Research Article

Plasmapheresis in sepsis: does it have any role to change the outcome?

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Iraqi New Medical Journal, 2014;1(1): P 17-21

Abstract

Background: Sepsis is a common problem in the intensive care units and carry high mortality rate because of the central mechanism initiating systemic inflammatory response syndrome and associated with abnormal secretion of cytokines. To decrease the mortality and increase the survival rates of patients plasmapharesis was added to conventional therapy for sepsis after assessment of the severity of illness of patients by APACHE II score; acute physiological and chronic health evaluation.

Objectives: To determine the therapeutic efficacy and safety of plasmapheresis in the treatment of Patients with severe sepsis.

Methods: 30 patients with severe sepsis or septic shock were included and they were randomized to receive either conventional therapy (control group) or conventional therapy plus plasmapheresis (plasmapheresis group).

Results: Mean APACHE II score at entry was 29.4 in the plasmapheresis group and 26.12 in the control group. After 7-days, the reduction in mean score was 21.4% in plasmapheresis group and 12.6 in the control group. Mean difference of death rate was 16.3 ± 4.7 in the Plasmapheresis group and 9.05 ± 1.7 in the control group.

Conclusions: Plasmapheresis can be used as an adjuvant to conventional treatment for sepsis. It significantly improves the outcomes of the patients with severe sepsis who are admitted to the intensive care unites.

Keywords: APACHE II score, Plasmapheresis, Sepsis ·

INTRODUCTION

Sepsis is an umbrella term including conditions where there are pathogenic microorganisms in the body. Sepsis may result in life-threatening conditions precipitated by the organisms, their toxins, and the body's own defensive inflammatory response. Sepsis is a spectrum of disorders on a continuum with localized inflammation at one end and severe generalized inflammatory response with multiorgan failure at the other end.[1] Surgery and anesthesia should ideally be postponed until sepsis is at least partially treated. However, sometimes the underlying cause of sepsis requires urgent surgical intervention; this may be termed source control. Examples include: abscesses, infective endocarditis, bowel perforation or infarction, infected prosthetic device (e.g. intravenous catheter, intrauterine device, and pacemaker), endometritis, and necrotizing fasciitis. Organisms frequently implicated in sepsis include Streptococcus pyogenes, Streptococcus pneumoniae, S. aureus, gram-negative bacilli (e.g., Klebsiella spp., E. coli, P. aeruginosa, H. influenzae), Neisseria meningitides, C. albicans, and C. perfringens.

Bacterial components such as endotoxin and lipoteichoic acid, through their action on neutrophils and macrophages, induce a wide range of proinflammatory factors, including; tumor necrosis factor α and interleukin-1 and interleukin-6, and counterregulatory host responses, interleukin-4 and interleukin-10, that turn off production of the proinflammatory Cytokines.[2] Recently, the pivotal roles of Toll-like receptors on cell surfaces have been recognized in binding to bacterial components and in promoting cytokine production and cellular activation. Normally there is a balance between pro- and anti-inflammatory responses.[2,3] As a result

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of sepsis, the pro-inflammatory reaction (systemic inflammatory response syndrome) can cascade, out of control, with activation of complement, coagulation, widespread arterial vasodilatation, and altered capillary permeability. A range of abnormalities may result, leading to multiorgan dysfunction and death.[2] If there is a predominance of the compensatory anti-inflammatory response syndrome, which often occurs subsequently, patients become more vulnerable to infection, including opportunistic organisms.[3]

Signs and symptoms of sepsis are often nonspecific. Presentation varies according to the initial source of infection. The systemic inflammatory response syndrome (**table 1**) is an important component of sepsis.[4]

Sepsis may result in multiple organ system failure. Features of infection, including fever, altered mental status, encephalopathy, and deranged blood sugar may be present. Septic shock refers to hemodynamic instability that may accompany sepsis. Classically, there is hypotension, bounding pulses, and wide pulse pressure. These are characteristic signs of high-output cardiac failure and distributive shock, both of which may occur with sepsis.[3-6]

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.

Table 1: systemic Inflammatory Response Syndrome
White blood cell count> 11,000 or < 4000x 109/ or > 10 % immature forms Heart rate > 90 beat per minute Temperature > 38°C or < 36°C Respiratory rate> 20 breath per minute or PaCO2 < 32 mmHg
For the diagnosis we need the presence of two of the above criteria

Autoantibodies, immune complexes, toxins or substances bound to proteins, immunoglobulins, thrombotic factors, coagulation factors, lipoproteins, and other immunologic factors are removed during plasmapheresis for a number of different immunologic, hematologic, neurologic, renal, rheumatologic, and metabolic disorders.[7-9]

APACHE II score (acute physiological and chronic health evaluation) is a score of characterizing ICU patients according to their severity of illness and likely outcome is important in terms of prognostication, ICU organization and resource allocation, and for the inclusion in and the interpretation of clinical trials.[10]

APACHE II was developed in 1985 by Knaus et al from a database of 5815 intensive care admissions to 13 ICUs in the USA. The severity of illness of patients is assessed using the worst values of 12 physiological variables in the first 24 hours following admission to the ICU. The APACHE II weights for physiological variables (temperature – rectal, mean arterial pressure, heart rate (ventricular), respiratory rate, PaO2 (mm Hg) arterial pH, serum sodium (mmol/litre), serum potassium (mmol/litre), serum creatinine, (mg/100 ml), haematocrit (%), WBC (total/mm3; 1000s), Glasgow coma score; Score = 15 - actual GCS. The APS is summed with age points and Total acute physiology score (APS) = sum chronic health points according to APACHE II definitions. **Table 2** shows the interpretation of APACHE II score with respect to mortality rate.

METHODS

This is a prospective, randomized clinical trial conducted at the intensive care unit of Ghazy Al-Hireeri Teaching Hospital, medical city complex in Baghdad/ Iraq during the period of March 2011 to March 2012.

Thirty patients who were admitted to the intensive care fulfilling the definition of severe sepsis were included in this study. Patients with terminal cancer, terminal cardiac failure, end-stage renal failure and potentially lethal injuries had been excluded.

Each patient was randomly assigned into either plasmapheresis or control group. Plasmapheresis group included those who received plasmapheresis in addition to the conventional treatment. Control group included patients who received only conventional therapy. The conventional treatment included antibiotics, fluid resuscitation (plasma, colloids, and/or crystalloid), surgical procedures, and cardiovascular and ventilatory support when indicated.

Before we gave treatment we calculated baseline APACHE II score for every patient in both group.

Systemic inflammatory response to infection was defined as having 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 minute), tachypnoea (respiratory rate more than 20 breaths per minute) or hyperventilation (PaCO2 less than 4.2 kPa), and leukocytosis (white blood cell count greater than 12,000/mm3) or leucopenia (white blood cell count less than 4000/mm3).

Severe sepsis was defined as sepsis associated with organ dysfunction, hypoperfusion abnormality, or sepsis induced hypotension (systolic blood pressure < 90 mmHg). Combination therapy of antibiotics was chosen according to the 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. Prothrombine time (PT), International normalized ratio (INR), partial thromboplastine time (PTT) were used for monitoring of anticoagulant level.

Plasmapheresis is initiated within 24 to 48 hours after the diagnosis. It was repeated once within 48 hours in patient 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 (HEMONETICS MCS+ USA) continuous flow plasmapheresis machines using veno-venous access. ACD-A solution (sodium citrate + glucose monohydrate + citric acid monohydrate) 500 ml per session was used as anticoagulant. During each exchange session a volume of 20 ml/kg body weight of patient's plasma was exchanged with replacement of an equal volume of fresh-frozen plasma. For comparison of disease severity the Acute Physiology and Chronic Health Evaluation (APACHE) II score was calculated at study entry, after 24 hours and 7 days.

Statistical analysis: By using SPSS (statistical package for social science) software for windows, version 16, 3. US, was used in the analysis of data. Data of all patients were entered

and analyzed using appropriate statistical tests and procedures; chi square was used to compare both groups regarding the categorical variables (gender, site of infection, concomitant therapies), Independent T-test was used to compare continuous variables at entry to the study

Paired T-test was used to compare the differences in APACHE II score and to compare the mean differences in death rates before and after intervention. In all statistical procedures and analysis level of significance was set at $P \leq 0.05$ to be considered as a significant difference. Finally all data and

RESULTS

The total sample was 30 patients, nineteen were men and 11 were women. Mean age was 46.1±15.8 years with a range of 19-70 years. On entry to the study, the mean baseline APACHE II score was 27.9 ± 4.72.

Some demographic features of plasmepheresis and control groups are reported in **(table 3)**. No significant differences in gender or age in between groups had been found ($p > 0.05$).

(**Table 4**) summarizes the concomitants therapies received by the patients during the observation period in addition to standard sepsis treatment, fresh frozen plasma was significantly more used in the plasmapheresis group compared to control group ($P< 0.05$), while there was no significant differences in the other therapies which had been used (P value > 0.05). No P value for mechanical ventilation because it was used for all patients in both groups.

The mean score of plasmapheresis group on pre-intervention was (29.4 ± 4.2), and decreased to 23.12±3.8 post-plasmapheresis, with a mean score difference of 6.28±0.4 (21.4%). In comparison to control group; pre-intervension APACHE II score was 26.12± 5.2 reduced to 21.83±3.45 post-conventional treatment. So the mean difference was 3.95 ± 0.7(12.6%). The score differences in the two groups were statistically significant. **(Table 5)**

On the other hand the Death rate reduced significantly in plasmapheresis than control group, (P value < 0.001), (**Table 5**).

Table 2: Interpretation of Score with the expected death rate

0 to 4 = ~4% death rate	10 to 14 = ~15% death rate	20 to 24 = ~40% death	30 to 34 = ~75% death
5 to 9 = ~8% death rate	15 to 19 = ~25% death rate	25 to 29 = ~55% death	Over 34 = ~85% death
§ Adapted from Crit Care Med 1985;13:818-829			

Table 3: Distribution of patients in both groups by gender.

		Plasmapheresis group	Control group	Total	P Value
Age (year)	Mean± SD	46.67 ± 17.3	45.47 ± 14.7	46.1 ± 15.8	0.84*
	Range	19-70	21-70	19-70	
Gender	Male	9	10	19	0.98*
	Female	6	5	11	
	Total	15	15	30	
* n.s. = not significant					

Table4: Concomitant therapies during observation period in both groups.

Variable	Plasmapheresis	Control group	P value
Fresh frozen plasma	15 (100%)	10 (67%)	0.002
Anticoagulation	11 (73%)	13 (87%)	0.67
Surgery	8 (53%)	7 (47%)	1
Inotropes	7 (47%)	8 (53%)	1
Mechanical ventilation	15 (100%)	15 (100%)	-

Table 5: Mean APACHE II score and death rate probability, Pre intervention and 21 day post-intervention

Variable		Plasmapheresis group (%)	Control group (%)	P value
APACHE II score Mean ± SD	Pre	29.4 ± 4.2	26.12 ± 5.2	
	Post intervention	23.12 ± 3.8	22.83 ± 3.45	
	Mean difference	6.28 ± 0.4 (21.4)	3.29 ± 0.7(12.6)	0.0001
Death rate (%) Mean ± SD	Predicted	57.6 ±18.4	48.32 ± 9.6	
	Post intervention	41.3 ± 13.7	39.27 ± 11.3	
	Mean difference	16.3 ± 4.7	9.05 ± 1.7	0.00013

DISCUSSION

Controlled clinical trials are aimed at evaluating the therapeutic efficacy and safety of plasmapheresis in the treatment of sepsis have long been needed,[11,12] although some authors have suggested that such trials would be difficult to carry out.[13] Our study, found that patients treated by plasmapheresis had a significantly higher survival rate and better response than those receiving conventional treatment alone.

The APACHE II score dropped in both groups from day 1 to day 7. However, the change in APACHE II score from day 1 to day 7 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[14] as well as in patients with surgical and postoperative intra-abdominal infections.[15,16] Mean APACHE II score in our series and the mortality rate is somewhat higher than would be expected in comparison the previous repots.[4] 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,[15,16] 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.

Both clinical and experimental studies have shown that plasmapheresis lowers circulating levels of endotoxin and cytokines such as tumor necrosis factor α and interleukin I.[17-19] 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, will replenishes deficiencies such as the immunoglobulins IgM and IgA[20] and coagulation factors, and inhibitors such as proteins C and S and antitrombin III. Plasmapheresis may thus restore coagulation abnormalities and improve oppsonic capacity and serum bactericidal activity. This may lead to enhancement of the humoral and cellular inflammatory response and normalisation of DIC and clotting parameters.[21,22]

Support for this is given in placebo-controlled trials which have tested supplemental immunoglobulin therapy on patients with post-operative sepsis and septic shock.[23] 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.[24,25] A prospective randomized multicenter trial involving whole spectrum of septic patients is essential to verify our results and to assess the drawbacks of this modality in the management of sepsis.

CONCLUSION

Plasmapheresis can be used as an adjuvant to conventional treatment for sepsis.

Use of plasmapheresis can improve the outcome and reduce mortality of patients with sepsis. However, large size controlled trials are needed to prove this fact.

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