Is There a Place for Apheresis in Patients with Severe Sepsis or Multi Organ Dysfunction Syndrome?

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ABSTRACT

Severe sepsis and multiorgan dysfunction syndrome may develop in the course of severe sepsis, intoxication, poisoning, crush injury, asystole, drowning, and several other complications. When normal intensive care is insufficient despite vasoactive drugs, respiratory aid, and dialysis, the risk for death is extremely high. Only very little benefit has been noted in various trials using drug administration such as antibodies against TNF-alfa, immunoglobulin, pentoxifylline and high dose steroids. The use of apheresis (plasma exchange, plasmapheresis, adsorption) to remove toxins, cytokines, and other compounds has been tried in an unselective as well as selective manner. Data now exists that indicate increased survival by this type of therapy. It is time to focus on randomised controlled trials with these techniques to decide the efficacy of apheresis in this area.

Key Words: Sepsis, Multi organ dysfunction syndrome, Acute renal failure, Apheresis, Plasma exchange, Plasmapheresis, Adsorption, Toxins, DIC, MODS, Intensive care.

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Acute Multi Organ Dysfunction Syndrome (MODS) may develop in various situations such as severe sepsis, crush injury, coagulopathy, extensive surgery, drug-adverse effects, poisoning and intoxication. In these occasions various types of exogenous toxins enter the body or endogenous substances deriving from cell debris cause a more extensive activation of various cascade systems including cytokine release. Besides cytokine release, central parts of these processes are the activation of the complement-and the coagulation systems. During a septic shock these mechanisms cause an activation of the coagulation cascades which may progress into a disseminated intravascular coagulation (DIC) with subsequent multi organ dysfunction syndrome and death[1-8]. The extent of this reaction varies individually, thus most patients are able to balance these processes and recover, before they have progressed to a non-reversible state. This is depending on the

extent and type of the toxin in relation to the ability of the host to respond, thereby not overreacting. In anergic patients, this host-reaction may be limited and the primary consequences not as severe as in those with extensive host response.

The most common organisms at our hospital causing DIC and subsequent MODS are Group A streptococci, mainly of type 1 M1. In patients suffering from such infection, within a few days, an infection, through, e.g., a tiny scar, rapidly may cause a progress into septic shock, DIC and MODS. This process is exagerated due to the production of superantigens by these bacteria[9]. Superantigens are defined to be extensively more potent, initiating a host response, than regular antigens[9-11].

The conventional treatment in septic shock is the use of antibiotics, and fluid replacement. Once they do not respond prompt to fluid replacement to prevent development of septic shock, the patient is worsening into a more severe condition, necessitating intensive care treatment, including vasoactive pressor support (inotropics), besides respiratory aid and dialysis. Since there is an extensive release of cytokines during these processes, various studies have focused on the administration of antibodies against cytokines or their receptors[12-17]. However, those studies have not been successful. There is also a reported lack of beneficial outcome after the administration of immunoglobulins[18], antithrombin III[19], pentoxifyllin[20] and high dose steroids[21,22]. A possible favourable effect may be present using supraphysiologic steroids[23].

Another approach would be to remove compounds that act toxic and aggravate the cascade systems. Since there seems to be little benefit by hemodialysis or various types of hemofiltration, another approach would be to remove toxins and waste products, e.g., apheresis[24]. Apheresis could basically be divided in processing of blood unselectively (plasma exchange by centrifugation or single filtration) or in a selective way, removing specific substances (cascade filtration or various adsorption techniques). Whereby there is only limited clinical experience in selective therapy by adsorption; most of those studies using polymyxin B adsorbers[25-27]. Whereby a study by Tani et al.[25] showed significantly better survival in the patients treated with adsorption than in a selected group of controls. Other adsorbers under development aim to adsorb mainly the bacterial toxins and to some extent cytokines[28-33].

Most clinical experiences have been achieved by unselective plasma exchange, removing plasma by centrifugation or filtration (plasmapheresis) and replacing it with albumin or plasma. Such approaches have been used in smaller series during the 80th and in larger series during the 90th (Table 1). Recently an open randomised controlled study performed in Archangels comparing conventional therapy to a group additionally treated by plasma[34]. They achieved a significantly better survival in the treatment group than in the controls (66% versus 44%, p = 0.04). In an Australian multicenter study, 30 patients were randomised to either conventional treatment or to additionally long-term continuous plasmafiltration for at least 24 hours[35]. Survival in the treatment-group was 57% and was not different from the control group (50%). Notable is that treatment was by plasmafiltration (plasmapheresis) continuously for at least 24 hours. This long-term blood-membrane exposure may be counteracting eventually beneficial effects, since it is known that when using filters for plasma exchange this will cause a further activation of the complement system[36,37].

In our centre, we have performed plasma exchange for severe sepsis and MODS using the centrifugation technique. The concept is to remove compounds from plasma that may contribute to the activation of the cascade systems. To avoid lack of essential products, which only recovers slowly, additionally we have replaced removed plasma with plasma from healthy donors (mainly 1:1). This substitutes for essential products in the blood[38] necessary to modulate the inflammatory response and the consumption coagulopathy. We mostly substituted with liquid stored plasma (stored at 4°C until use, optimal 7-10 days, Table 2) that, compared to fresh frozen plasma, contains less of coagulation factors and relatively more of fibrinolytic factors [39]. Additionally, patients who were given liquid stored plasma had fewer and

Table 1. Various studies using plasma exchange/plasmapheresis in the treatment of severe sepsis and in MODS

Study	n	Main mode of therapy	Survival (%)	p =
Bjorvatn et al. 1984[46]	4	PLF	100	
Brandtzaeg et al. 1985[47]	8	PE	75	
Graf et al. 1987[48]	2	PF	100	
Häuser et al. 1987[49]	4	PF	0	
Stegmayr & Wirell 1987[50]	4	PE	100	
Asanuma et al. 1989[51]	19	BE	68	
Stegmayr et al. 1990[52]	13	PE	69	
McClelland et al. 1990[53]	2	PF	100	
v Deuren et al. 1992[54]	15	PF+BE	80	
Gårdlund et al. 1993[55]	14	PF	79	
Stegmayr et al. 1995[56]	27	PE	81	
Stegmayr et al. 1998[40]	56	PE	79	
Reeves et al. 1998[35]				
- controls, random	16	-	50	
- plasmafiltration > 24h	14	PF	57	n.s.
Koukline et al.1999[34]				
- controls, random	50	-	44	
- plasma exchanged	50	PE	66	= 0.04
Tani et al. 1999[26]	88	AdsPmx	51	
Tani et al. 1998[25]				
- controls, selected	33	-	36	
- adsorption	37	AdsPmx	54	< 0.05
Kanesaka et al.1999[27]	34	AdsPmx	59	

PE: Plasma exchange by centrifugation technique; PLF: Plasmalymphapheresis; PF: Plasma filtration; BE: Blood exchange; AdsPmx: Adsorption column using polymyxin B.

less severe side effects than was expected by fresh frozen plasma[39]. In our recent study[40] we included 56 patients with DIC and MODS, all with acute renal failure and at least 3 organs failing, according to Pinsky [41]. The study was not randomised. Patients included were those who worsened, despite optimal conventional intensive care treatment (attempt of rescue therapy). Normally the chance for survival, having such severe criteria, would be at the most 20%[42-44]. In that study 79% of the patients survived and were able to leave the hospital. However, 21% died. Would it be possible to reduce the extent of death? Probably, if the treatment is started earlier in the course of the disease. However, since this treatment is not generally accepted, it needs to be confirmed by a controlled trial. To reduce the risk for death in these patients in such trial the inclusion of patients should be in an earlier level of the disease. Thereby patients progressing into severe levels of a disease could be considered as failures to treat if they are controls and offered to be treated with apheresis. To have more strict criteria classification could be made by a modification of criteria given by Pinsky[41]. Thereby, patients who will be susceptible for inclusion should have signs of a

Table 2. Levels of various parameters in fresh frozen plasma (FFP), liquid stored plasma for 7 d (LSP), and cryoprecipitate-poor plasma (CCP). Various preparations were obtained from five healthy donors (standard deviation in brackets). With permission by Karger[39]

	Normal range	FFP	LSP	CPP
Prothrombin complex	70-130 (%)	89 (± 15)	74 (± 7)	79 (± 5)
APT-time	24-36 (sec)	32 (± 2)	41 (± 1)	51 (± 2)
Fibrinogen	2.4-4.0 (g/L)	2.1 (± 0.4)	2.2 (± 0.4)	1.3 (± 0.2)
F VIIIC	65-165 (%)	94 (± 22)	30 (± 15)	7.2 (± 2)
F VIII R Ag	65-165 (%)	80 (± 20)	50 (± 44)	0
Plasminogen	1.2-1.8 (µmol/L)	1.4 (± 0.1)	1.5 (± 0.1)	1.4 (± 0.2)
Kallikrein-like activity	1-6 (mA/min)	33 (± 11)	27 (± 6)	32 (± 8)
Antithrombin	80-120 (%)	88 (± 5)	76 (± 15)	85 (± 6)
C1-inhibitor	1.3-1.9 (µmol/L)	1.6 (± 0.3)	1.8 (± 0.4)	1.6 (± 0.3)
C3	100 ± 17 (%)		84 (± 11)	82 (± 17)
C4	100 ± 26 (%)		79 (± 26)	90 (± 31)

C= Complement component

progressive consumption coagulopathy[6,7,42] including lowering of platelets by more than 40%, lowering of prothrombin complex, antithrombin III and fibrinogen besides an increase in activated partial thrombin time and fibrin degradation products. Additionally, they should have signs of at least 2 dysfunctioning organs, with criteria according to Pinsky[41]. In addition, pancreas dysfunction could be included, indicated by a more than double increase of serum amylase from the upper normal limit[7]. The motif to include pancreas as a dysfunctioning organ is based on the fact that severe pancreatitis may by itself cause a progress into MODS[7]. A grading of shock severity is defined by Pinsky as[41] evidence of tissue hypoperfusion: urine output < 30 mL/h, decreased sensorium, and diaporesis, and/or an elevated serum lactate level (> 2 mmol/L). Level 0: defined by hypotension or vascular instability rapidly reversible without specific therapy, and serum lactate < 2 mmol/L; Level 1: rapidly reversible with intravascular fluid replacement associated with evidence of altered organ perfusion; Level 2: requiring vasoactive support; Level 3: not responsive to maximal resuscitative therapy for 2 h or more. We would like to add to level 1, that fluid replacement should be at least 5% of the body weight (e.g. 2.5 litres if 50 kg). An addition to Level 2 would be a limitation of the vasoactive drugs used to be comparable to dobutamin in doses at the most of 6 µg/kg body weight and minute. Larger doses offer no benefit[45]. Patients included in such a trial could suffer from various reasons for acute septic shock, extensive crush injury, extensive surgery, poisoning (e.g., snake bites, mushroom) or intoxication and adverse drug reactions, haemorrhagic pancreatitits, inducing an acute progressive DIC with subsequent MODS.

Our local Ethical Committee has accepted such design of a multi-center trial. However, the committee did not accept randomisation of patients that were in the most severe level of shock (Level 3). This decision was based on the favourable results achieved by plasma exchange at our center, since they considered plasma exchange so beneficial that all of those severely ill patients should be offered plasma exchange as a rescue treatment.

In conclusion the patients with severe sepsis and other reasons for MODS have a poor prognosis. Data lack of beneficial studies that favour adjunct drug therapy to threat these patients when conventional therapy fails. A possible approach to treat these severely ill patients could be the addi-

tion of apheresis. A controlled trial is necessary to help deciding if there is a benefit to this more extensive approach.

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