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Plasmapheresis in severe sepsis and septic shock: a prospective, randomised, controlled trial

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Abstract *Objective:* To determine the therapeutic efficacy and safety of plasmapheresis in the treatment of patients with severe sepsis and septic shock. *Design:* Prospective, randomised, clinical trial with a planned, midstudy, interim analysis. *Setting:* Intensive care unit in a university hospital in Archangels, Russia. *Patients:* Consecutive patients with severe sepsis or septic shock. *Interventions*: One hundred and six patients were randomised to receive either standard therapy or an add-on treatment with plasmapheresis. *Measurements and results:* The primary endpoint was 28-day survival. Septic shock was diagnosed in 57% of the plasmapheresis-treated patients and 54% of the control patients. Mean APACHE III score at entry was 56.4 in the plasmapheresis group and 53.5 in the control group. The 28-day, all-cause mortality rate was 33.3% (18/54) in the plasmapheresis group and 53.8% (28/52) in the control group. This represents a relative risk for fatal outcome in the plasmapheresis group of 0.61, an absolute risk reduction of 20.5% and a number of patients needed to treat of 4.9. Apart from six transient episodes of hypotension and one allergic reaction to fresh frozen plasma, no adverse reactions were attributable to the plasmapheresis treatment in this study. *Conclusions:* Plasmapheresis may be an important adjuvant to conventional treatment to reduce mortality in patients with severe sepsis or septic shock. Plasmapheresis is a safe procedure in the treatment of septic patients. A prospective randomised multicentre trial is warranted to confirm our results and to determine which subgroups of septic patients will benefit most from this treatment modality.

Keywords Acute Physiology and Chronic Health Evaluation · Randomised controlled trial · Plasmapheresis · Sepsis · Septic shock · Outcome

Introduction

Sepsis is an increasingly common cause of morbidity and mortality, particularly in elderly, immunocompromised and critically ill patients [1]. Estimated mortality from severe sepsis and septic shock ranges from 20% to 60% [2, 3]. Sepsis therefore represents the leading cause of death in intensive care units [4, 5], and the incidence will probably continue to rise because of demographic trends and increased use of immunosuppressive agents, broad-spectrum antibiotics and invasive technology. In recent years many new therapies for sepsis have been tested in randomised clinical trials. A common concept of these innovative therapies is the attempt to counteract the physiological response to sepsis mediators by administration of specific antibodies, inhibitors and antagonists directed against these mediators. However, most of these innovative therapies have failed to have an effect on mortality [6]. During sepsis, particularly Gram-negative sepsis, the entire spectrum of host effector molecules are

released, many of which have been confirmed to be responsible for the clinical syndrome of sepsis. This suggests that while blocking or down-regulating any single mediator may modify or at least partially abrogate the organ dysfunction seen in sepsis, it is highly unlikely that any single modulatory regimen targetting one single mediator would be successful in reducing mortality in a clinical setting of severe sepsis or septic shock. Furthermore, many of the mediators of sepsis are probably yet undiscovered, and our knowledge of the mediators that have been discovered is far from complete.

Plasmapheresis is a non-selective method with the potential to remove harmful or toxic mediators from the circulation. Using fresh-frozen plasma as replacement fluid, consumed plasma factors are substituted, thereby possibly restoring the opsonic capacity and improving the coagulation abnormalities, both of which are disturbed in sepsis. Since 1979 several reports have been published on plasmapheresis and whole blood exchange for sepsis [7, 8, 9, 10, 11, 12, 13, 14, 15, 16]. These reports, based on a small number of patients and without appropriate control patients, are inconclusive and conflicting with respect to whether plasmapheresis provides any beneficial effects in the treatment of sepsis. Conflicting results are also reported in animal studies, which have sought to evaluate the efficacy of plasmapheresis in sepsis and septic shock [17, 18, 19].

In Archangels plasmapheresis has been used in the treatment of sepsis for many years, but the method has not been evaluated by a proper clinical trial. The aim of the present study was to determine the therapeutic efficacy and safety of plasmapheresis in the treatment of patients with severe sepsis and septic shock in a prospective, randomised, controlled trial.

Materials and methods

The protocol was approved by the institutional review board at the City Emergency Hospital #1. Informed consent was obtained from all conscious patients enrolled in the study. Delayed consent was obtained from surviving patients who were unconscious at the time of enrolment.

Patient selection and definitions

Eligible patients were aged between 17 and 70 years and had severe sepsis or septic shock. Sepsis was diagnosed according to the criteria proposed by Bone et al. [20]. The systemic inflammatory response to infection included more than one of the following clinical manifestations; temperature higher than 38°C or lower than 36°C, tachycardia (heart rate higher than 90 beats per min), tachypnoea (respiratory rate more than 20 breaths per min) or hyperventilation ($PaCO_2$ less than 4.2 kPa), and leukocytosis (white blood cell count greater than 12,000/mm^3) or leucopenia (white blood cell count less than 4000/mm^3). Severe sepsis was defined as sepsis associated with organ dysfunction, hypoperfusion abnormality, or sepsis induced hypotension (systolic blood pressure less than 90 mmHg). Hypoperfusion markers used were lactic acidosis, oliguria, and alteration in mental status. Septic shock was defined as sepsis-induced hypotension, persisting despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction. Patents with hypoperfusion abnormalities or organ dysfunction receiving inotropic support were considered to have septic shock even if they had normal blood pressures. Patients treated for severe sepsis or septic shock in other hospitals for more than 12 h before they were transferred to City Hospital #1, and patients with severe underlying disease were not included in the study. Severe underlying disease includes patients with terminal cancer, terminal cardiac failure, end-stage renal failure and potentially lethal injuries.

Randomisation, treatment procedures and endpoint

As soon as the diagnosis of severe sepsis or septic shock was established, the patients were randomised to receive plasmapheresis in addition to conventional sepsis treatment or conventional sepsis treatment alone. The patients were block-randomised in two stages allowing an interim analysis after inclusion of 50 patients. All patients received conventional sepsis treatment according to the indication in each case. This treatment included antibiotics, fluid resuscitation (plasma, colloids, and/or crystalloid), surgical procedures, and cardiovascular and ventilatory support when indicated. Combination therapy of antibiotics was chosen according to source of infection and micro-organisms suspected to be involved, and corrected according to positive bacteriological culture and resistance patterns when available. Patients in both groups who did not have contraindications to anticoagulation therapy received heparin. Activated partial thromboplastin time, used to monitor the anticoagulation therapy, was kept below 80 s except during the periods when patients were undergoing plasmapheresis. Plasmapheresis was initiated within 6 h after the diagnosis was established. It was repeated once within 24 h in 27 patients in whom the clinical condition did not improve, or in whom the clinical condition still deteriorated after the first procedure as judged by the presence or progression of haemodynamic instability and the development of organ dysfunction. Plasmapheresis was performed employing a PF-0.5 (Lvov, Russia), and a DK2-0.3 (Rjazan, Russia) continuous flow plasmapheresis machines using veno-venous access. Heparin doses of 200–300 U/kg bodyweight was used as anticoagulant. Activated clotting time was kept between 250 and 300 s. during plasmapheresis. During each exchange session a volume of 30–40 ml/kg bodyweight of patient's plasma was exchanged with an equal volume of fresh-frozen plasma from healthy donors, diluted with an equal volume of 5% human albumin solution. The duration of the first plasmapheresis session was 133±23 min and the second session 137±21 min. The mean exchange plasma volume during the first session was 1820±402 ml and 1763±312 ml during the second session.

The patients were followed for 28 days or until they died. For comparison of disease severity the Acute Physiology and Chronic Health Evaluation (APACHE) III score was calculated at study entry, after 24 h and after 48 h [21]. Primary endpoint was 28-day survival.

Patient characteristics

The study included 106 consecutive patients (60 men, and 46 women; mean age 44±15 years) treated between December 1994 and March 1997. At study entry 56% of the patients were in septic shock (31/54 in the plasmapheresis group patients and 28/52 in the control group). Mean baseline APACHE III score was 54.9±17.4 (56.4 in the plasmapheresis group and 53.5 in the control group). The largest number of infections originated in the abdomen, with 33 patients in the plasmapheresis group and 16 in the control group. The next largest group had respiratory tract infections

Table 1 Baseline characteristics in 106 patients with severe sepsis or septic shock randomly assigned to plasmapheresis or not in addition to standard sepsis treatment

Variable[a]	Plasmapheresis (*n*=54)	Control (*n*=52)	*p*
Gender: M/F	34/20	26/26	0.24
Mean age (years)	41±15	48±16	0.03
Septic shock	31 (57%)	28 (54%)	0.84
Mean APACHE III score	56.4±18.8	53.5±15.8	0.40
Mean APACHE III score for respiratory functions			
Respiratory rate	5.2±2.6	4.8±2.8	0.42
PaO_2	3.5±3.5	2.7±3.1	0.24
Site of infection			0.04
Abdominal	33	16	
Lung	3	9	
Urological	2	8	
Skin/soft tissue	5	5	
Female genital	2	7	
Brain	3	4	
Other sites[b]	6	3	

[a] Number of p atients except where stated otherwise
[b] Other sites includes three patients with orthopaedic infections, one patient with endocarditis, and patients in whom the site of infection was uncertain, i.e., five multitrauma patients and one patient with burn injury

Table 2 Concomitant therapies during the observation period in 106 patients with severe sepsis or septic shock randomly assigned to plasmapheresis or not in addition to standard sepsis treatment

Variable	Plasmapheresis (*n*=54)		Control (*n*=52)		*p*
	n	%	*n*	%	
Surgery	35	65	38	73	0.41
Inotropes	30	56	27	52	0.85
Anticoagulation[a]	49	91	48	92	1.0
Mechanical ventilation	25	46	35	67	0.03
Fresh frozen plasma	54	100	43	82	0.001

[a] Anticoagulation therapy in plasmapheresis group denotes anticoagulation given in addition to the heparin delivered during the plasmapheresis procedure

(*n*=12) followed by urinary tract infections (*n*=10). Except for age and distribution of sites of infection, there were no statistically significant differences between the groups with respect to these baseline characteristics (Table 1). Surgical procedures were performed on 65% (35/54) of plasmapheresis treated patients and on 73% (38/52) of control patients. Inotropes were used in 56% (30/54) of patients in the plasmapheresis group and in 52% (27/52) of patients in the control group. Mechanical ventilation was required by 46% in the plasmapheresis group and by 67% in the control group (Table 2).

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 10.0 (SPSS, Chicago, Ill., USA). Univariate comparisons of baseline characteristics were made by unpaired *t* test for continuous variables and Fisher's exact test for categorical variables. Pearson's χ^2 was used to test differences in infectious origin between the two groups. Changes in APACHE III score from baseline values were assessed by paired *t* test. Fisher's exact test was used to test differences in survival between the groups. Multiple logistic regression was used to assess the effect of the treatment variable and the baseline demographic and prognostic variables on survival. The reported mortality rates represent all cause mortality in the two groups, and the analysis was completed on an intention to-treat-basis. Data are presented as mean ±SD. Differences were considered significant at *p* values less than 0.05. All reported *p* values are two-sided.

Results

Efficacy and safety of plasmapheresis

The interim analysis revealed a mortality of 14/25 in the control group compared to 8/25 in the plasmapheresis group (n.s.). Consequently the study was continued. No fatal adverse reactions were attributable to the plasmapheresis procedure in this study. Six patients had short and undramatic periods of hypotension during the plasmapheresis procedure, and one patient had an allergic reaction to fresh-frozen plasma. Two patients in the plasmapheresis group died of bleeding. One patient with mediastinitis due to a stab wound that penetrated the abdominal aorta, the omentum and the lower part of the oesophagus died of massive rebleeding from the abdominal aorta 4 days after his last plasmapheresis procedure. The second patient that died from bleeding had a haemorrhagic pancreatitis and died 17 days after the plasmapheresis procedure. Thus none of them could be related to the plasmapheresis procedure. During the first 24 h APACHE III score decreased by 20% in the plasmapheresis group ($p<0.001$) compared to 8% in the control group ($p<0.05$), making the change in APACHE score from day 1 to day 2 significantly different between the

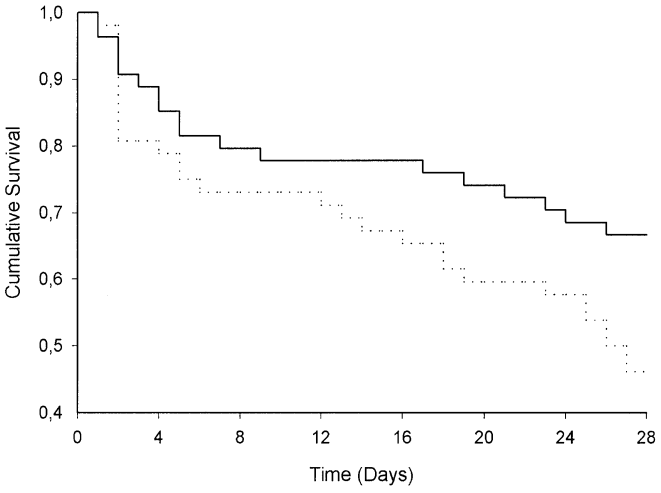

Fig. 1 Cumulative survival in 106 patients with severe sepsis or septic shock randomly assigned to plasmapheresis (*solid line*) or not (*dotted line*) in addition to standard sepsis treatment

Table 3 Prognostic score, outcome and cause of death in 106 patients with severe sepsis or septic shock randomly assigned to plasmapheresis or not in addition to standard sepsis treatment (*n.a.* not assessed, *ARDS* adult respiratory distress syndrome, *DIC* disseminated intravascular coagulation)

Variable[a]	Plasmapheresis (n=54)	Control (n=52)	p
Mean APACHE III score			
Day 1	56.4±18.8	53.5±15.8	0.40
Day 2	44.5±18.5*	49.0±19.7	0.24
Difference days 1–2	11.5±15.6	4.5±15.7	0.03
28-day mortality			
Total study population	18 (33.3%)	28 (53.8%)	0.05
Abdominal group	11/33 (33.3%)	11/16 (68.5%)	0.03
Other groups	7/21 (33.3%)	17/36 (47.2%)	0.4
Cause of death			
Respiratory failure/ARDS	2	4	n.a.
Cardiovascular	7	10	n.a.
Multiorgan failure	6	13	n.a.
Brain herniation	0	1	n.a.
DIC	1	0	n.a.
Bleeding	2	0	n.a.

[a] Number of patients except where stated otherwise
* p<0.001 vs. baseline

groups (p<0.03). The 28-day all-cause mortality in the plasmapheresis group was 33.3%, compared to 53.8% in the control group (p=0.050). This represents a relative risk of fatal outcome in the plasmapheresis group of 0.61 (95% CI 0.39–0.97), an absolute risk reduction of 20.5% (95% CI 2%–39%) and a number of patients needed to treat of 4.9 (95% CI 2.5–50; Fig. 1, Table 3). Correcting for the variables that were significantly different between the groups at baseline (age and site of infection) using multiple logistic regression, reduced the significance of the treatment variable on mortality (p=0.07, odds ratio 0.41, 95% CI 0.15–1.09; Table 4).

Table 4 Multiple logistic regression analysis evaluating the adjusted effects of unbalanced baseline characteristics and plasmapheresis on mortality in patients with severe sepsis or septic shock

Independent variable	Odds ratio	95% CI	p
Age (10 years)[a]	1.48	1.03–2.12	0.03
Site of infection			0.04
Abdominal	Reference		
Female genital	0.54	0.07–4.00	
Urological	0.15	0.02–0.93	
Lung	4.04	0.74–22.2	
Skin/soft tissue	0.41	0.07–2.53	
Brain	1.60	0.30–8.62	
Other	1.71	0.33–8.88	
Plasma exchange	0.41	0.15–1.09	0.07

[a] Denotes odds ratio by increase of 10 years

Post-hoc sub-group analysis

A hypothesis generating post-hoc sub-group analysis was performed in the group of 49 patients with abdominal infections, which was the only group large enough to be assessed separately. Mortality in this subgroup was 33% in the plasmapheresis-treated patients and to 69% in the control group (p<0.05; Table 3). Except for age, no significant differences were calculated between the two groups with respect to baseline characteristics (data not shown).

Discussion

Controlled clinical trials aimed at evaluating the therapeutic efficacy and safety of plasmapheresis in the treatment of sepsis have long been needed [22], although some authors have suggested that such trials would never be carried out [23]. Our study, the first reported randomised study to address this issue, found that patients treated by plasmapheresis had a significantly higher survival rate than those receiving conventional treatment alone. However, patients in the control group were older, and the study population was heterogeneous with respect to site of infection, both being factors that could bias the interpretation of the results. Correcting for these factors by multiple logistic regression diminished the beneficial effect of plasmapheresis (now with only a trend towards significance; Table 4).

The APCHE III score dropped in both groups from day 1 to day 2. However, the change in APACHE III

score from day 1 to day 2 was significantly better in the plasmapheresis group. The APACHE score has been shown to be a reliable predictor of outcome in critically ill patients in general [24] as well as in patients with surgical and postoperative intra-abdominal infections [25, 26]. Mean APACHE III score in our series was 54.9 (17.4) with a corresponding overall mortality of 43%, which is somewhat higher than would be expected form the APACHE score if we compare our material with previous reports [24]. However, international comparisons may be biased by differences in laboratory tests, differences in patient populations and case selections for ICU treatment. As this may influence the calibration of the APACHE estimates [27], the most useful and reliable estimate to determine the patient's response to therapy is the relative trend or change in APACHE score from one day to the next (Table 3). This concept is supported by Knaus et al. [21], who state that changes in the APACHE III score on each subsequent day of ICU therapy provide daily updates in the risk estimates.

Both clinical and experimental studies have shown that plasmapheresis lowers circulating levels of endotoxin and cytokines such as tumor necrosis factor α and interleukin 1β [10, 18, 28, 29, 30]. Most authors claim that the beneficial effect of plasmapheresis is due to the removal of these mediators. However, the beneficial effect of plasmapheresis is probably not explained solely by the removal of toxic mediators. Using fresh-frozen plasma as replacement fluid, the procedure also replenishes deficiencies such as the immunoglobulins IgM and IgA [11] and coagulation factors and inhibitors such as proteins C and S and antitrombin III. Plasmapheresis may thus restore coagulation abnormalities and improve opsonic capacity and serum bactericidal activity. This may lead to enhancement of the humoral and cellular inflammatory response and normalisation of DIC and clotting parameters [7, 9, 10]. Support for this is given in placebo-controlled trials which have tested supplemental immunoglobulin therapy on patients with postoperative sepsis and septic shock [31]. The role of anticoagulation therapy in sepsis is still unsettled, and we cannot rule out the possibility that the additional heparin delivered during the plasmapheresis procedure affected outcome; however, this can be resolved only in future trials.

Using the rather broad sepsis definition proposed by Bone et al. [20] as inclusion criteria, we obtained a heterogeneous study population including patients with both Gram-negative and Gram-positive sepsis of various origins. A post hoc analysis in the group of patients with abdominal sepsis (comprising 46% of the overall study population) revealed a significantly higher survival rate in the plasmapheresis group than in the control group, while the difference in survival for the rest of the study population was not significant. The bacterial species with the greatest potential for invasiveness in abdominal sepsis are considered to be the Gram-negative bacilli *Escherichia coli* and *Bacteroides fragilis* [32]. The majority of septic patients successfully treated by plasmapheresis have suffered from systemic meningococcal disease or other Gram-negative sepsis [7, 8, 10, 12, 13, 16]. Most of the experimental studies in favour of plasmapheresis have been performed on animals challenged with Gram-negative bacilli or endotoxin. Our data demonstrating improved survival in patients with abdominal sepsis following plasmapheresis are in line with these previous reports and suggest that the beneficial effect of plasmapheresis in septic patients may be limited to patients with Gram-negative sepsis.

Due to negative bacteriological cultures or missing values on more than one-half of the patients, we were not able to confirm that the antibiotics given had any effect on the causative micro-organism. Studies have shown that treatment with appropriate antibiotics may reduce shock and mortality rate by 50% [33]. It is unlikely, however, that there is any difference in resistance pattern between the two groups who both have been treated with combination therapy of broad-spectrum antibiotics in accordance with the local traditions. Furthermore, according to Astiz and Rackow [5], bacteraemia occurs only in 40–60% of patients with septic shock, and the causative organism is not isolated in 10–30% of patients, possibly because of previous exposure to antibiotics. The presented data on mechanical ventilation represents ventilator treatment after randomisation. As we do not have the baseline data on mechanical ventilation, we cannot rule out the possibility that differences in mechanical ventilation between the two groups may have affected outcome. This is unlikely, however, since the baseline APACHE III score for the respiratory variables respiratory rate and PaO_2 were not significantly different between the groups.

In conclusion, our study shows that plasmapheresis can be performed safely in patients with severe sepsis or septic shock. The data also support the hypothesis that plasmapheresis reduces mortality in these patients, although unbalanced baseline characteristics prevents us from making general recommendations based on this study. A larger scale, phase III, prospective randomised multicentre trial is needed to confirm our results and to determine which groups of septic patients will particularly benefit from this treatment modality.

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