Introduction

At the end of the twentieth century, mortality in surgically treated patients with sepsis remains high in spite of the advanced diagnostic methods and interventional therapies now available. Depending on the specific patient group, morbidity ranges from 25% to 90% [1, 2, 3, 4, 5]. Endotoxin as a membrane component in gram-negative bacteria may induce activation of cytokine cascades and produce both endothelial and cellular damages. This pathway is relevant particularly in multiple organic failure (MOF) [6]. Endotoxin may also induce secretion of tumor necrosis factor (TNF), which subsequently promotes organic failure as well [7, 8, 9]. Several authors have reported that high levels of TNF are correlated with septic shock and outcome of septic patients [8, 10, 11, 12, 13].

During the past 10 years means of extracorporeal detoxification such as continuous venovenous hemofiltration (CVVHF) and plasmapheresis (total plasmatic...
exchange, TPE) have been used in cases of sepsis and septic shock to remove the pathogenic mediators from the patient in distress. Our own team has previously demonstrated the positive effect of TPE on patients with acute necrotizing pancreatitis [14], and others have supported high-flow CVVHF in patients with septic and nonseptic MOF [15]. Only few case reports have been published regarding plasmapheresis and hemofiltration as a combined therapy [16, 17, 18]. No substantial data are presently available on indications for this invasive extracorporeal therapy.

Encouraging results arising from our own research on TPE noting higher efficacy of combined extracorporeal detoxification in patients with persistent renal insufficiency led us to carry out a pilot study in cases of persistent severe sepsis after sufficient surgical treatment of the septic source [14].

Materials and methods

We investigated the effect of combined extracorporeal detoxification therapy in 43 patients with sepsis treated in a surgical intensive care unit. We compared 19 patients receiving CVVHF plus TPE with 24 patients who had been treated earlier and received no additive extracorporeal therapy. Randomization was thus not performed. The mean age was 60.3 years in the therapy group and 64.2 years in the untreated group; there was no difference in sex distribution. All patients with sepsis had either surgical (n = 21), interventional (n = 12), or both types (n = 10) of treatment of the septic focus, so that at the start of the study the septic source had been already eliminated or at least substantially diminished. The placement of drains in interventional treatment was guided by computed tomography and/or sonography. Patients in both groups had standard intensive care with monitoring of arterial blood pressure, cardiac output, and determination of systemic vascular resistance values.

TPE was performed by administration of two fresh-frozen plasma units per 10 kg body weight over a period of 2–3 h. During this procedure a polypropylene filter (Gambro) was used. Hemofiltration was carried out in high flow mode (2 l substitute per hour) using the 100 Multiflow filter from Hospal. The substitute presented the following electrolyte concentrations: 140 mmol/l sodium, 2 mmol/l potassium, 2.13 mmol/l calcium, 0.75 mmol/l magnesium, 112 mmol/l chloride, 35.75 mmol/l lactate.

Organic failure was defined according to internationally established agreements in intensive care medicine [19, 20, 21, 22, 23, 24]. Pulmonary failure was present when the Horowitz ratio (PaO2/FiO2) was lower than 300 mmHg, or when ventilation therapy lasted longer than 12 h [20]. Renal failure was diagnosed when creatinine level was higher than 2.5 mg/dl and urea was higher than 150 mg/dl or urinary excretion was lower than 500 ml/day [21, 22]. Hepatic failure was diagnosed when the bilirubin level was higher than 3.0 mg/dl or the elevation in transaminase activity more than twice the normal level ( > 36 U/l) [23]. Cardiac failure was diagnosed when the dopamine dose was higher than 20 mg/h for at least 12 h or it was lower than 20 mg/h with additional administration of inotropic drugs (such as dobutamine, adrenaline, noradrenaline) for at least 12 h [24].

During TPE the CVVHF was either recirculated or completely stopped. Combined extracorporeal therapy had to be started within 24 h after sufficient treatment of the septic focus. TPE was installed first and repeated once every following day. CVVHF was started immediately after the plasmapheresis course was completed. TPE was withdrawn when hyperdynamic circulation diminished at least 1.0 l/min and remained constant for more than 12 h. CVVHF was stopped when the septic situation had stabilized, with a drop in C-reactive protein values and leukocyte counts together with restoration of renal function (creatinine < 2.0 mg/dl, production of urine > 100 ml/h, urea < 100 mg/dl). At the end of each day (12 p.m.) we calculated the scores for the revised Acute Physiology and Chronic Health Evaluation (APACHE II), MOF, and sepsis severity [25]. The total doses of dopamine, dobutamine, adrenaline, and noradrenaline were determined every day, and the correlation was examined between these values and the course of cardiocirculatory data. In the tables they are presented as mean values for the entire group at the start, 48 h after therapy onset, and when therapy ended.

For statistical calculation of significance the χ2 test and Fisher’s exact test were used; significance was set at P < 0.05. Computer software was SPSS for Windows. Statistical tests were carried out by a specialized consultant in charge of evaluating ongoing clinical and experimental studies in the Department of Surgery. The study was approved by the Institutional Review Board. All relatives of the patients concerned were contacted during the ongoing therapy, and written consent was obtained. Data were evaluated according to the guidelines for good clinical practice.

Results

Morbidity regarding heart, renal, pulmonary, or hepatic dysfunction was similar in the two groups and did not reach statistical difference. Initial APACHE II score was also similar (26.6 vs. 27.3 in the control group; n.s.). In the therapy group 12 of 19 patients had postoperative peritonitis, whereas in the control group there were only 9 of 24 patients. The underlying disease was malignant in 8 patients in the therapy group and in 11 patients in the control group (Table 1). The two groups also did not seem to differ in terms of diagnosis (abdom-