ACUTE DIALYTIC SUPPORT FOR THE CRITICALLY ILL: CONTINUOUS VENOVENOUS HAEMODIALYSIS VERSUS CONTINUOUS VENOVENOUS HAEMOFILTRATION

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UNIVERSITI SAINS MALAYSIA

JABATAN PERUBATAN
DEPARTMENT OF MEDICINE

Tarikh: 5 Februari 2005

Professor Zabidi Azhar Mohd Hussin
Pengerusi Jawatankuasa Penyelidikan dan Etika
Pusat Pengajian Sains Perubatan,
Kampus Kesihatan USM,
16150 Kubang Kerian,
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Tuan,

Per: PENYERAHAN LAPORAN AKHIR BAGI PROJEK PENYELIDIKAN R&DJANGKA PENDEK (GERAN NO. 304/PPSP/6131205)

Merujuk kepada perkara di atas.

Saya telah menjalankan satu kajian bertajuk "Acute Dialytic Support for the Critically Ill: Continuous Venovenous Haemodialysis versus Continuous Venovenous Haemofiltration". Sehubungan dengan itu, laporan yang berkaitan telah disiapkan. Berikut disertakan tiga salinan Laporan Komprehensif Kajian beserta dengan Borang Laporan Akhir (USM R&D/JP-06) bagi tindakan tuan selanjutnya.

Sekian, terima kasih.

Yang benar,

.....
Prof. Madya Kamaliah Mohd. Daud
Pensyarah/Pakar Perubatan
Jabatan Perubatan
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BAHAGIAN PENYELIDIKAN
PUSAT PENGAJIAN SAINS PERUBATAN

SALINAN :
- Bhg. Penyelidikan, PPSP
- ✓ Perpustakaan Perubatan, USMKK
- RCMO

T/Tangan : ..... Tarikh : 14/3/05

Sk : i) Tuan Haji Halim Othman, Ketua Pegawai Sains, Bahagian Penyelidikan
ii) Puan Latiffah Latif, Penolong Pendaftar, Pejabat Pengurusan dan Kreativiti Penyelidkan, RCMO

BAHAGIAN PENYELIDIKAN & PEMBANGUNAN

CANSELORI

UNIVERSITI SAINS MALAYSIA

Laporan Akhir Projek Penyelidikan Jangka Pendek

1) **Nama Penyelidik:** Prof. Madya Dr. Kamaliah Mohd Daud (304/PPSP/6131205)

Nama Penyelidik-Penyelidik Lain *(Jika berkaitan)* :
1) Dr. Goh Bak Leong, Hospital Selayang
2) Dr. Azmil Othman, Hospital Selayang
3) Dr. Ravindran Visvanathan, Hospital Kuala Lumpur.
4) Dr. Melor Mohd Mansor, Hospital Kuala Lumpur.

2) **Pusat Pengajian/Pusat/Unit :** Pusat Pengajian Sains Perubatan

3) **Tajuk Projek:** Acute Dialytic Support for The Critically Ill: Continuous Venovenous Haemodialysis Versus Continuous Venovenous Haemofiltration.

4. (a) **Penemuan projek/Abstrak**

(Perlu disediakan makluman di antara 100-200 perkataan di dalam Bahasa Malaysia dan Bahasa Inggeris, ini kemudiannya akan dimuatkan ke dalam laporan Tahunan Bahagian Penyelidikan dan Pembangunan sebagai satu cara untuk menyampaikan dapatan projek tuan/puan kepada pihak Universiti.)

ABSTRAK

Satu kajian prospektif rambang terkawal telah dijalankan untuk membandingkan kesan 2 jenis rawatan penggantian fungsi ginjal berterusan (CRRT), iaitu venovenous hemofiltrasi berterusan (CVVH) dan venovenous hemodialisis berterusan (CVVHD) di kalangan pesakit-pesakit yang tenat dengan kegagalan ginjal akut di dalam unit rawatan rapi (ICU) di Hospital Selayang dan Hospital Kuala Lumpur. Tanda-tanda klinikal penting, jumlah urin dan keputusan biokimia dicatit setiap hari semasa rawatan dijalankan. Tempoh rawatan CRRT dan tempoh berada di ICU, tahap pemulihan ginjal dan status hidup pesakit semasa discaj dari ICU juga direkodkan. Serum untuk analisa sitokin (IL-6 dan TNF-α) diambil pada masa 0 dan 24 jam rawatan CRRT. Dalam tempoh 28 bulan (September 2001 hingga Disember 2003), sejumlah 20 orang pesakit telah diselidik. Data demografi, aspek klinikal dan data makmal adalah sebanding di antara kedua-dua kumpulan rawatan. Peningkatan TNF-α adalah 35.6% berbanding 173.0% dan penurunan IL-6 adalah 48.8% berbanding 18.0% di kalangan pesakit CVVH dan CVVHD. Kadar kematian secara keseluruhan adalah 85%. Tempoh berada di ICU, peratus pemulihan lengkap ginjal dan kadar kematian untuk pesakit-pesakit CVVH berbanding CVVHD adalah 16 hari berbanding 8 hari ($p = 0.16$), 11.8% berbanding 9.1% ($p = 1.0$) dan 77.7% berbanding 90.9% ($p = 0.57$). Kesimpulannya, di kalangan pesakit-pesakit rawatan CVVH, profil perubahan tahap sitokin adalah lebih baik namun kesan klinikal rawatan CVVH dan CVVHD adalah sama.

ABSTRACT

A prospective randomized controlled study was performed to compare the effect of 2 modalities of continuous renal replacement therapy (CRRT) i.e. continuous venovenous haemofiltration (CVVH) versus continuous venovenous haemodialysis (CVVHD) on the clinical outcome in critically ill patients with acute renal failure in the intensive care units in Hospital Selayang and Hospital Kuala Lumpur. Patients' vital signs, urine volume and biochemical variables were recorded daily while on treatment. The duration of CRRT treatment and ICU stay, extent of renal recovery and survival status at discharge from ICU were also recorded. Serum for cytokines assay (IL-6 and TNF-α) were taken at 0 hour and 24 hours of CRRT treatment. Over a period of 28 months (September 2001 till December 2003), a total of 20 patients were included in the study. Patients' demographic, clinical features and laboratory data were comparable between the 2 treatment groups. The increase of TNF- α was 35.6% versus 173.0% and drop in IL-6 was 48.8% versus 18.0% in patients treated with CVVH and CVVHD respectively. The overall mortality rate was 85%. The duration of ICU stay, % of complete renal recovery and death rates for CVVH compared to CVVHD patients were 16.0 days versus 8.0 days ($p = 0.16$), 11.1% versus 9.1% ($p = 1.0$) and 77.7% versus 90.9% ($p = 0.57$) respectively. In conclusion, patients treated with CVVH had more favourable changes in cytokines level but the clinical outcomes were similar between CVVH and CVVHD treated groups.

(b) **Senaraikan Kata Kunci yang digunakan di dalam abstrak:**

Bahasa Malaysia	Bahasa Inggeris
1. kegagalan ginjal akut	1. acute renal failure
2. hemodialisis veno-venous berterusan	2. continuous venovenous haemodialysis
3. hemofiltrasi veno-venous berterusan	3. continuous venovenous haemofiltration
4. sitokin	4. cytokines

5) **Output Dan Faedah Projek**

(a) Penerbitan *(termasuk laporan/kertas seminar)*
(Sila nyatakan jenis, tajuk, pengarang, tahun terbitan dan di mana telah diterbit/dibentangkan).

i). Akan dibentangkan semasa "3rd World Congress of Nephrology - Post Congress Satellite Symposium on Acute Renal Failure, 1st-3rd July 2005 in Penang, Malaysia. (abstrak dikembarkan)

ii) Telah dihantar kepada Editor, International Medical Journal untuk penerbitan (surat dan manuskrip dikembarkan).

(b) Faedah-Faedah Lain Seperti Perkembangan Produk, Prospek Komersialisasi Dan Pendaftaran Paten.
(Jika ada dan jika perlu, sila gunakan kertas berasingan)

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(c) Latihan Gunatenaga Manusia

i) Pelajar Siswazah .....

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ii) Pelajar Prasiswazah: .....

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.....

iii) Lain-Lain : .Menambah.kemahiran.penyelidik.dalam.aspek.....

.....rawatan.kegagalan.ginjal.akut.pesakit.kritikal.di ICU

.....-.menggunakn.teknik.CRRT.yang.kemudiannya.di.aplikasi

.....di.HUSM.....

6. **Peralatan Yang Telah Dibeli:**

1. Double lumen central venous catheter.
2. ELISA kit for cytokines assay
3. Bicaflac bacarbonate solution
4. Digital camera - Canon Ixus 330
5. Stationeries.

UNTUK KEGUNAAN JAWATANKUASA PENYELIDIKAN UNIVERSITI

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TANDATANGAN PENGERUSI
JAWATANKUASA PENYELIDIKAN
PUSAT PENGAJIAN

UNIVERSITI SAINS MALAYSIA
JABATAN BENDAHARI
KUMPULAN PENYELIDIKAN GERAN J/PENDEK
PENYATA PERBELANJAAN SEHINGGA 31 DISEMBER 2004

Jumlah Geran		19,990.00	Ketua Projek	DR KAMALIAH DAUD
Peruntukan 2002 (Tahun 1)	RM	1,990.00	Tajuk Projek	ACUE DIALYTIC SUPPORT FOR THE CRITICALLY ILLCONTINUOUS VENOVENOUS HAEMODIALYSIS VERSUS CONTINUOUS
Peruntukan 2003 (Tahun 2)	RM	0.00		
Peruntukan 2004 (Tahun 3)	RM	0.00	Tempoh	
			No.Akaun:	304/PPSP/6131205

Akaun	PTJ	Projek	Donor	Peruntukan Projek	Perbelanjaan Terkumpul sehingga Tahun lalu	Peruntukan Semasa	Tanggungan Semasa	Bayaran Tahun Semasa	Belanja Tahun Semasa	Baki Projek
11000	PPSP	6131205		-	-	-	-	-	-	-
14000	PPSP	6131205		-	-	-	-	-	-	-
15000	PPSP	6131205		-	-	-	-	-	-	-
21000	PPSP	6131205		600.00	864.00	(264.00)	-	-	-	(264.00)
22000	PPSP	6131205		-	-	-	-	-	-	-
23000	PPSP	6131205		100.00	99.50	0.50	-	-	-	0.50
24000	PPSP	6131205		-	-	-	-	-	-	-
25000	PPSP	6131205		-	-	-	-	-	-	-
26000	PPSP	6131205		-	-	-	-	-	-	-
27000	PPSP	6131205		19,040.00	34.00	19,006.00	-	14,270.00	14,270.00	4,736.00
28000	PPSP	6131205		-	-	-	-	-	-	-
29000	PPSP	6131205		250.00	-	250.00	-	-	-	250.00
35000	PPSP	6131205		-	1,699.00	(1,699.00)	-	-	-	(1,699.00)
				19,990.00	2,696.50	17,293.50	-	14,270.00	14,270.00	3,023.50

COMPREHENSIVE STUDY REPORT OF R&D SHORT TERM RESEARCH PROJECT

(Grant Number : 304/PPSP/6131205)

Title :

ACUTE DIALYTIC SUPPORT FOR THE CRITICALLY ILL: CONTINUOUS VENOVENOUS HAEMODIALYSIS VERSUS CONTINUOUS VENOVENOUS HAEMOFILTRATION

Authors :

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UNIVERSITI SAINS MALAYSIA

JANUARY 2005

ABSTRACT

Introduction : Acute renal failure occurs frequently among critically ill patients in the Intensive Care Unit (ICU) and carries significant mortality: Continuous renal replacement therapy (CRRT) has been favoured to conventional intermittent haemodialysis in such patients predominantly because of better haemodynamic stability. However no data is available on which modality of CRRT has better impact on patient's outcome.

Objectives : To compare the impact of two forms of CRRT i.e. continuous venovenous haemofiltration (CVVH) versus continuous venovenous haemodialysis (CVVHD) on the following parameters : (i) changes in inflammatory cytokines (IL-6 and TNF-α), (ii) duration of survival in ICU, (iii) renal recovery, and (iv) patient's outcome.

Method : A prospective randomized controlled trial was performed on critically ill patients who developed acute renal failure (ARF) in intensive care unit (ICU) in Hospital Selayang and Hospital Kuala Lumpur, Malaysia. At enrolment, patient's demographic data, clinical conditions and SAPS II score were recorded. Patient's vital signs, urine volume and biochemical variables were recorded daily. Serum for cytokines were taken at 0 and 24 hours of CRRT treatment.

Results : Over a period of 28 months (September 2001 till December 2003), a total of 20 patients were included in the study. Patient's demographic and clinical background were comparable between the two treatment groups.. There were no statistically significant differences in the laboratory results and vital signs. The increase of TNF-α was 35.6% versus 173.0% and drop in IL-6 was 48.8% versus 18.0% in patients treated with CVVH and CVVHD respectively. The duration of ICU stay, % of complete renal recovery and death rates for CVVH compared to CVVHD patients were 16.0 days versus 8.0 days ($p = 0.16$), 11.1% versus 9.1% ($p = 1.0$) and 77.7% versus 90.9% ($p = 0.57$) respectively.

Conclusion : Patients treated with CVVH had a more favourable changes in inflammatory cytokines level but the clinical outcome (ICU stay, renal recovery and death rates) were similar between CVVH and CVVHD treated groups.

Keywords: Acute renal failure, venovenous haemodialysis, haemofiltration, cytokines

INTRODUCTION

Acute renal failure (ARF) occurs frequently in critically ill patients in intensive care.[1,2] It is most often a multifactorial clinical syndrome characterized by acute, but potentially reversible reduction in renal excretory function. If pre renal causes are excluded, ARF is mostly caused by a systemic disturbance such as septicaemia, pancreatitis and burns and very often it forms part of the multiple organ failure/dysfunction syndrome (MODS). Such patients are critically ill and they usually require various pharmacological and life-support treatments. Over several decades, the mortality of patients with ARF appear to have remained unchanged despite advances in supportive care.[2] This has been attributed to the changes in patient demographics. Patient age has increased,[3] illness severity has worsened,[4] and the causes of renal failure in young adults associated with a good outcome (predominantly obstetric complications and trauma) have become progressively less common.[3] The primary aim of renal replacement therapy in these circumstances is to achieve adequate correction of homeostatic disorders with good clinical tolerance. Intermittent haemodialysis and peritoneal dialysis have some limitations in efficiency and clinical tolerance.[5-6] Continuous renal replacement therapy (CRRT) is increasingly being used to treat ARF in critically ill patients.[8] The advantages of continuous treatments are steady biochemical correction, slow continuous fluid removal, and excellent cardiovascular stability.[7-9] Despite these advantages, there are few data to indicate a survival advantage from continuous treatment. In a recent review article, Forni and Hilton suggested a substantial improvement in survival coincident with the introduction of continuous haemofiltration in their experience, despite similar severity of illness. [10]

For more than 20 years, the continuous techniques of renal replacement therapy (CRRT) have acquired a well-established role in intensive care medicine, however the most appropriate mode of CRRT is yet to be defined. [11] Furthermore, there is no

consensus on adequate treatment dose or on the impact of dose delivery on outcome. In a recent randomized controlled trial, Ronco et al[12] found that increasing the rate of plasma water exchange rate from 1.5 liters/h to approximately 2.5 liters/h reduced mortality in ICU patients with multiorgan failure treated with CVVH by 30%. This is the first randomized controlled trial which demonstrates that a modulation of a blood purification therapy decreases mortality in MODS with ARF. The findings of this trial have tremendous clinical and biological implications. Firstly, they demonstrate that extracorporeal blood purification therapy (EBPT) can affect mortality in a subset of critically ill patients. Secondly, they demonstrate that we need to explore that correct dose for all EBPT before we dismiss its clinical value.

As for the impact of modality selection on patient outcome, there are still no data comparing patient outcomes for patients treated with continuous haemofiltration, continuous haemodialysis or continuous haemodiafiltration. Based on the available data, no recommendations regarding the use of predominantly convective therapies as compared to diffusive therapies can be made. Efficiency of removal of low molecular weight solutes is similar with convection and diffusion. Efficiency of middle and high molecular weight solute removal is greater with convective therapies, [13] however data do not exist on the clinical implications of this enhanced solute removal. We undertook a prospective randomized controlled study to compare the effect of convective and diffusive therapy (CVVH versus CVVHD) on the clinical outcome in critically ill patients with ARF. The doses of dialysate and ultrafiltration rates were standardized to achieve equal urea clearance rate and the primary aim of the study was to compare both patient and renal outcomes. Duration of survival in ICU and changes in the blood cytokines profile were also studied.

OBJECTIVES

Primary Objectives

To compare the impact of two forms of continuous renal replacement therapies (CRRT), continuous venovenous haemofiltration (CVVH) versus continuous venovenous haemodialysis (CVVHD) on patient and renal outcome in critically ill patients with acute renal failure.

Secondary Objectives

To compare the duration of survival in ICU in both study groups and to compare the changes in inflammatory cytokine profile (IL-6 and. TNF-α).

Materials and Methods

Design: Prospective randomized controlled trial.

Inclusion Criteria

1. Critically ill patients on ventilatory support in intensive-care unit or coronary care unit with
2. Acute renal failure, defined by a sudden rise in serum creatinine concentration to over 2.3 mg/dL (200 umol/L) in patients with prior normal renal function, and/or a rise by more than 2.3 mg/dL (200 umol/L) in patients with prior renal dysfunction plus one of the following :-
   - (i) Oliguria (urine output of less than 200 ml in the preceeding 12 hours) despite fluid resuscitation and frusemide administration
   - (ii) Severe acidaemia (pH < 7.1) due to metabolic acidosis
   - (iii) Hyperkalaemia (plasma K > 6.5 mmol/L)
   - (iv) Suspected uraemic organ involvement (pericarditis,encephalopathy)

Exclusion Criteria

1. Age < 13
2. Pregnant patients.
3. End stage renal failure patients – patients on chronic dialysis or calculated creatinine clearance < 10 mls/min
4. The presence of more than 3 major organ failures at study recruitment
5. Systolic blood pressure of < 90 mm Hg at study recruitment despite ionotropic support

Study Protocol

Approval from the Ministry of Health Ethical Committee and Universiti Sains Malaysia Ethical Committee were obtained prior to the study. Informed consent was taken from legally authorized people (patients' close relatives i.e. parents, children of patients' aged > 21 years old, siblings or spouses). The study population included adult patients who were critically ill and on ventilatory support in ICU/CCU with acute renal failure (as defined earlier). Patients were randomized to receive either CVVH or CVVHD At enrolment, the following were recorded: - patients' demographic data, underlying clinical disorder, background medical history and simplified Acute Physiological Scoring II (SAPS II) . Urine volume & the following biochemical variables : renal profile (RP), arterial blood gases (ABG), full blood count (FBC) activated clotting time (ACT) and liver function test (LFT) were recorded at study enrolment & daily while patients were on treatment as well as on the day of discharge from ICU/CCU. Blood were collected for cytokine analysis from patients in both groups at 0 hour and 24 hours of treatment with CVVH or CVVHD. CVVH and CVVHD were performed using standard techniques[14]. All treatment were performed using a 0.6 m^2 AN 69 hemofilter (Hospal Multiflow 60) and Prisma (predilution) machine. Vascular access

was achieved through the use of double-lumen central venous catheters inserted into the internal jugular, subclavian or femoral veins. Blood flow was adjusted to deliver a minimum of 120 ml/min using a rotary blood pump. For CVVH, ultrafiltrate was replaced intravenously with sterile bicarbonate buffered solutions to achieve an ultrafiltrate of 2L/hour. For CVVHD, the dialysate outflow rate was set at 1.7L/hour (so as to achieve an equivalent urea clearance rate of 28.5 ml/hour as achieved by CVVH of 2L/hour).[13] Hemofilters were changed every 24 hours. Anticoagulation was achieved using heparin bolus of 1000 U followed by an infusion rate adjusted to maintain the activated clothing time (ACT) between 150 to 200 sec or activated partial thromboplastin time (A.P.T.T.) 2-3 times that of control. CVVH and CVVHD were performed without anticoagulation if heparin administration is contraindicated. Blood for cytokine analysis were drawn into pyrogenfree heparinised vials chilled immediately. Plasma was separated by centrifugation within 1 hour of collection. Aliquot of 250 μL was frozen at -70°C until used for each assay to avoid multiple freezing and thawing. Interleukin (IL)-6 and TNF-α were measured by enzyme – linked immunosorbent assay (ELISA) according to manufacturer's instruction. Cytokines were assayed in duplicate. An intrameasurement variability of <10% is considered acceptable, results outside these limits were repeated. Each set of assays were checked against known standards. The primary outcome measures were survival at discharge from ICU and the recovery of renal function at discharge from ICU which is classified into:-

i) Full Recovery - Restoration of concentration of serum creatinine and blood urea ± diuresis

ii) Partial recovery- Restoration of diuresis and patients no longer requiring renal replacement ,but with serum creatinine and blood urea remaining abnormal

iii) No recovery- Requirement for further renal replacement therapy after discontinuation of CRRT.

The duration of the study was 28 months. Patients' duration of survival in ICU/CCU was calculated in days. The percentage change in interleukin (IL) – 6 and TNF-α was calculated from 24 hours value as compared to baseline value at 0 hours.

STATISTICAL ANALYSIS

Analysis was done by intention to treat, according to the randomized modality of CRRT treatment. Calculation of sample size was based on the percentage difference of 36 % in cytokine levels between the two modalities of treatment.[15] Power of the test was set at 80 % with the ratio of the two modalities at 1:1.

Statistical analysis was done by comparing proportions of death (dichotomous outcome), renal recovery (ordinal outcome) and duration of survival (survival time) . Univariate analysis (Fisher's Exact test and Mann-Whitney U test) were applied to identify significant differences between the two modalities of treatment. Data was expressed as median (interquartile range) or percentage where appropriate. Level of significant (p) is taken at less than 0.05. SPSS version 11.5 was used for data entry and analysis.

RESULTS

Over a period of 28 months (September 2001 till December 2003), a total of 20 patients with acute renal failure (ARF) who required continuous renal replacement therapy (CRRT) in ICU were included in the study. The demographic and clinical features for patients treated with either CVVH or CVVHD are listed in Table 1.

Table 1 : Demographic and clinical characteristics of acute renal failure patients treated with CVVH and CVVHD.

	CVVH (n=9)	CVVHD (n=11)	z	p* +
Age (years)	52.0(26.50)	49.0(36.00)	-0.61	0.54
Sex (% male)	55.6%	63.6%	-	1.00
Primary service				
-medical	88.8%	54.6%	-	-
-surgical	11.2%	45.4%	-	-
Sepsis	88.8%	90.9%	-	1.00
Co-morbidity				
-diabetes	55.6%	45.5%	-	-
-hypertension	22.2%	27.2%	-	-
-liver disease	0	0	-	-
-heart disease	22.2%	9.1%	-	-
SAPS II Score	65.1(15.50)	66.5(11.00)	-0.96	0.34
CRRT duration (hours)	47.0(123.50)	45.0(52.00)	-0.15	0.88

Data expressed as median(interquartile range) or number (per cent) where appropriate.
* Mann Whitney U test, $p<0.05$ significant at 95% confidence interval.
+ Fisher Exact test, $p<0.05$ significant at 95% confidence interval.

The age, sex, SAPS II score and duration of CRRT treatment were comparable between the two groups. In terms of primary service, about half of the patients treated with CVVHD were surgical cases and majority of cases treated with CVVH were medical cases. Eighteen patients (90%) had sepsis and this was equally distributed between the 2 groups of treatment. The laboratory data and vital signs for patients treated with CVVH and CVVHD are shown in Table 2.

Table 2 : Comparison of laboratory data and vital signs for CVVH and CVVHD cases

	CVVH (n=9)	CVVHD (n=11)	z	p*
Blood urea (mmol/L)	19.0(7.40)	19.4(9.40)	-0.99	0.32
Serum creat (μmol/L)	288.6(169.62)	242.2(194.67)	-1.10	0.27
Serum albumin (g/dL)	23.4(7.20)	20.0(3.50)	-1.22	0.22
Total bilirubin (mmol/L)	17.6(30.17)	74.0(62.50)	-1.94	0.05
Serum bicarbonate (mmol/L)	19.8(4.162)	15.4(10.86)	-1.86	0.06
Haemoglobin (g/dL)	9.5(2.18)	10.2(2.60)	-0.34	0.73
White blood count ($x10^9$/L)	11.7(10.06)	18.3(7.64)	-1.18	0.24
Platelets ($x10^9$/L)	176.4(150.85)	69.0(153.38)	-0.99	0.32
Systolic blood pressure (mmHg)	117.4(22.97)	112.7(41.63)	-0.72	0.47
Urine volume (ml)	590.3(1095.00)	77.4(405.17)	-1.22	0.23

Data expressed as median(interquartile range)
* Mann Whitney U test, $p<0.05$ significant at 95% confidence interval.

Patients treated with CVVHD had lower median urine volume, higher serum bilirubin, higher total white blood count and lower platelet counts compared to patients on CVVH. However these differences were not statistically significant.

In terms of the percentage change in the serum level of two inflammatory cytokines, TNF-α and IL-6, a complete set of cytokine assay (at 0 and 24 hours) were only obtained in three patients. In two patients who received CVVHD treatment, the average rise in TNF-α was 173.0% and the average drop in IL-6 was 18.75%. For the one patient treated with CVVH, TNF-α rose by 35.6% and IL-6 drop by 48.8%. The outcome of patients treated with CVVH and CVVHD are demonstrated in Table 3.

Table 3 : Comparison of outcome for CVVH versus CVVHD cases

	CVVH (n=9)	CVVHD (n-11)	z	p*+
Survival in ICU (days)	16.0(14.00)	8.0(12.00)	-1.40	0.16
Complete Renal Recovery	11.1%	9.1%	-	1.00
Death	77.7%	90.9%	-	0.57

Data expressed as median (interquartile range) or number (per cent) where appropriate.
* Mann Whitney U test, $p<0.05$ significant at 95% confidence interval.
+ Fisher Exact test, $p<0.05$ significant at 95% confidence interval

Regardless of clinical characteristics or co-morbidity, the overall mortality rate for all patients in the study during hospitalization in ICU was 85%. However the differences in length of ICU stay, renal recovery and death rates between the two treatment groups were not statistically significant. In the CVVH treatment group, three patients (30%) had partial renal recovery compared to no patients (0%) in the CVVHD treated group.

DISCUSSION

Acute renal failure (ARF) necessitating renal replacement therapy is common in intensive care units (ICUs). The condition generally occurs in the course of multiorgan failure and is associated with a poor prognosis.[2,16] Mortality rates range between 50% and 80%.[12,17] Overall, the mortality rate for ARF patients treated with CRRT in ICU in this study (85%) is somewhat more dismal than that reported elsewhere. This high mortality may be explained by the pre- selection of patients who required CRRT i.e. more seriously ill patients who may not be suitable to undergo intermittent haemodialysis or peritoneal dialysis. A high percentage of septic patients in this study (90%) may also contribute to this overall high mortality. Sepsis is known as an independent risk factor for poor outcome, it is associated with a high in-hospital mortality rate that dramatically increases when ARF superimposes.[18,19]

The continuous renal replacement therapies (CRRT) comprise a spectrum of treatments that include both haemofiltration (convection-based solute and water removal) and haemodialysis (diffusion-based solute removal) techniques. These techniques have gained favour in the treatment of critically ill patients with renal failure primarily because of improved haemodynamic stability as compared to intermittent haemodialysis. Although some investigators have suggested that the use of CRRT is associated with improved outcomes in acute renal failure, this has not yet been demonstrated by prospective randomized trials.[20]

In terms of comparing the outcome for patients treated with continuous haemofiltration or continuous haemodialysis, there are still no data on the clinical implications of the differences in solute removal between these two modalities.

In this study, it was noted that in the CVVHD treated group, there were more surgical cases and the laboratory data appears to be less favourable (though not

statistically significant). However all the three outcomes (ICU stay, renal recovery and death rates) were not significantly different between the two treatment groups. This may suggest that patients treated with diffusive technique (CVVHD) had a similar clinical outcome despite the confounding factors.

Unfortunately, the sample size in this study was too small to make strong conclusion on the outcome of treatment modality. This was due to the difficulty in choosing patients who fulfilled the inclusion criteria and there was also problem of getting consent from patient's relatives. Bearing this limitation in mind, the apparent mortality effect by treatment choice may be attributable largely to the patient's clinical status and not specific to the type of renal replacement therapy modality itself.

In terms of cytokines removal by the CRRT, our data was too limited to make any conclusion. However our results show that patients treated with CVVH seem to have more favourable outcome in terms of rate of accumulation or removal of TNF-α and IL-6. Tumour Necrosis Factor-α and IL-6 were chosen in this study because these inflammatory cytokines have been shown to correlate with severity of meningococcaemia (TNF-α and IL-6) and sepsis severity score as well as with mortality in patients developing sepsis in the ICU (TNF-α).[21,22,23] Tumour Necrosis Factor-α is a cytokine produced by activated macrophages shown in experimental studies to be a primary mediator of the deleterious effects of endotoxin.[24]

Our finding seems to agree with the previously reported decrease in plasma TNF-α being more marked in patients with systemic inflammatory response syndrome and ARF who were treated with CVVH compared to CVVHD.[15] This ability of haemofiltration to remove immunomodulatory substances may lead to an improvement in patient outcome among those with sepsis and acute renal failure Experimental and preliminary human evidence suggests that large volume haemofiltration more effectively removes some of these immunomodulatory substances in septic or highly

catabolic patients, possibly leading to better preservation of cardiovascular function.[25,26]. Despite this observation, a review of the literature examining the effect of CRRT in sepsis found that benefits with this modality remained unclear.[27]

In conclusion, patients treated with CVVH had more favourable changes in cytokines profile but the clinical outcome (ICU stay, renal recovery and death rates) were similar between CVVH and CVVHD treated groups. However, due to the limited sample size, we were not able to demonstrate the independent effect of treatment modality on outcome.

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REFERENCES

1 Nissenson AR. Acute renal failure:definition and pathogenesis. *Kidney Int* 1998;53 (Suppl 66):S7-10

2 Cameron JS. Acute renal failure thirty years on.*Q J Med* 1990 ;74:1-2

3 Turney JH, Marshall DH, Brownjohn AM, Ellis CM, Parsons FM. The evolution of acute renal failure,1956-88.*Q J Med* 1990;74:83-104

4 Chew SL, Lins RL, Daelemens R, De Broe ME. Outcome in acute renal failure. *Nephrol Dial Transplant* 1993;8:101-107

5 Briglia A, Paganini EP. Acute renal failure in the intensive care unit:therapy overview, patient risk stratification,complications of renal replacement, and special circumstances. *Clin Chest Med* 1999;20:347-66

6 Schetz MRC. Classical and alternative indications for continuous renal replacement therapy. *Kidney Int* 1998;53(Suppl 66):S129-32

7 Ronco C, Bellomo R, eds. Critical care nephrology. Dordrecht, Netherlands: Kluwer Academic Publishers,1998

8 Bellomo R, Mansfield D, Rumble S, Shapiro J, Parkin G, Boyce N.A comparison of conventional dialytic therapy and acute continuous haemodiafiltration in the management of acute renal failure in the critically ill. *Ren Fail* 1993;15:595-602

9 Jones CH, Richardson D, Goutcher E, et al. Continuous venovenous high flux dialysis in multiorgan failure: a 5 year single center experience.*Am J Kidney Dis* 1998;31:227-33

10 Forni LG, Hilton PJ: Continuous haemofiltration in the treatment of acute renal failure. *N Engl J Med* 1997;18:1303-9

12 Ronco C,Bellomo R,Homel P,et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomized trial.*Lancet* 2000;355:26-30

13 Brunet S,Leblanc M,Geadah D,et al.Diffusive and convective solute clearances during continuous renal replacement therapy at various dialysate and ultrafiltration flow rates.*Am J Kidney Dis* 1999;34:486-92

14 Bellomo R.Choosing a therapeutic modality:Hemofiltration vs hemodialysis vs hemodiafiltration.*Seminars in Dialysis* 1996;9:88-92

15 Kellum JA,Johnson JP,Kramer D,et al.Diffusive vs convective therapy:Effects on mediators of inflammation in patients with severe systemic inflammatory response syndrome.*Crit Care Med* 1998;26:1995-2000.

16 Schaefer JH, Jochimsen F, Keller F, Wegscheider K, Distler A. Outcome prediction of acute renal failure in medical intensive care. Intensive Care Med 1991; 17:19-24

17 Heering P, Ivens K, Thumer O, et al. The use of dialysate buffers during continuous hemofiltration in critically ill patients with acute renal failure. Intensive Care Med 1999; 25:1244-1251

18 Heering P, Morgera S, Schmitz FJ, et al. Cytokine removal and cardiovascular hemodynamics in septic patients with continuous venovenous hemofiltration. Intensive Care Med 1997;23:288-296

19 Sasse KC, Nauenberg E, Long A, Anton B, Tucker HJ, Hu TW. Long-term survival after intensive care unit admission with sepsis. Crit Care Med 1995;23:1040–1047

20 Palevsky PM. Continuous venovenous haemodialysis : Technical Consideration Uptodate Aug 2004 ; version 12.3 : page 1