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Blood filtration in children with severe sepsis: safe adjunctive therapy

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Abstract *Objective:* To review the safety and efficacy of haemofiltration and plasmafiltration in children with severe sepsis.
Design: Retrospective case notes analysis.
Setting: University Paediatric Intensive Care Unit.
Patients: All children admitted to the intensive care unit between November 1985 and May 1992 with a primary diagnosis of severe sepsis who also received blood filtration therapy.
Interventions: Continuous haemofiltration (HF) 18 patients; continuous haemofiltration and plasmafiltration (PF) 9 patients.
Measurements and results: 27 children with sepsis-induced MOSF, median age 26.6 months (range 0.33–185), median weight 12 kg (range 2.5–58), mean PRISM score 19.4 (SD 8.6), mean number of organs failing 2.78 (SD 0.9) received filtration for a median duration of 36 hours (range 2–145). Eight (30%) survived (HF 5/18, PF 3/9). There was no significant difference in the demographic features between the HF group and the PF group and no difference in mortality. The two groups were pooled to assess the effect of commencement of filtration on clinical wellbeing. Arterial blood gases, electrolytes, full blood examination, ventilator settings and doses of inotropes were recorded immediately prior to commencement of filtration and 18 h after commencement. Serum anion gap and osmolality were calculated using conventional formulae. There were no significant changes in the level of cardiorespiratory support, or biochemical markers of severity following commencement of filtration. Platelet count fell 32% ($p = 0.029$) but no bleeding was encountered. No severe complications were observed during 1222 h of filtration. No bleeding or infection was observed at the site of cannulation. One child developed haemodynamic instability following commencement of plasmafiltration necessitating abandonment of the procedure.
Conclusion: Haemofiltration or plasmafiltration can be performed safely in children with severe sepsis but their effect on outcome remains unknown.

Key words Haemofiltration Plasmafiltration · Sepsis · Novel therapies · Outcome · Safety Paediatric

Introduction

Continuous haemofiltration is an established supportive therapy for children with acute renal failure in intensive care [1]. Plasmafiltration, i.e. plasmapheresis with a large pore haemofilter, is an experimental therapy for severe sepsis which has been described in small series in adults [2, 3] and individual case reports in children [4].

Between November 1985 and April 1992, 27 children received haemofiltration during their admission to our intensive care unit with the diagnosis of severe sepsis. Nine of them also received plasmafiltration. The purpose of this report is to review our experience of filtration in these 27 children and assess the effect of the therapy on haemodynamic, respiratory, haematological and biochemical markers of illness severity.

Patients and methods

Patients who received haemofiltration (HF) or haemofiltration and plasmafiltration (PF) and whose major diagnosis was suspected or proven infection, were identified on the intensive care database and their clinical notes reviewed. All identified case notes were available for analysis. Patients were excluded if they had received other experimental therapies such as immunoglobulins, colony stimulating factors or extracorporeal membrane oxygenation. The severity of the presenting illness was quantified with the Paediatric Risk of Mortality (PRISM) score using the most abnormal values in the first 24 h after admission to intensive care. The number of organs failing in the first 24 hours after admission was identified using criteria defined in children [5]. The level of respiratory support was quantified using ventilatory index (VI) VI = respiratory rate (min^{-1})×peak inspiratory pressure (cmH_2O)×arterial PCO_2 (mmHg)/1000; gas exchange was measured with the alveolar-arterial partial pressure gradient for oxygen (A-a DO_2).

The level of cardiovascular support was quantified using a weighted average of the infusion rates of all inotropes. The weighting was chosen empirically to reflect the comparative potencies of the agents in children. Weighted inotrope score = dopamine μg/kg/min×10+dobutamine μg/kg/min×7.5+adrenaline μg/kg/min ×50+noradrenaline μg/kg/min×50+10% calcium gluconate ml/kg/h×25.

Arterial blood gases, serum sodium, potassium, glucose, creatinine, urea and chloride were recorded at the time of commencement of filtration and 18 h later. The anion gap and serum osmolality were calculated using standard formulae [6]. A full blood examination was performed before commencement of filtration and 18 h later.

Filtration technique

Before 1987, a continuous arteriovenous technique was used. From 1987, a continuous venovenous technique was used. Blood was pumped by a calibrated roller pump incorporting alarms for air entrainment, line occlusion or overpressure. Two types of hollow fibre filter were used for haemofiltration: the Renaflo HF250 (Renal Systems, Minneapolis, USA), and the Gambro FH22 (Gambro, Lund, Sweden). Bicarbonate buffered replacement solutions were prepared by pharmacy to the following concentrations (mmol/l) Na^+ 135, K^+ 3.0, Ca^{2+} 1.5, Mg^{2+} 0.7, HCO_3^- 25, PO_4^{2-} 1.0, acetate 16.4, Cl^- 100 and dextrose 0.3%. Filtrate production and replacement infusions were controlled with volumetric infusion pumps. Haemofiltration was suspended during plasmafiltration.

Plasmafiltration was performed with the Gambro PF1000 filter. All patients who underwent plasmafiltration received at least one double plasma volume exchange (100 ml/kg). The replacement solution for the first three quarters of plasmafiltration exchange contained the same electrolyte concentrations as above, with the addition of 40 g/l of human albumin; fresh frozen plasma was used as replacement solution for the last quarter of the exchange.

Other therapy

In addition to blood filtration, all patients received conventional supportive treatment consisting of antibiotics, fluids, inotropic drugs, mechanical ventilation and early feeding (parenteral or enteral).

Statistics

Results are presented as means with standard deviations or medians with ranges where the data is skewed. Non parametric analyses were used to avoid assumptions regarding the distribution of data. Paired data were compared using the Wilcoxon matched pairs signed rank sum test and unpaired data were compared using Mann-Whitney U test. Mortality in the two groups was compared with Fisher's exact test. All analyses were performed using Systat for Windows Version 5.02. (SYSTAT, Inc, Evanston, Illinois, USA).

Results

Between November 1985 and April 1992, 27 children with sepsis-induced MOSF, median age 26.6 months (range 0.33–185), median weight 12 kg (range 2.5–58), received filtration for a median duration of 36 hours (range 2–145). Eight survived. The mean PRISM score was 19.4 (SD 8.6) and the mean number of organs failing was 2.78 (SD 0.9). Their individual clinical details are presented in Table 1. No neonates received plasmafiltration. Three patients had underlying immunocompromise (HF 2, PF 1).

The survival rate decreased with increasing numbers of failing organ systems and with increasing PRISM scores: one organ 1/1 survived, two organs 5/15 survived, three organs 2/9 survived, four organs 0/5 survived, five organs 0/1 survived: PRISM 0–15 5/10 survived, PRISM 16–30 3/16 survived, PRISM >30 0/1 survived.

The causative organisms were: Gram positive bacteria 8, meningococcus 7, other Gram negative bacteria 2, virus 2, bowel flora 6, fungus 1, unknown 2. The primary sites of infection were: blood 10, respiratory tract 1, abdomen 7, central nervous system 3, urinary tract 1, unknown 5.

The demographic features of the haemofiltered group were comparable with the plasmafiltered groups (Table 2). There was no significant difference between the two groups with respect to age, weight, PRISM score, number of organs failing in the first 24 h after admission to inten-

Table 1 Clinical details of children with sepsis receiving haemofiltration and/or plasmafiltration (*HSV-II* Herpes simplex virus type 2; *NEC* Necrotising enterocolitis; *Ex 30/40* Ex 30 weeks gestation; *CAPD* Continuous ambulatory peritoneal dialysis; *BMTx* Bone marrow transplant; *ARDS* Adult respiratory distress syndrome; *FA* Fanconi's anaemia; *ALL* Acute lymphoblastic leukaemia; *HUS* Haemolytic uraemic syndrome; *L* Live; *D* Dead)

Pt.	Age (months)	Weight (kg)	Diagnosis	PRISM	Organs failed	Duration filtration (h)	Outcome L or D
Haemofiltration							
1	0.33	3.2	HSV-II	27	3	13	D
2	0.56	3.7	*E. coli* meningitis	19	5	27.5	D
3	1.22	3.5	NEC peritonitis	27	4	5	D
4	1.32	2.5	Ex 30/40 mucor mycosis	12	2	21	D
5	3.45	5.8	Hirschsprung's peritonitis	10	2	65	D
6	5.19	7.3	Meningococcaemia	27	2	41.5	D
7	14.8	10	Meningococcaemia	21	2	24	D
8	16.7	12	Meningococcaemia	28	3	60.5	D
9	26.6	12	CAPD peritonitis	19	4	145.7	D
10	36	16.5	Febrile BMTx	7	3	12	D
11	43.4	15	Pneumococcaemia ARDS	21	3	45.5	D
12	55.4	11	FA. pneumococcaemia	35	4	36	D
14	27.9	13	Group A strep. pneumonia	15	1	12.25	L
15	30.4	15	Haemophilus meningitis	9	2	44.5	L
16	47.1	15	Staph toxic shock	24	2	24	L
17	84.6	25	Peritonitis	25	4	13.8	D
18	165	43	Staph toxic shock	25	3	43.8	L
19	185	58	Peritonitis	5	3	20.5	L
Plasmafiltration and haemofiltration							
19	5.75	8.3	Meningococcaemia	30	3	3.25	D
20	13.1	13	Abdominal sepsis	29	2	74.5	D
21	43	15	Febrile neutropaenic	15	2	83.6	D
22	49	20	Meningococcaemia	25	3	2	D
23	93.3	24.3	Pneumococcaemia, *varicella*	11	3	102	D
24	112	35	*E. coli* sepsis ALL	18	4	74.5	D
25	3.72	8	Meningococcaemia	10	2	2.75	L
25	8.02	9.6	Pneumococcal meningitis HUS	4	2	106	L
27	24	18	Meningococcaemia	27	2	117.8	L

sive care, time to commencement of filtration or total duration of filtration. There was no statistically significant difference between the survival rate in the two groups.

Effects of filtration on biochemistry, haematology and the level of cardiorespiratory support

There was no significant changes in the level of cardiorespiratory support following commencement of filtration (Table 3). None of the biochemical or haematological variables studied changed significantly following commencement of filtration except for the platelet count which fell by 32% in the 18 h after commencement of filtration ($p = 0.029$) (Table 4).

Filter performance

The median filter life including elective discontinuations after plasmafiltration was 24 h (range 2–60.5 h).

Complications of filtration

During more than 1200 hours of filtration, there were no episodes of mechanical failure, no circuit disconnections

Table 2 Comparison of demographic features of septic children receiving haemofiltration or plasmafiltration

	HF	PF
Number	18	9
Age (months) median (range)	27 (0.33–185)	24 (3.7–112)
Weight (kg) median (range)	12 (2.5–58)	13 (8–35)
PRISM score mean (SD)	19.8 (8.4)	18.8 (9.4)
Number organs failed mean SD	2.89 (1.02)	2.56 (0.73)
Time (h) to commence filtration median (range)	18.75 (2.5–131)	7.5 (2.5–23)
Duration (h) filtration median (range)	25.8 (2–145)	74.5 (2–117)
Survivors (%)	5 (28%)	3 (33%)

$p > 0.05$ for all comparisons

Table 3 Effect of commencement of filtration on cardiorespiratory support (*VI* Ventilatory index; *A-a* DO_2 Alveolar arterial partial pressure gradient for oxygen; *WIS* Weighted inotrope score)

Variable	Pre filtration	18 h
VI mean (SD)	23.3 (13.2)	27.6 (17.8)
A-a DO_2 mean (SD)	260 (212)	268 (208)
WIS median (range)	126 (0–2700)	113 (0–1581)

$p > 0.05$ for all comparisons

Table 4 Effect of commencement of filtration on biochemical and haematological variables. Mean (SD). (*Anion gap* ($[Na^+]+[K^+]$) $+[K^+]-([Cl^-]+[HCO_3^-])$; *Osmolality* $2*[Na^+]+[Urea]+[Glucose]$)

Variable	Pre filtration	18 h
Anion gap mmol/l	23.3 (2.58)	27.6 (2.59)
Osmolality mmol/l	309 (5.56)	311 (4.18)
Creatinine mmol/l	0.19 (0.04)	0.16 (0.03)
Urea mmol/l	19.4 (3.65)	17.2 (3.27)
Haemoglobin g/dl	10.6 (0.38)	10.4 (0.38)
White cells $10^3/mm^3$	10.6 (1.57)	12.8 (1.91)
Platelets* $10^3/mm^3$	100 (16.6)	68.7 (13.7)

* $p = 0.029$
$p > 0.05$ for all other comparisons pre vs 18 h

or emboli. On average, each patient was exposed to two filters and therefore at least two circuit changes. There were no instances of superinfection with nosocomial organisms or uncontrolled systemic bleeding. There were no bleeding or infectious complications at the sites of cannulation. One child developed haemodynamic instability during plasmafiltration necessitating cessation of therapy.

Discussion

Continuous haemofiltration might exert beneficial effects in MOSF via a number of mechanisms: correction of uraemia improves platelet and neutrophil function and reversal of overhydration improves cardiac and respiratory function [7–9]. However, extracorporeal circulations may cause haemodilution, and increase the risk of infection, embolism and bleeding. Exposure of the blood to artificial surfaces can cause the release of inflammatory mediators and platelet consumption; complement-induced pulmonary leukosequestration may cause a deterioration in gas exchange and hypotension. We observed a 32% drop in platelet count following the connection of new haemofilters but no clinical bleeding occurred. We observed no significant change in the alveolar-arterial oxygen gradient or the ventilatory index during the first 18 h following commencement of haemofiltration and no change in the requirements for inotropes. Biochemical markers were unchanged.

Plasmafiltration has been proposed as an experimental treatment for severe sepsis [10] because it removes bacterial toxins and inflammatory mediators. However, Parillo cautioned against its use in sepsis where it may remove beneficial host factors such as immunoglobulins, acute phase proteins and anti inflammatory cytokines [11]. Data from animal models is balanced. Natanson showed a deleterious effect from plasmapheresis in a canine model of septic shock [12] and Muraji showed a beneficial effect in a puppy model [13]. There are a number of clinical reports of favourable results in human sepsis [3, 4, 14]. The majority of these cases were adults. In our retrospective study of children with severe sepsis, we observed no difference in mortality in the group which had received plasmafiltration compared with a comparable group receiving continuous haemofiltration alone. However, the patient numbers were small and the indication for the use of plasmafiltration over haemofiltration was not standardised. Therefore conclusions about the relative efficacy of plasmafiltration compared to haemofiltration are not possible from this study.

However, we have shown that haemofiltration or plasmafiltration can be commenced in severely ill children without requiring an escalation in cardiovascular or respiratory support and without biochemical or haematological evidence of clinical deterioration. This pilot study paves the way for a prospective randomised controlled trial of plasmafiltration in sepsis. Such a trial has commenced at this institution.

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