigs were given a continuous infusion of endotoxin during this 6 h prospective, randomized, parallel-grouped placebo-controlled experimental study. At the onset of endotoxemic shock, defined as the moment when the mean pulmonary arterial pressure reached the double baseline value, the pigs were either given a single intravenous dose of hydrocortisone (5 mg kg^{-1}) or the corresponding volume of saline.
Results: Mean arterial pressure and systemic vascular resistance index were significantly higher (both $p < 0.05$), and heart rate was significantly lower ($p < 0.05$), in the endotoxin + hydrocortisone group as compared to the endotoxin + saline group. Body temperature and blood hemoglobin levels increased significantly in the endotoxin + saline group (both $p < 0.05$). Urinary hydrocortisone increased significantly in both groups ($p < 0.05$). There were no significant differences in the plasma levels of TNF-alpha, IL-6 or nitrite/nitrate between the groups.
Conclusion: Early treatment with hydrocortisone ameliorates some endotoxin mediated circulatory derangements, fever response and microvascular outflow. Our results suggest that these effects are not directly mediated by the pro-inflammatory cytokines TNF-alpha or IL-6, nor by NO.
© 2012 Elsevier Inc. All rights reserved.

1. Introduction

Severe sepsis and vasopressor unresponsive shock is one of the major causes of death in the ICU. Various types of severe sepsis affect approximately 0.5–1 million people annually in the US alone [1]. Despite early goal-directed therapy [2] and improvement in many aspects of supportive care, septic shock is still associated with an overall hospital mortality of approximately 50% [3,4].

Steroid treatment in septic shock has been an issue of debate for approximately 50 years [5–7]. In the early eighties, conventional treatment (e.g., antibiotics, fluid therapy, inotropic support and mechanical ventilation) was supplemented by 30 mg kg^{-1} of methylprednisolone administered immediately at the time of diagnosis of septic shock and re-administered after 4 hours if the initial response was not beneficial [8]. A controlled clinical trial showed significantly higher mortality at 14 days in patients receiving high dose methylprednisolone compared to those receiving placebo [9]. In contrast, treatment with low-dose hydrocortisone shortened the time to cessation of vasopressor support and reduced the production of pro-inflammatory cytokines in patients with early hyperdynamic shock [10]. The CORTICUS trial did not show any difference in survival between hydrocortisone treated groups and placebo treated groups even though the time to shock reversal in the hydrocortisone treated group was significantly shorter [6]. Nevertheless, according to a meta-analysis, a daily dose of 200–300 mg hydrocortisone (or equivalent) may be beneficial in adults with vasopressor-dependent septic shock [7].

Timing of corticosteroid therapy seems to be crucial, since administration of steroids within 6 h (h) after the onset of sepsis-mediated persistent arterial hypotension significantly reduced 28-day mortality as compared to corticosteroid therapy initiated after 6 h of hypotension (32% vs. 51%, $p = 0.01$) [11]. Although these

* Corresponding author. Tel.: +46 18 611 0000.
E-mail address: ewa.soderberg@surgsci.uu.se (E. Söderberg).

0039-128X/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.steroids.2012.06.001

findings speak in favor of early onset of steroid therapy, it must be born in mind that these findings were obtained retrospectively.

Glucocorticoids may also interfere with the cytokine cascade. Steroids administered together with or shortly before i.v. endotoxin to human volunteers prevented the increase in TNF [12]. However, when glucocorticoids were administered 12 h or more before endotoxin challenge, the rise in TNF was not blunted. In a clinical study, hydrocortisone administered to patients with septic shock requiring inotropic support was followed by improvements in SOFA (Sepsis Related Organ Failure Assessment) score and reduced plasma levels of IL-6, but not in TNF [13].

No experiment has previously been designed aiming to prospectively evaluate, from a theoretical perspective, the effects of hydrocortisone on central hemodynamics and pro-inflammatory cytokines tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), when administered at the onset of endotoxemic shock. We hypothesized that treatment with hydrocortisone, administered at the onset of endotoxin-mediated shock, might have anti-inflammatory and shock-reversing effects. Thus, we decided to explore, in a porcine endotoxemic shock model, whether hydrocortisone given at the onset of established endotoxemic shock, might have effects on central hemodynamics and, possibly also, immunomodulatory effects. Our primary outcome measure was the effect of hydrocortisone administered at a clinically relevant dose in early endotoxin – mediated shock on mean arterial pressure (MAP). In septic shock there is an extensive production of NO, which mediates peripheral vasodilatation, catecholamine resistance, contributing to hypotension and organic dysfunctions [14–17]. Since the plasma levels of nitrite/nitrate, the main stable product of cytokine-induced nitric oxide metabolism, was reduced in septic patients receiving low-dose hydrocortisone treatment, accompanied by hemodynamic stabilization [18], we also decided to analyze this quotient.

This experimental model mimicking human gram-negative septic shock, has previously been described in detail by our research group and others [19–22]. Onset of endotoxemic shock was defined as the moment when the mean pulmonary arterial pressure (MPAP) reached the double baseline value [23,24].

2. Materials and methods

2.1. Animals and concession

Domestic-breed pigs of male gender, 9–11 weeks old, weighing between 25.5 and 28.9 kg (mean ± SD, 26.2 ± 1.7 kg) were included in this study. All animals received water and food ad libitum until one hour before the experiment. The following criteria were applied for inclusion; no obvious pre-existing disease, PaO_2 of >10 kPa (75 mm Hg) and MPAP of <2.7 kPa (20 mm Hg) at baseline, which was 30 min after accomplishment of the preparatory procedures. All animals were handled according to the guidelines of the Swedish National Board for Laboratory Animals and the European Convention on Animal Care. The Animal Ethics Committee of the Swedish animal welfare agency, Sweden, approved (C225/8) the experiments.

2.2. Anesthesia and preparatory procedures

The anesthesia and preparatory procedures used in this experiment have been described in detail by our group previously [25,26]. During anesthesia, the animals were mechanically ventilated by a Servo 900C® (Siemens Elema, Stockholm, Sweden). Throughout the experiment, FiO_2: 0.3 in medical air was delivered and respiratory status was controlled with arterial blood samples.

The following catheters were inserted into the blood stream for monitoring and blood sampling: an arterial catheter was placed into the right cervical artery, a central venous catheter was introduced through the internal jugular vein into the superior caval vein and a 7F Swan-Ganz pulmonary artery catheter, equipped with thermistor for cardiac output measurement, was inserted via the internal jugular vein into the pulmonary artery. Systemic vascular resistance index (SVRI), left ventricular stroke work index (LVSWI) and cardiac index (CI) were derived from their conventional formulas [27].

A balanced solution containing glucose, with electrolytes, 25 mg mL^{-1} was administered i.v. at a rate of 8 mL kg^{-1} h^{-1}, and a sodium chloride, 9 mg mL^{-1}, infusion was administered i.v. at a rate of 22 mL kg^{-1} h^{-1} resulting in a total fluid administration rate of 30 mL kg^{-1} h^{-1} during the experiment, aiming to keep both central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) constant during the experiment.

All measurements and samplings were performed at baseline and thereafter hourly. A minor vesicotomy was performed and a urinary catheter was inserted into the urinary bladder. All animals were placed on a heating pad (Operatherm 200W™, KanMed, Bromma, Sweden), which was used to prevent hypothermia. After the completion of the surgical preparation, all animals were allowed to stabilize for 30 min after which baseline measurements were performed.

2.3. Protocol

All pigs received a 6 h continuous endotoxin infusion at 2 μg kg^{-1} h^{-1} [20], (*Escherichia coli*: 0111:B4; Sigma Chemical Co., St. Louis, MO) obtained from the same batch. Endotoxin was administered through a peripheral vein. The pigs were randomly allocated into two equally sized groups, denoted the "endotoxin + hydrocortisone group" ($n = 4$) and the "endotoxin + saline group" ($n = 4$), respectively. Randomization was performed by the sealed envelope method.

When the MPAP increased to twice the baseline value, a single dose of hydrocortisone 5 mg kg^{-1} was given intravenously to the pigs in the hydrocortisone group. The steroid dose was chosen because it is in the upper range of what is being used in the intensive care unit at our hospital. The dose used by us is in the same range as previously used both in clinical and experimental settings [18,21]. The control group received the corresponding volume of saline. After completion of the 6 h endotoxemic period, all pigs were killed by an i.v. overdose of potassium chloride.

2.4. Blood- and urine-analysis

After each hourly measurement, blood and urine samples were drawn. Sandwich enzyme-linked immunosorbent assays (DY686 and DY690, R&D Systems, Minneapolis, MN) were used to determine TNF-α and IL-6 in plasma. Blood cell count and hemoglobin were analyzed on a CELL-DYN 4000 (Abbott, Abbot Park, IL) and plasma creatinine (reagent: 14.3600.01, Synermed International, Westfield, IN) was analyzed on an Architect Ci8200® analyzer (Abbot, Abbott Park, IL). Creatinine clearance was calculated as urinary creatinine × hourly diuresis/plasma creatinine × 60. Hydrocortisone in plasma and urine was analyzed on a Modular E170 (Roche Diagnostics, Mannheim, Germany) with reagents from the same manufacturer. The total analytical imprecision of the assay was 2.5% at 114 nmol/L and 1.7% at 672 nmol/L. Arterial- and mixed venous blood gases were analyzed hourly by a ABL™300 and Hemoximeter™, Radiometer, Brønhøj, Denmark. Lactate was analyzed by the i-STAT® System (Abbott Point of Care, Princeton, NJ). Total nitrate/nitrite and nitrite was measured with Parameter™ kit after deproteinising the samples (KGE001, R&D Systems, Minneapolis, MN). The samples were analyzed for nitrite and for total nitrite/nitrate after converting nitrate to nitrite. All

Download English Version:

https://daneshyari.com/en/article/2028294

Download Persian Version:

https://daneshyari.com/article/2028294

Daneshyari.com