ORIGINAL ARTICLE

Application of endotoxin and cytokine adsorption haemofilter in septic acute kidney injury due to Gram-negative bacterial infection

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Objective Endotoxins and cytokines play an important role in the pathogenesis of multi-organ failure and mortality in patients suffering from severe Gram-negative bacterial infection. The aim of this study was to determine whether in patients with such infections, use of a haemofilter with enhanced endotoxin haemoadsorption and cytokine removal properties helps to overcome organ dysfunction.

Design Prospective case series study with historical controls.

Setting A regional hospital in Hong Kong.

Patients From October 2011 to June 2012, patients with sepsis-induced acute kidney injury due to Gram-negative bacteria were recruited. Continuous venovenous haemofiltration using oXiris haemofilter was performed. The patients' APACHE (Acute Physiology And Chronic Health Evaluation) II and inclusion criteria matched those of a series of selected historical controls who had been treated with continuous venovenous haemofiltration using polysulfone-based haemofilter from 2009 to 2011. The percentage reduction in the Sequential Organ Failure Assessment score by 24 and 48 hours, the percentage reduction of noradrenaline equivalent usage by 48 hours, as well as intensive care unit and hospital mortality in the two groups were compared.

Results Pre-treatment biochemical parameters and vasopressor use in the six patients undergoing the intervention and the 24 historical controls were similar. The mean circuit life of oXiris was about 61 hours. The Sequential Organ Failure Assessment score was significantly reduced by 37% at 48 hours post-initiation of oXiris-continuous venovenous haemofiltration versus an increment of 3% in the historical controls. No significant side-effect was detected. Mortality was similar in the two groups.

Conclusion The haemofilter membrane with enhanced endotoxin adsorption and cytokine removal capacity was a safe alternative to traditional polysulfone-based continuous venovenous haemofiltration and expedited improvement in organ dysfunction.

Key words
Acute kidney injury; Cytokines; Endotoxins; Hemadsorption; Sepsis

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New knowledge added by this study

- Using continuous venovenous haemofiltration with a haemofilter incorporating enhanced endotoxin/cytokine haemoadsorption capacity may provide faster improvement of organ dysfunction in septic acute kidney injury due to Gram-negative bacterial infection.

Implications for clinical practice or policy

- This treatment can be considered an alternative to conventional continuous venovenous haemofiltration.
- A randomised controlled trial is warranted to evaluate possible clinical benefit of this treatment.

Introduction

Sepsis is an important cause of acute kidney injury (AKI) in critically ill patients.[1] Compared with critically ill patients without sepsis, septic patients are more prone to severe organ dysfunction, longer intensive care unit (ICU) stays, and mortality.[2] Hospital mortality in septic patients is around 30% overall, and up to 50% in those with septic shock.[3] Cytokines play an

內毒素及細胞因子吸附血液濾器在革蘭氏陰性細菌感染引起的急性腎損傷之應用

目的 內毒素和細胞因子與嚴重革蘭氏陰性細菌感染引起的多器官功能衰竭及死亡有莫大關係。本研究探討內毒素及細胞因子吸附血液濾器在革蘭氏陰性細菌感染引起的急性腎損傷之應用。

設計 前瞻性病例系列研究結合歷史個案對照。

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患者 2011年10月至2012年6月期間因革蘭氏陰性細菌感染引起的急性腎損傷的患者被納入研究範圍。他們使用oXiris血液濾器進行連續性靜脈血液過濾，其臨床表現與APACHE II和納入標準相匹配的歷史個案進行對比，而歷史個案皆於2009至2011年期間接受聚碸血液濾器的連續性靜脈血液過濾。然後比較兩組在24小時內和48小時內序貫器官衰竭評分減少的百分比、48小時內去甲腎上腺素減少的百分比，以及在深切治療病房和住院死亡率的分別。

結果 6名患者和24個歷史對照組的病人進行了比較，他們在治療前的生化指標和血管加壓素用量相似。oXiris血液濾器使用壽命約為61小時。在48小時治療後患者的序貫器官衰竭評分明顯減少37%，而歷史對照組反而增加3%。oXiris血液過濾沒有顯著的副作用，而兩組之間的死亡率相近。

結論 在革蘭氏陰性細菌感染引起的急性腎損傷患者中，相對傳統連續性靜脈血液過濾，內毒素及細胞因子吸附血液過濾不但安全，更可加快改善器官功能。

important role in the pathogenesis of sepsis, septic shock, and multi-organ failure.[4,5] In Gram-negative bacterial infection, endotoxins trigger the release of both pro-inflammatory and anti-inflammatory cytokines.[6] Excessive or overwhelming cytokine release can cause deleterious multi-organ damage via their direct cytotoxic action and subsequent 'immunoparalysis' effects.[5,7,8] The application of blood purification techniques in sepsis was built on these concepts. Endotoxin haemoadsorption can effectively neutralise the pathogenic activity of endotoxin and reduce organ dysfunction.[9] Cytokine removal by haemofiltration or haemoadsorption can attenuate the effect of cytokine over-production or expression and restore the state of immune homeostasis. This is also reflected clinically by improved patient morbidity and mortality.[10,11]

Semi-permeable membrane use with enhanced endotoxin adsorption and cytokine removal capacity is postulated to be a valuable treatment option in septic shock due to Gram-negative bacterial infection. The oXiris haemofilter (oXiris, Gambro Hospal, Sweden) is an AN69-based membrane, surface treated with a polyethyleneimine (PEI) and grafted with heparin. The AN69 core membrane has an efficient cytokine removal capacity.[12,13] The surface treatment with PEI enhances endotoxin binding by the AN69 membrane,[14] while heparin coating reduces membrane thrombogenicity, prolongs filter life, and improves efficiency.

Since October 2011, our ICU started using the oXiris haemofilter in patients suffering from refractory septic shock with AKI due to Gram-negative bacterial infection. This study reports our clinical experience with its use for citrate-based continuous venovenous haemofiltration (CVVH). The clinical response and outcomes of patients treated by this means were therefore compared with those of disease severity–matched historical controls treated with a conventional haemofilter.

Methods

This study was a prospective case series with historical controls from a 22-bed adult medical-surgical ICU in a regional medical centre serving a community of 600 000 inhabitants in Hong Kong. The study protocol was approved by the Ethics Committee of the Hong Kong East Cluster, and written informed consent was obtained from all patients or their surrogates having renal replacement procedures. Since October 2011, all patients clinically indicated for continuous renal replacement therapy were prospectively screened for the use of oXiris-CVVH based on the criteria indicated in the Box.[15,16] A double-lumen 12-F haemodialysis catheter (ARROWg+ard Blue Plus antimicrobial catheter, Arrow International Inc,

BOX. Inclusion and exclusion criteria in screening patients for the use of oXiris–continuous venovenous haemofiltration[15,16]

Inclusion criteria
- Age ≥18 years
- Presence of septic shock (defined using the American College of Chest Physicians/Society of Critical Care Medicine/European Society of Intensive Care Medicine criteria[15])
- Development of acute kidney injury (categorised as "Risk" or more in the Risk, Injury, Failure, Loss and End-stage [RIFLE] criteria[16])
- Suspected or confirmed Gram-negative bacterial infection (based on clinical or microbiological findings)

Exclusion criteria
- Documented chronic kidney disease stage 5 (glomerular filtration rate <15 mL/min/1.73 m^2)
- End-stage renal failure on long-term dialysis
- Those treated with renal replacement therapy prior to intensive care unit admission

US) was inserted into either the internal jugular or femoral vein for vascular access. Thereafter, oXiris-CVVH was performed using the Prismaflex machine (Gambro Hospal, Stockholm, Sweden) fitted with an oXiris haemofilter. The citrate-based predilutional CVVH regimen was developed by our institution and has been described previously.[17] The blood flow rate was maintained at 150 mL/min. Prismocitrate 10/2 solution running at a fixed rate of 2500 mL/h was the main predilution replacement fluid (3.33 mmol of citrate/citric acid per litre of blood withdrawn). An 8.4% sodium bicarbonate solution was infused at 50 mL/h for the first 2 hours via the 'heparin port' of the circuit (pre-filter) and subsequently decreased to 30 mL/h. Pre- and post-filter ionised calcium (iCa) levels were maintained at less than 0.3 mmol/L. Ten percent calcium gluconate solution was infused via a separate central venous catheter. The infusion rate was titrated to achieve a systemic iCa level of 1 to 1.2 mmol/L. Potassium was added to the prismocitrate 10/2 solution for patients warranting supplementation. Phosphate and magnesium were replaced via a separate venous line. The overall fluid withdrawal rate was adjusted to achieve the desired fluid balance at the discretion of physician-in-charge. The circuit was run for 72 hours based on the manufacturer's recommendations unless there was filter clotting or the patient was deemed not to require further renal replacement therapy. All patients received oXiris-CVVH for one session only. Patients considered to need continuation of renal support were placed on conventional CVVH using a polysulfone high-flux haemofilter (FX80; Fresenius Medical Care, Germany).

Historical controls were selected from patients who were treated with CVVH between 2009 and 2011. They had to meet the same inclusion criteria as the newly recruited patients. All the controls had been treated with post-dilutional CVVH using Gambro AK200 Ultra S (Gambro Hospal, Stockholm, Sweden) with a polysulfone high-flux haemofilter (FX80). Blood flow was maintained at 150 mL/min. Citrate anticoagulation using anticoagulant citrate dextrose solution A was run at 240 mL/h pre-filter. Pre- and post-filter iCa were maintained at ≤0.3 mmol/L. The ultrafiltration rate was fixed at 2000 mL/h. Replacement fluid was generated online and its electrolyte contents adjusted based on laboratory results. Calcium gluconate (10% solution) was infused via a separate central venous catheter and titrated to achieve a systemic iCa level of 1-1.2 mmol/L. The circuit was run for 30 hours, unless there was filter clotting or patient transferral (eg to an imaging facility or operating theatre). The circuit and haemofilter were changed and a further 30-hour session of CVVH continued based on clinical indications. Four historical controls with closest disease severity (based on Acute Physiology And Chronic Health Evaluation [APACHE] II risk of death) were matched for each case. The renal support for both case and control patients was stepped down from CVVH to slow low-efficiency haemodialysis (SLED) or haemodiafiltration (SLED-f), whenever they were haemodynamically stabilised without the use of any vasopressors. Organ dysfunction was quantified by the Sequential Organ Failure Assessment (SOFA) score.[18] Demographic data, co-morbidities, APACHE II score, noradrenaline equivalent usage, and biochemical parameters were recorded. Noradrenaline equivalent was calculated as[19]:

(Noradrenaline [μg/min] + dopamine [μg/kg/min] ÷ 2) + adrenaline (μg/min) + phenylephrine (μg/min) ÷ 10

Appropriateness of antibiotic use was defined based on the bacterial culture sensitivity pattern and the antibiotics being administered within 6 hours of ICU admission. Length of stay (ICU and hospital) and survival (ICU and hospital) data were obtained as outcome parameters. Due to resource limitations, in this study inflammatory markers were not checked.

Statistical analysis

To compare cases and controls, where appropriate, univariate analysis was performed using Fisher's exact test for categorical data or the Mann-Whitney *U* test for continuous data. The Friedman test was used to detect any improvement of SOFA score during 0 to 48 hours of CVVH. Secondary analyses were not performed due to the small sample size. The analysis was performed using the Statistical Package for the Social Sciences (Windows version 16.0; SPSS Inc, Chicago [IL], US).

Results

Between October 2011 and June 2012, seven patients were treated with oXiris-CVVH. One of them who had intra-abdominal sepsis was excluded from the analysis owing to violation of the treatment protocol, as the patient also received alternative cytokine adsorption treatment (polymethylmethacrylate). Table 1 shows the baseline characteristics of the remaining six patients. The controls were older than the oXiris-CVVH–treated patients, but the difference was not quite significant (P=0.052). The majority of patients suffered from intra-abdominal sepsis; *Escherichia coli* accounted for 71% of the infections in the controls and 100% in the oXiris-CVVH group. The patients usually started CVVH within 24 hours of ICU admission and about half were started using the RIFLE classification at 'Injury' grade or earlier. The post-dilutional ultrafiltration rate was within the recommended range (≥25 mL/kg/h). The mean circuit life of the oXiris haemofilter using the Prismocitrate 10/2–based regimen was 61 hours. The biochemical parameters were similar in both groups. All patients

TABLE 1. Baseline characteristics*†

Characteristics	oXiris-CVVH group (n=6)	Control group (n=24)	P value
Age (years)	62 (58 to 73)	76 (66 to 81)	0.052
Gender (male:female)	4:2	15:9	1.0
Body weight (kg)	61 (51 to 67)	60 (53 to 61)	0.500
Source of sepsis			0.366
Intra-abdominal	5	23	
Other	1	1	
Bacterial culture findings			0.170
Escherichia coli	6	17	
Klebsiella	0	7	
Appropriate antibiotic use within 6 hours of ICU admission	4	18	0.645
APACHE II score	36 (28 to 41)	34 (31 to 37)	0.602
APACHE II ROD	0.85 (0.64 to 0.92)	0.85 (0.78 to 0.91)	0.795
APACHE II SMR	0.62	0.60	N/A
Baseline GFR (mL/min)	67 (55 to 88)	67 (45 to 77)	0.533
Starting creatinine (μmol/L)	213 (138 to 298)	207 (164 to 272)	0.364
RIFLE class on starting of CVVH			0.218
Risk	0	6	
Injury	3	5	
Failure	3	13	
Starting pH	7.28 (7.22 to 7.37)	7.31 (7.16 to 7.37)	1.0
Starting base excess	-7.7 (-2.0 to -14.5)	-8.9 (-4.8 to -13.4)	0.815
Starting mean arterial pressure (mm Hg)	71 (65 to 87)	76 (70 to 84)	0.421
Noradrenaline equivalent on starting of CVVH (μg/min)	28.9 (11.4 to 40.8)	22.8 (11.9 to 47.5)	0.979
SOFA score on starting of CVVH	12 (9 to 15)	13 (10 to 15)	0.667
Time for CVVH initiation after ICU admission (hours)	20.7 (10.3 to 36.2)	20.4 (8.7 to 34.7)	0.795
Post-dilutional ultrafiltration rate (mL/kg/h)	32.0 (29.3 to 38.1)	35.7 (32.7 to 37.7)	0.254
CVVH duration (hours)	61.1 (34.6 to 71.8)	41.2 (26.3 to 75.0)	0.604

* Data are shown as median (interquartile range), unless otherwise specified

† APACHE denotes Acute Physiology And Chronic Health Evaluation, CVVH continuous venovenous haemofiltration, GFR glomerular filtration rate, ICU intensive care unit, N/A not applicable, ROD risk of death, SMR standardised mortality ratio, and SOFA Sequential Organ Failure Assessment

received similar vasopressor support prior to CVVH initiation and their APACHE II expected risk of death was very high (85%).

Table 2 shows the outcome parameter results. The SOFA score improved significantly in the oXiris-CVVH (P=0.011) group but not in the controls (P=0.515). The SOFA score decreased by 37% at 48 hours post-initiation of oXiris-CVVH compared with an increase of 3% in the controls (P=0.013). Figure 1 illustrates the relationship between SOFA scores with time in both groups. There was a trend towards an appreciable decrease in vasopressor use in both groups after commencement of treatment (Fig 2). There was no significant difference between the groups in terms of mean ICU/hospital length of stays and ICU/hospital mortality. Nor did the average amount of dialysis given to the two groups differ at 28 days, 3 months, and 6 months from the recruitment date. Due to the small sample size, regression analysis was not performed. There was no significant side-effect detected during the treatment process.

Discussion

For patients with septic shock and sepsis-induced AKI due to Gram-negative bacterial infection, CVVH using a haemofilter incorporated with enhanced endotoxin/cytokine removal capacity was associated with expedited improvement in organ function (within 48 hours) compared with using conventional CVVH.

Non-specific broad-spectrum cytokine removal was proposed as a treatment option after failure to improve the clinical outcome of

TABLE 2. Outcome parameters*†

Parameter	oXiris-CVVH group (n=6)	Control group (n=24)	P value
Total SOFA score	‡	§	
0 Hour	12 (8.75 to 15)	12.5 (10.25 to 15)	0.667
24 Hours	11 (8 to 11)	12 (9.25 to 14)	0.073
48 Hours	7.5 (4 to 11)	12.5 (9 to 15.75)	0.015
Reduction of SOFA score (%)			
By 24 hours	17.5 (3.1 to 31.1)	7.5 (-14.7 to 17.8)	0.186
By 48 hours	36.7 (11.5 to 66.0)	-3.3 (-31.3 to 24.5)	0.013
Reduction of noradrenaline equivalent (%)			
By 24 hours	67.9 (-12.8 to 88.8)	27.5 (-23.8 to 70.2)	0.287
By 48 hours	95.0 (26.1 to 100)	73.3 (-26.3 to 99.0)	0.280
Dialysis requirement			
At 28 days	0 (n=3)	1 (n=12)	1.0
At 3 months	0 (n=3)	1 (n=12)	1.0
At 6 months	0 (n=3)	1 (n=12)	1.0
ICU LOS (days)	6.2 (4.0 to 18.5)	7.5 (5 to 18)	0.716
Hospital LOS (days)	21.0 (17.5 to 25.8)	19.5 (10.5 to 51.5)	0.876
ICU mortality	2 (33%)	10 (42%)	1.0
Hospital mortality	3 (50%)	12 (50%)	1.0

* Data are shown as median (interquartile range), unless otherwise specified

† CVVH denotes continuous venovenous haemofiltration, ICU intensive care unit, LOS length of stay, and SOFA Sequential Organ Failure Assessment

‡ Friedman test to compare 0-hour with 48-hour SOFA score changes (P=0.011)

§ Friedman test to compare 0-hour with 48-hour SOFA score changes (P=0.515)

septic patients by targeting individual cytokines.[20] Multiple theories espouse the potential benefit of blood purification therapy in septic patients. The 'Peak concentration theory' by Ronco et al,[21] the 'Threshold immunomodulation theory' by Honoré and Matson,[22] the 'Mediator delivery theory' by Di Carlo and Alexander,[23] the 'Cellular level theory' by Peng et al,[24] and recently the 'Cytokinetic theory' by Rimmelé and Kellum[25] all endorse the importance of cytokine modulation. They also shed light on techniques that achieve clinical benefit. Although high-volume haemofiltration (HVHF) and pulse HVHF may improve haemodynamic stability and patient survival in those with septic shock,[26] large-volume ultrapure replacement solutions significantly increase treatment costs, risks of severe electrolyte disturbance, and nursing workload. Haemoperfusion with cytokines and/or endotoxin adsorption columns require relatively simple setups and equipment, which is more feasible in ICU settings. Favourable effects on haemodynamics, oxygenation, and survival are also more readily accepted by critical care physicians.[9] However, associated thrombocytopenic effects impose a significant hurdle when used in septic patients who frequently have clotting defects and severe thrombocytopenia. Moreover, the cost of an individual haemoperfusion cartridge is very high (approximately HK$20 000), which limits its clinical utility. Despite good initial clinical outcomes,[26] coupled plasma filtration adsorption is still an investigational tool and the requirement of special equipment means that an inordinate amount of training is necessary. Cytokines can also

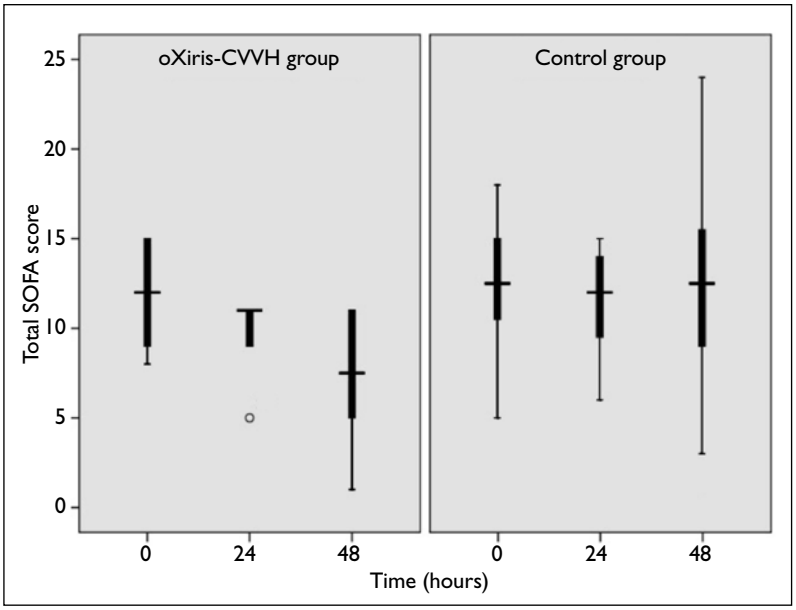

FIG 1. Total Sequential Organ Failure Assessment (SOFA) score changes with time
CVVH denotes continuous venovenous haemofiltration. The horizontal lines within the boxes represent the medians, the lower and upper bounds of the boxes represent the 25th and 75th percentiles, and the I bars represent the 5th and 95th percentiles. The circle indicates an outliner

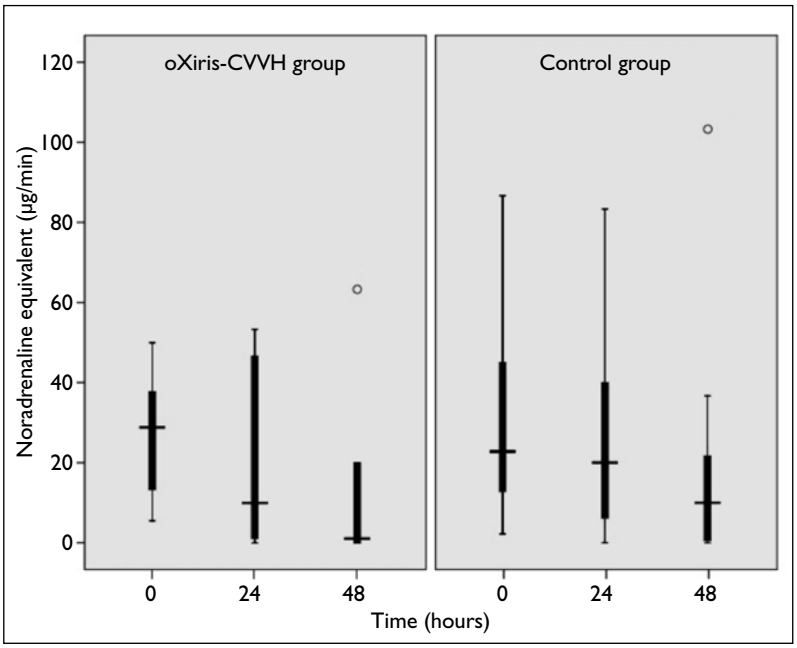

FIG 2. Noradrenaline equivalent usage changes with time
CVVH denotes continuous venovenous haemofiltration. The horizontal lines within the boxes represent the medians, the lower and upper bounds of the boxes represent the 25th and 75th percentiles, and the I bars represent the 5th and 95th percentiles. The circles indicate outliners

be removed by haemodialysis or haemodiafiltration using a high cut-off membrane. However, with this method albumin loss is the key problem that demands particular attention. Use of a haemofilter with enhanced cytokine and/or endotoxin binding capacity seems to provide a balance of all these techniques. The equipment used is readily available in general ICUs and the associated technique (ie CVVH) is well established.

In this study, CVVH was started relatively late; around half of the patients started it at "Failure" grade of the RIFLE classification. Late CVVH initiation may affect the outcome of the patients. However, the standardised mortality ratio for all recruited patients was around 0.6 which was similar to the standard for ICU patients. Although the mean age of the historical controls was slightly more than the intervention group, their APACHE II risk of death was adjusted for and so we believe the groups were well matched.

Initial experience on the use of this new haemofilter seems to have been promising and our study provides a stepping stone to conduct further large-scale randomised control trials to gain a more thorough understanding about the potential benefit of broad-spectrum cytokine removal. We nevertheless believe that identification and control of the infective source, early appropriate antibiotic use, and aggressive initial fluid resuscitation coupled with late conservative fluid management continue to be the essential key components for the successful treatment of patients with sepsis. Supportive therapies that target removal of endotoxin and/or cytokines will not have any significant clinical impact, if one or more of these key components are omitted.

Limitation

A major limitation of this study was the small number of cases, predicated by resource limitations. Thus, its results cannot be accepted with a degree of high confidence. A second limitation related to time period bias and selection bias resulting from recourse to historical controls may have influenced the SOFA scores, although the time bias was probably minimal as in the recent 5 years our treatment strategies had scarcely changed. To reduce potential selection bias, only historical controls with the closest disease severity were chosen for each of our new cases, though this did give rise to an age difference. However, as the APACHE score was the most important factor believed to determine ICU patient outcomes,[27] our focus on matching was very likely appropriate. In fact, the APACHE score was calculated from age, presence of significant chronic illness, and physiological measurements. A third limitation was that the follow-up period was relatively short (up to hospital discharge) and whether the treatment being tested can offer any long-term benefits is unclear. We expect that cytokine levels should gradually normalise after the acute phase of a septic illness, and that follow-up till hospital discharge should correlate well with clinical recovery. Improvement of the SOFA score was the only significant finding in our study, which may be subject to information bias. Among the six components (namely respiratory system, nervous system, cardiovascular system, renal system, liver, and coagulation), bias regarding nervous system assessment by using the Glasgow coma scale (GCS) may have occurred. However, all GCS assessments were performed by ICU nurses, not the investigators. Therefore, this bias should be minimal. Finally, our oXiris-CVVH protocol was purely citrate anticoagulation–dependent. So the results may not be extrapolated to continuous venovenous haemodialysis with citrate anti-coagulation or CVVH together with other forms of anticoagulation.

Conclusion

Using CVVH and a haemofilter with enhanced endotoxin/cytokine adsorption capacity can offer expedited yet safe organ function improvement compared with a conventional polysulfone-based haemofilter. We could not identify any significant side-effect in this small group of patients. The haemofilter life was acceptable. Randomised controlled trials are recommended to further delineate the potential benefits of this treatment.

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Declaration

oXiris haemofilters for CVVH were donated by Gambro Hospal, Sweden. Gambro Hospal had no role in study design and conduction, data collection and storage, data analysis and interpretation, preparation, review, or approval of this manuscript. All investigators did not receive any other form of financial support from Gambro Hospal on study-related issues.

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