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ผลสัมฤทธิ์จากโครงการวิจัย (Output)

ผลงานที่เกิดขึ้นระหว่างดำเนินโครงการวิจัยโดยได้ล เกิดงานวิจัยเพิ่มเติมขึ้นมาอีก 3 ชิ้นงาน ซึ่งได้เผยแพร่ ด้วยช่องทางต่างๆ ดังนี้

- การนำเสนอในที่ประชุมวิชาการนานาชาติ

1. "Regional Citrate Anticoagulation Reduces Polymorphonuclear Cell Degranulation in Critically Ill Patients Treated with Continuous Veno-Venous Hemofiltration (CVVH): A Randomized Controlled Trial" in **Free Communication**: AKI Dialysis: Hemodialysis, CRRT, SLED. The American Society of Nephrology (ASN) Annual Renal Week 2010, Colorado Convention Center, **Denver, Colorado, USA**, November 19th, 2010.

2. "Accuracy of Using Online Clearance Monitor to Measure Vascular Access Flow in High-Efficiency On-line Hemodiafiltration" in Poster Session: XL VII ERA-EDTA Congress, **Munich, Germany**, June 27th, 2010.

3. "Long-term comparison of dialyzer reuses and clinical parameters between pre and post-dilution online hemodiafiltration" in Poster Session: The 12th Asian Pacific Congress of Nephrology, COEX, **Seoul, Korea**, June 5th-8th,2010

- ตีพิมพ์ในรูปแบบบทคัดย่อในวารสารนานาชาติ (ดังแสดงใน ภาคผนวก ก)

1. **Khajohn Tiranathanagul**, Onanong Jearnsujitwimol, Paweena Susantitaphong, Narin Kijkriengkraikul, Kearkiat Praditpornsilpa, Somchai Eiam-Ong._Regional Citrate Anticoagulation Reduces Polymorphonuclear Cell Degranulation in Critically Ill Patients Treated with Continuous Veno-Venous Hemofiltration (CVVH): A Randomized Controlled Trial [Abstract]. J Am Soc Nephrol 2010; 21: 37A.

2. **Khajohn Tiranathanagul**, Paweena Susantitaphong, Piyaporn Towannang, Kearkiat Praditpornsilpa, Somchai Eiam-Ong. Accuracy of using online clearance monitor to measure vascular access flow in high-efficiency on-line hemodiafiltration [Abstract]. Nephrol Dial Transpl 2010

3. **K Tiranathanagul**, P Susantitaphong, C Sakunsrijinda, K Praditpornsilpa, K Tungsanga, S Eian-Ong. Long-term comparison of dialyzer reuses and clinical parameters between pre and post-dilution online hemodiafiltration. Nephrology 2010; 15(Suppl 3): 101.

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ภาคผนวก ก

PO02-050
THE REMOVAL RATIO OF FREE LIGHT CHAIN BY SEVERAL DIALYSIS MEMBRANES IN PATIENTS WITH RENAL AMYLOIDOSIS

N SUGA[1], H YAMADA[2], N MIURA[1], K NISHIKAWA[1], H IMAI[1]
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Introduction: Primary amyloidosis (AL-type) is a disease that causes end-stage renal failure and cardiac arrest. High dose chemotherapy and/or auto-PBSCT has been recommended for patients without multi-organ involvement. If patients have renal failure or cardiac involvement, no specific therapy is taken. In order to clarify which dialysis membrane is the best on the removal of serum free light chain (FLC), we performed hemodialysis (HD) and haemodiafiltration (HDF) by using several dialysis membranes in patients with renal amyloidosis.
Methods: We performed HD and HDF by using several dialysis membranes for primary amyloidosis patients who were excluded the indication of the chemotherapy. We measured serum FLC value on pre- and post-dialysis, and calculated the removal ratio as the formula that (pre value –post value)/pre value (%), the post value was corrected by serum albumin in order to prevent the influence of blood concentration.
Results: chain on ABH1.8F (HDF) was about 70%, that of lambda chain was about 50%, HDF by using ABH1.8F is the best method on the removal of serum FLC (Table 1). chain are greater than those of lambda chain in all membranes. HDF can remove more kappa and lambda chains than HD in all membranes. The removal ratio of kappa The removal ratios of kappa
Conclusion: The HDF by using ABH1.8F membrane is recommended to remove serum FLC in patients with renal amyloidosis.

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	APS-1.8SA (HD)	ABH1.8F (HDF)
kappa	36.0	68.8
lambda	18.0	48.7
	FLX1.8 (HD)	FLX1.8 (HDF)
kappa	25.2	32.1
lambda	17.6	21.5
	FDX1.8 (HD)	FDX1.8 (HDF)
kappa	47.1	57.5
lambda	29.7	41.8

The removal ratio (%) of serum FLC on HD or HDF by using several membranes.

PO02-051
EXPERIMENTAL STUDY OF A NEW HEMODIAFILERATION METHOD WITH DUAL FLOW DIALYZER

M MIYATA[1], T YASUDA[2], S TERAO[3], B ACHRYA[3], M KANESHIRO[1], Y KIKUCHI[1], K KONISHI[1], K MORIMOTO[1], H MASTUSHIMA[2], A GOTOH[3], T HAYASHI[4]
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Introduction: One of the most important aims of recent renal replacement therapy is middle-molecular-weight toxins removal. It is well known that hemodiafiltration method (HDF) is more effective to remove of these solutes than conventional hemodialysis method (HD). However, HDF has some disadvantages. Therefore, we developed a new hemodiafiltration method (DF-HDF) with modified dialyzer as dual flow dialyzer (DFD).
Methods: The system of DF-HDF is the same as on-line HDF. However, on-line prepared substitution fluid is directly injected into the DFD. The DFD, which was modified from APS-15SA (Asahikasei – Kurare medical, Tokyo, Japan.), has a substitution fluid-inlet-port in the other side of a dialysate-inlet-port, and has two fins to adjust these substitution-fluid and dialysate flows. The effect of middle and small molecule removal on DF-HDF were evaluated by dextoran (MW: 15,000–20,000 Dalton) clearance (CL) and urea (MW: 60 Dalton) CL, and results were compared with HD using APS-15SA in the water experiment (Blood flow: 200 ml/min, substitution fluid and dialysate flows of DF-HDF: 100 and 400 ml/min, dialysate flow of HD: 500 ml/min).
Results: No significant differences were observed with respect to urea CL between DF-HDF and HD. However, dextoran CL of DF-HDF was significantly higher than HD (52.3 ± 6.0 ml/min vs. 39.2 ± 5.1 ml/min, $P < 0.05$).
Conclusion: DF-HDF succeeded in improving the middle molecule removal without decreasing small molecule removal. Furthermore, DF-HDF is including the possibility that can achieve higher removal effects by the changes in balance and/or volume of substitution – fluid and dialysate flows.

PO02-052
LONG-TERM COMPARISON OF DIALYZER REUSES AND CLINICAL PARAMETERS BETWEEN PRE AND POST-DILUTION ONLINE HEMODIAFILTRATION

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[1]*King Chulalongkorn Memorial Hospital;* [2]*Faculty of Medicine, Chulalongkorn Univ. and King Chulalongkorn Memorial Hospital, Thailand*

Introduction: Growing evidence demonstrated the potential survival benefit of online hemodiafiltration (ol HDF) over conventional hemodialysis (HD). Previous studies regarding ol HDF utilized single use dialyzer. The present study was conducted to compare the long term effect of reuse dialyzer in pre and post-dilution of ol HDF.
Methods: This prospective study was performed in 20 chronic hemodialysis patients. The patients firstly underwent pre-dilution ol HDF for 1 year and post-dilution ol HDF for another 1 year. Reuse dialyzers were used in both methods.
Results: No pyrogenic reactions had been detected during the 2-year study period. The CRP and nutritional parameters were in good normal ranges. The nPNA was significantly higher in post-dilution period (1.24 ± 0.21 vs. 1.13 ± 0.17 g/kg/d, $p < 0.01$). The adequacy of hemodialysis in term of small molecule showed significantly better Kt/V in post-dilution than pre-dilution mode (2.46 ± 0.35 vs. 2.35 ± 0.36, $p = 0.03$) whereas the predialysis β2-microglobulin levels were not different (23.95 ± 5.57 vs. 22.68 ± 5.24 mg/L, $p = 0.07$). The number of reuse in post-dilution did not differ from pre-dilution periods (17.32 ± 2.59 vs. 16.37 ± 2.72, NS).
Conclusion: Utilizing reuse dialyzer in ol HDF could provide safely, efficacy, cost saving, and environmental benefit. Furthermore, the limited backfiltration and protein coating layer during ol HDF could prevent the backfiltration of the germicide remnant from the fiber. The post-dilution technique showed the better adequacy and appetite without causing the limitation in the reuse number and would be the standard mode-of-choice for ol HDF.

PO02-053
THE EFFECT OF HEMODIALYSIS MODALITY ON INSULIN RESISTANCE

SI MOON[1], JK KIM[1], DH LEE[2], JH LEE[2], TH YOO[2], BS KIM[2], HC PARK[1], SW KANG[2], KH CHOI[2], HY LEE[2], SK HA[1]
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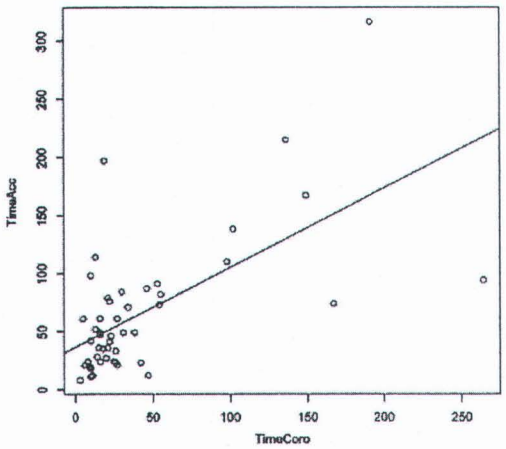
Introduction: Cardiovascular disease (CVD) is the leading cause of mortality in patients with end-stage renal disease (ESRD). Insulin resistance (IR) is associated with development of the CVD. We examined the factors containing hemodialysis modalities, associated with insulin resistance in hemodialysis patients.
Methods: In a cross-sectional study, 82 non-diabetic HD patients (47 men, mean age 59.2 ± 14.4 years) were enrolled and divided into two groups by median homeostasis model assessment index (HOMA-IR). Other clinical and bio-chemical data associated with IR were collected.
Results: Higher HOMA-IR group had higher BMI (23.0 ± 3.1 vs. 20.9 ± 2.3 kg/m^2, $p = 0.001$) and lower HDL cholesterol (42.4 ± 11.0 vs. 47.5 ± 10.4 mg/dL, $p = 0.038$) levels. In addition, lower HOMA-IR group had more β-2 microglobulin reduction rate (39.1 ± 25.1 vs. 16.0 ± 22.8%, $p = 0.001$) and more proportion of hemodiafiltration (HDF) modality ($p = 0.002$). HOMA-IR was significantly correlated with β-2 microglobulin reduction rate ($r = -0.318$, $p = 0.004$). On multivariate logistic regression analysis adjusted by age, sex, BMI, hemodialysis modality, HDL cholesterol, and medication of statins and beta blockers, BMI and HDF modality were significant factors associated with HOMA-IR.
Conclusion: Lower HOMA-IR was significantly associated with HDF modality. It suggests that HDF therapy, enhancing removal of middle-molecular-weight substances by convection may reduce insulin resistance in hemodialysis patients.

Results: A strong correlation was found betweeen vascular access life time and the time to coronary imaging performing linear regression analysis ($p< 1,268$ e-06).



Cox analysis found that the life time of vascular access in dialysis patients, in a model that considered also patient survival, could possibly depend on number of coronary affected ($p<0.08$) and PTH values detected during imaging ($p<0.048$)

Conclusions: Dialysis patients are at risk of coronary heart disease and a low life span of vascular access with a worsening of dialysis treatment and patient life quality. Calcifications from uncontrolled secondary hyperparathyroidism could be a linkage factor between theese vascular diseases, pointing to a needing of a better comprehension of mechanisms that may affect all vascular district. These data could evidence a systemic disease threatening our patient's life.

Su487 THE SURVIVAL RATE OF NATIVE ARTERIOVENOUS FISTULA (AVF) AS VASCULAR ACCESS AND RISK FACTORS ON THE SURVIVAL

Kenji Tsuchida, Jun Minakuchi, Kazuhiro Yoshikawa, Yuki Kitamura, Shu Kawashima. *Department of Urology, Nephrology, Kawashima Hospital, Tokushima City, Tokushima, Japan*

Introduction and Aims: The maintenance of vascular access in hemodialysis (HD) patients is causing serious problems not only in terms of the quality of life of patients but also in the medical economy. In this regard, we investigated the cumulative patency rate of native arteriovenous fistula (AVF) as vascular access.

Methods: The cumulative patency rate of AVF was compared among the patients who have AVF ("AVF group"; 616 limbs). More particularly, the patency rates of AVF were investigated by different factors including primary diseases, age at the time of surgical operation, gender, condition and site. Furthermore, the influences of factors including primary disease, gender, age at the time of operation (/1 year old), and dialysis period (/1 year) on the patency rate were investigated using Cox's proportional hazard model.

Results: The patency rates of AVF in 1, 2, 3, 5 and 10 year were 85.6, 78.9, 75, 67.5 and 52.2%, respectively. According to the investigation by factors, the rates were significantly higher in males as to the gender factor. The investigation of the influences of risk factors on the patency rate showed that the significant and independent risk factors in all cases were "female" and "short dialysis duration (/year)."

Conclusions: The AVF is considered as the vascular access with the highest patency rate in the chronic HD patients. However, the gender factor influences this rate. That is, "female" has a higher risk in comparison with "male."

Su488 ACCURACY OF USING ONLINE CLEARANCE MONITOR TO MEASURE VASCULAR ACCESS FLOW IN HIGH-EFFICIENCY ON-LINE HEMODIAFILTRATION

Khajohn Tiranathanagul, Paweena Susanthiwong, Piyaporn Towannang, Kearkiat Praditpornsilpa, Somchai Eiam-Ong. *Division of Nephrology, Department of Medicine, Faculty of Medicine, King Chulalongkorn Memorial Hospital and Chulalongkorn University, Bangkok, Thailand*

Introduction and Aims: The good vascular access flow is fundamental in attaining the high quality of hemodiafiltration (HDF). Measurement of the vascular access flow rate (Qa) is widely accepted as the best method for surveillance and predicting failure of the access. Among current practical methods, the ultrasound dilution technique (UDT) is standard, but this requires a costly device available in liminted hemodialysis (HD) centers. The two conductivity clearance values in normal and reversed positions of the blood lines were applied to determine the Qa and reported the accuracy in diffusive hemodialysis. However, this affordable technique has never been tested for high-efficiency HDF.

Methods: The present study was conducted to compare the values of Qa measured by Online Clearance Monitoring (OCM-Qa) in Fresenius 4008H hemodiafiltration machine with those determined by the standard UDT (UDT-Qa) in the high-efficiency pre-dilution on-line HDF (pre ol HDF).

Results: The values of Qa were determined in each of 17 patients who were treated with pre ol HDF by OCM technique and then, in the same session, by UDT using Transonic HD03 device. The values of standard UDT-Qa and OCM-Qa were 670.28±294.94 and 678.38±278.47 mL/min (NS). There was a significant correlation between the two techniques ($r = 0.96$, $p<0.01$). A Bland-Altman plot comparing the OCM-Qa and UDT-Qa was displayed in figure 1.

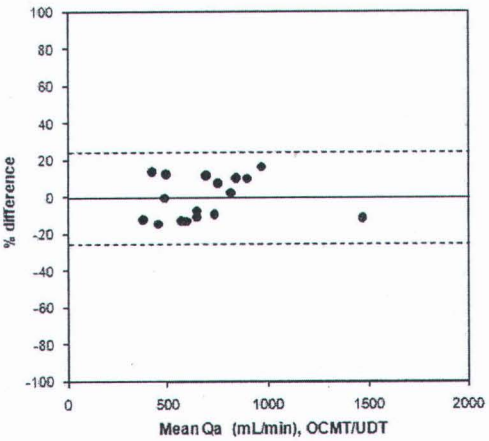


Figure 1. Bland-Altman OCMT/UDT. Qa = vascular access flow rate; OCMT = online clearance monitor technique; UDT = transonic HD03 ultrasound dilution technique.

Conclusions: The vascular access flow determined by OCM which is integrated mostly in current hemodiafiltration machine is highly accurate, easy to perform, and economical and can be used for vascular access surveillance in high-efficiency ol HDF.

Peritoneal dialysis 2

Su489 EFFECT OF ICODEXTRIN USE AT STARTING PD ON PERITONEAL PERMEABILITY

Maria José Fernández-Reyes[1], María Auxiliadora Bajo[2], Gloria del Peso[2], Teresa Olea[2], Rafael Sánchez-Villanueva[2], Elena Gonzalez[2], Manuel Heras[1], Rafael Selgas[2]. *[1]Nephrology, Hospital General, Segovia, Spain; [2]Nephrology, Hospital Universitario La Paz, Madrid, Spain*

Introduction and Aims: Peritoneal permeability differs between patients at starting peritoneal dialysis (PD) and it can increase along with time on the technique.

The aim of this study was to evaluate if the use of one exchange a day of

F-FC164

Abstract Withdrawn

F-FC165

Regional Citrate Versus Systemic Heparin for Anticoagulation in Critically Ill Patients on Continuous Venovenous Hemofiltration: A Prospective Randomized Multicenter Trial Gerd R. Hetzel,[1] Michael Schmitz,[1] Rainer Himmele,[3] Adelheid Gauly,[2] Bernd Grabensee,[1] Lars C. Rump.[1] *[1]Heinrich-Heine-University Duesseldorf; [2]Fresenius Medical Care Germany; [3]Fresenius Medical Care NA.*

Background:

Continuous veno-venous hemofiltration (CVVH) in the intensive care setting requires anticoagulation to prevent clotting of the extracorporeal circuit. Several protocols avoiding heparin and using regional citrate anticoagulation have been developed to diminish bleeding risks. However, data from randomized trials comparing citrate anticoagulation with systemic heparinzation are very limited.

Methods:

We randomly assigned 174 patients to either CVVH treatment with systemic heparinization or to CVVH treatment with a system that uses citrate as the only anticoagulant and buffering substance. All patients were on mechanical ventilation, therefore written informed consent was obtained from a patient's legal representative. The primary objective was to compare treatment efficacy represented by the patients' acid base status on day 3 and on each consecutive day. Several parameters of safety and efficacy were analyzed as secondary objectives.

Results:

Comparison of standard bicarbonate from day 3 until day 11 confirmed equal effectivity of both treatment modalities. Use of citrate resulted in less systemic anticoagulation, a lower risk of bleeding and a longer hemofilter patency. However, episodes of hypercalcemia, hypocalcemia as well as the need for additional bicarbonate infusions occurred more often under citrate. The patients' high mortality was not influenced by the mode of anticoagulation.

Conclusion:

Citrate may be used as a regional anticoagulant and as the only buffering agent in CVVH with adequate treatment efficacy and safety. However, neither citrate nor heparin anticoagulation should be regarded as a therapeutic standard, since there is no advantage of one of these substances with regard to the patients mortality.

Disclosure of Financial Relationships: nothing to disclose

F-FC166

Regional Citrate Anticoagulation Reduces Polymorphonuclear Cell Degranulation in Critically Ill Patients Treated with Continuous Veno-Venous Hemofiltration (CVVH): A Randomized Controlled Trial Khajohn Tiranathanagul,[1] Onanong Jearnsujitwimol,[1,2] Paweena Susantitaphong,[1] Narin Kijkriengkraikul,[3] Kearkiat Praditpornsilpa,[1] Somchai Eiam-Ong.[1] *[1]Division of Nephrology, Department of Medicine, Chulalongkorn Memorial Hospital, Thai Red Cross Society and Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [2]Phrapokklao Hospital, Chanthaburi, Thailand; [3]National Blood Center, Thai Red Cross Society, Bangkok, Thailand.*

Background: The high mortality in critical acute kidney injury (AKI) patients treated with CVVH is associated with increased oxidative stress and systemic inflammation which are induced by the blood-membrane reaction. This is the first study conducted to examine the effect of regional citrate anticoagulant (RCA) on PMN cells degranulation of myeloperoxidase (MPO) and inflammatory cytokine levels in patients with critical AKI undergoing CVVH treatment.

Methods: This prospective study was carried out in 20 critical AKI patients who were treated with pre-dilution CVVH and randomized into RCA group (n=10) and heparin group (n=10). The pre-filter and post-filter MPO and inflammatory cytokine (IL-6, IL-8, and TNF-α) levels were measured at baseline, 6 hr and 24 hr after initiating CVVH.

Results: The baseline characteristics were similar between the two groups. In the heparin group, the pre-filter serum MPO levels were significantly increased at 6 hr (40.5 ± 21.3 vs. 66.0 ± 63.5 ng/mL, p <0.01) and the post-filter serum MPO levels were also significantly higher than the pre-filter (p<0.05). Interestingly, citrate could significantly decrease pre-filter serum MPO (56.7 ± 51.0 vs. 27.7 ± 36.6 ng/mL, p<0.01) as well as TNF-α and IL-8 levels (p<0.05) at 6 hr. There were no significant differences between pre- and post-dialyzer MPO levels in the citrate group. The mean CVVH circuit survival in the citrate group was longer than the heparin group (p=0.03).

Conclusions: Treatment with CVVH caused PMN degranulation and increased oxidative stress which might be mediated by the blood-dialyzer membrane reaction. RCA could diminish the oxidative stress, prolonged the circuit survival time, and minimized bioincompatibility during on CVVH.

Disclosure of Financial Relationships: nothing to disclose

F-FC167

Change in CRRT Dose Prescription after Recent Trials Flavio Basso,[1] Zaccaria Ricci,[2] Claudio Ronco,[1] Dinna N. Cruz.[1] *[1]S Bortolo Hosp, Vicenza, Italy; [2]Bambino Gesù Hospital, Rome, Italy.*

Recent studies on RRT dose (RENAL, ATN, DoReMi) showed no difference in outcomes with higher CRRT dose. They also underlined that a delivered dose of at least 20 ml/kg/h was important, but to achieve this, a higher prescribed dose is usually needed. The impact of these studies on clinical practice is yet unknown.

Methods

We compared the results of practitioner surveys distributed during the International Course on Critical Care Nephrology held in Vicenza, Italy in 2004, 2007 and 2010 to evaluate trends in CRRT practice patterns. We limited this analysis to physician responses only.

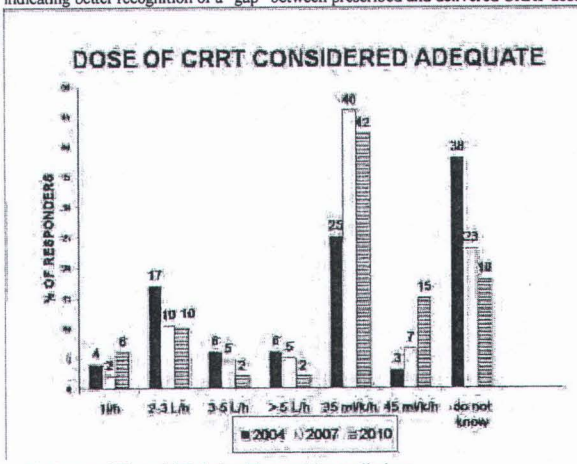
Results

In 2010, the overall response rate was 64%. Of 377 completed questionnaires, 338 were from physicians. Most were nephrologists (60%) followed by intensivists (36%); majority were from Europe (80%).

The use of individualized dose prescription based on body weight increased from 28% to 61.5% in 2010, while indiscriminate "by the liter dose" prescription decreased from 33% to 20%. The CRRT dose most commonly considered appropriate was 21-35ml/kg/h (42%), similar to 2007 (see Figure). The proportion of respondents who are "not sure" about adequate dose was fallen from 38% (2004) to 18% (2010). Fifty four percent of responders said they did not change their practice after publication of RENAL and ATN. Of the remainder, 28% increased their prescribed CRRT dose, while 22.5% decreased it.

Conclusion

Awareness regarding RRT dose has progressively improved over the past 6 years; in 2010, <20% expressed uncertainty about an "appropriate" CRRT dose. Less than half of surveyed physicians changed their practice after publication of recent landmark studies on CRRT dose. Interestingly, 28% actually increased their prescribed CRRT dose, perhaps indicating better recognition of a "gap" between prescribed and delivered CRRT dose.



Disclosure of Financial Relationships: nothing to disclose

F-FC168

An Updated Systematic Review of Extracorporeal Blood Purification in Prevention of Radiocontrast-Induced Nephropathy Ching Yan Goh,[1,2] Valentina Corradi,[1] Claudio Ronco,[1] Dinna N. Cruz.[1] *[1]Nephrology Dialysis & Transplantation, S Bortolo Hosp., Vicenza, Italy; [2]Nephrology, Selayang Hosp., Selangor, Malaysia.*

Background: Radiocontrast induced nephropathy (RCIN) is an important cause of acute kidney injury, increasing in-hospital and long term mortality. It is controversial whether extracorporeal blood purification (EBP) reduces patient's risk of RCIN. A systematic review in 2006 showed that periprocedural EBP did not decrease the incidence of RCIN compared with standard medical therapy (SMT). We conducted an update of this review.

Methods: We searched through Pubmed and bibliographies of retrieved articles. Published studies of EBP for RCIN prevention in patients receiving radiocontrast were included. The primary endpoint was the incidence of RCIN, defined as an increase in serum creatinine ≥0.5mg/dL. Results were combined on the risk ratio (RR) scale. Random-effects models were used. Sensitivity analyses were defined *a priori* to evaluate the effects of EBP modality, study design, and sample size.

Results: Nine randomized controlled trials and 2 nonrandomized trials were included (n=1100 patients). Eight trials assessed IHD, 3 trials assessed CRRT. Nine studies had data for primary endpoint; RCIN incidence was 23.3% in the EBP group and 21.2% in the SMT group. EBP did not decrease the incidence of RCIN compared with SMT (RR1.02; 95%CI 0.54,1.93, see Figure); however, intertrial heterogeneity was high. In sensitivity analyses, limiting to only IHD studies significantly reduced heterogeneity. IHD appeared to increase RCIN risk (RR1.61; 95%CI 1.13,2.28) and had no effect on need for permanent RRT or progression to ESRD (RR1.47; 95%CI 0.56,3.89).

ภาคผนวก ข

Hemodialysis International ISHD

Long-term Efficacy of Dialyzer Reuse in Online Hemodiafiltration

Journal:	*Hemodialysis International*
Manuscript ID:	Draft
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Long-term Efficacy of Dialyzer Reuse in Online Hemodiafiltration

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Short title: Dialyzer reuse in online hemodiafiltration

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INTRODUCTION

Enhancing large molecular weight uremic toxin clearance by convection using online hemodiafiltration (HDF) technique in patients with end-stage renal disease (ESRD) has provided superiority in many aspects[1] including better survival[2-4] when compared with conventional hemodialysis (HD).

However, this online HDF is still not worldwidely used and is predominant in Europe where the procedure is mostly operated with single-use high-flux dialyzer. The clinical experience of online HDF is still limited in several developing countries where the high cost of the single use dialyzer is an important issue and the reuse dialyzer program has been routinely practiced for the conventional HD. The benefits of the reuse program include not only the cost saving but also reducing the dialyzer waste that could provide the benefit for the environment[5].

Two standard methods of fluid replacement in online HDF comprise pre-dilution and post-dilution modes. Post-dilution online HDF is the more efficient mode in molecular clearance of uremic toxins but such efficiency is limited by hemoconcentration and high blood viscosity as plasma water is continually ultrafiltered along the length of the hollow dialyzer fibers. This might reduce the number of reusing the dialyzer. Such limitation and consequence do not occur in pre-dilution online HDF, in which the infusion rate of substitution fluid can be unlimitedly increased to augment clearance efficiency. However, this would cause dilution of the blood side solute concentration, leading to reduced clearances when compared with the post-dilution mode.

Most of the previous studies regarding long-term effect of online HDF utilized single-use dialyzer[6-8]. Only few reports operated with the reuse dialyzer[9, 10]; however, no comparative data with the single-use was determined in the same study. Furthermore, earlier studies comparing pre- and post-dilution online HDF were cross-sectionally designed and,

the post-dilution mode (the total dialysis fluid flow rate was 800 mL/min). The dialysis fluid purity utilized in the present study was met by the European Pharmacopoeia criteria for ultrapure water and dialysate indicated by total viable microbial counts of less than 0.1 CFU/mL and endotoxin concentrations of less than 0.03 EU/mL. The water and dialysate samples were monthly tested for biological contamination.

Blood samples for laboratory measurement were collected at the tenth time of reuse. All clinical and laboratory data assessed in the present study were protocolized and obtained from the standard regular clinical service of the dialysis unit. The mean data of 1-year reuse pre-dilution online HDF, and 1-year reuse post-dilution online HDF were compared.

Statistical analysis

All data were expressed as mean ±SD. Comparisons between reuse pre-dilution online HDF and baseline single-use as well as between reuse pre- and post-diltution online HDF modes were performed by Student's paired t-test or the Mann-Whitney's non-parametric test for non-normal distribution data. All statistical tests were performed by using the SPSS statistical package (version 11.5 for Windows, SPSS Inc, Chicago, IL). Statistical significance was defined when $p<0.05$.

RESULTS

Of the 20 chronic hemodialysis patients who were treated with single-use predilutional online HDF and included in the study, there were 7 male and 13 female subjects. The average age was 61.2 ± 13.2 years. The patient underwent pre-dilutional online HDF for 2.16 ± 1.41 years (AV fistula = 75.0%, AV graft = 25.0%). The causes of ESRD in these patients were diabetes mellitus (20.0%), chronic glomerulonephritis (20.0%), lupus

Regarding nutritional parameters, nPNA was significantly increased after switching from the pre-dilution to post-dilution online HDF ($p<0.01$) whereas the serum albumin levels were not significantly changed (Figure 2). The BMI values were not different. Other parameters including hemoglobin, calcium, phosphorus, and iPTH were comparable.

No pyrogenic reaction has been detected during all the study periods. The values of CRP in both groups were in good normal ranges (NS).

DISCUSSION

The present study was conducted to examine the efficacy and safety of the reuse dialyzer for online HDF. Regarding efficacy, the present study demonstrated the comparable various biochemical parameters between the reuse and baseline single-use pre-dilution online HDF with the same hemodiafiltration prescription. When compared with the reuse pre-dilution mode, the reuse post-dilution technique showed the better small molecule adequacy (Figure 1). This was the crucial aspect of the post-dilution technique that the blood was not diluted before entering the dialyzer, leading to the maximal concentration difference between blood and dialysate. This greater concentration gradient in post-dilution online HDF when compared with pre-dilution online HDF results in the greater diffusive clearance which is the important mechanism of small molecule clearance in HDF. When compared with previous long-term single-use online HDF studies, all of which were operated via post-dilution mode (Table 2), the online HDF with the reuse dialyzer in this study provided better spKt/V values. This might be caused by both high BFR and high dialysate fluid flow rate (Table 1,2) as well as relatively lower dry weight (correlated with volume of the distribution of urea of the patients) than other studies.

Although the clearance of β_2M was not determined in the present study, the pre-dialysis β_2M levels could reflex the long-term efficacy of middle molecule removal and

appetite [19]. One of the markers of nutritional status is predialysis serum albumin, the low levels of which have been associated with both malnutrition and poor survival[20]. Although the online HDF technique increases albumin loss when compared with the conventional HD, the serum albumin was still maintained during both pre and post-dilution online HDF over the two-year study period (Figure 2). Of note, the anthropometric parameters such as dry weight and BMI were not different.

The safety issue is usually a big concern about the reuse dialyzer policy. The strict adherence to the standard reprocessing protocols could prevent all the possible risks as obviously demonstrated in this study which showed no pyrogenic reaction and normal CRP levels throughout the study.

Regarding dialyzer waste, each single-use hemodialysis session is estimated to produce 2.5 kg of solid clinical waste[21]. Thus, the amount of the waste generated by each patient on thrice-a-week hemodialysis utilizing single-use dialyzer is estimated at 390 kg per year, the significant portion of which is contributed by the dialyzer [21]. The yearly dialyzer-related polymer waste would be approximately ten times with the single-use policy when compared with the re-use strategy[5].

As such, online HDF should be promoted for worldwide use not only in the single-use unit but also in the reuse center. Regardless to the dialyzer cost issue, the online HDF platform does not cost much higher than high-flux hemodialysis. The post-dilution online HDF technique showed the better adequacy and appetite without causing the limitation in the reuse number. When compared with the pre-dilution technique, the post-dilution online HDF would be considered as the standard mode-of-choice for online HDF. However, the new techniques including mid- and mixed-dilution online HDF which combine the advantages of pre- and post-dilution modes might be the optimal therapeutic modalities in the future.

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TABLES

Table 1 Comparison of dialytic and biochemical parameters between reuse pre-dilution and reuse post-dilution online HDF

Parameter	Reuse pre-dilution online HDF study period	Reuse post-dilution online HDF study period
Blood flow rate (mL/min)	411.3 ± 48.9	397.1 ± 10.9^{NS}
Dialysis fluid flow rate (mL/min)	800	800
Reinfusion flow rate (mL/min)	172.8 ± 14.0	98.1 ± 4.3*
Reinfusion fluid (L/session)	41.5 ± 3.4	23.6 ± 1.0*
Number of reuse	16.4 ± 2.7	17.3 ± 2.6^{NS}
Dry weight (kg)	53.89 ± 11.33	53.49 ± 10.42^{NS}
BMI (kg/m^2)	20.97 ± 3.24	20.79 ± 2.61^{NS}
Pre-dialysis β_2M (mg/L)	23.73 ± 5.55	23.43 ± 5.35^{NS}
Hemoglobin (g/dL)	11.61 ± 0.80	11.55 ± 0.74^{NS}
Calcium (mg/dL)	9.21 ± 0.83	9.45 ± 0.73^{NS}
Phosphorus (mg/dL)	4.43 ± 0.88	4.50 ± 0.78^{NS}
iPTH (pg/mL)	395.10 ± 272.82	376.99 ± 347.15^{NS}
CRP (mg/L)	5.02 ± 4.98	4.78 ± 3.14^{NS}

NS = non significant

* = $p<0.01$ when compared with reuse pre-dilution online HDF

Hemoglobin (g/dL)	11.36 ± 1.5	10.3 ± 0.2	12.3 ± 0.977	NA	NA
Calcium (mg/dL)	10.5 ± 1.0	9.2 ± 0.08	9.65 ± 0.507	9.96 ± 0.12	NA
Phosphorus (mg/dL)	5.0 ± 1.2	4.8 ± 0.2	5.27 ± 1.22	1.73 ± 0.09	NA
iPTH (pg/mL)	200 ± 216	NA	448 ± 326.2	NA	NA

Abbreviation: NA = not available

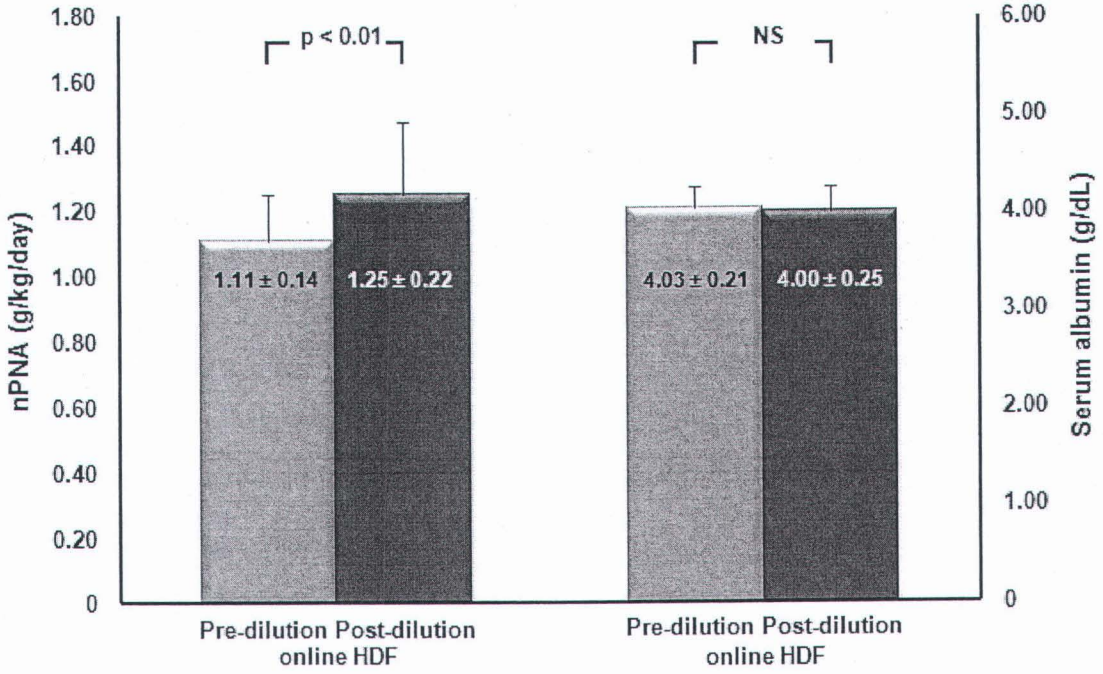

Figure 2 Tiranathanagul et al.

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This is the overview page

Measurement of Vascular Access Flow by Online Clearance Monitor in Online Hemodiafiltration

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Key Words:	hemodialysis vascular access flow, online clearance monitor, ultrasound dilution technique

Measurement of Vascular Access Flow by Online Clearance Monitor in Online Hemodiafiltration

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INTRODUCTION

The good vascular access flow is fundamentally important in attaining the high quality of hemodialysis (HD) and hemodiafiltration (HDF) [1]. The unexpected vascular access dysfunction increases morbidity and mortality. The European Best Practice guidelines[2] and NKF-K/DOQI[3] have recommended regular measurement of the vascular access flow rate (Qa) as the best method for surveillance and predicting failure of the access. Direct Qa measurements by either duplex doppler ultrasound (DDU) or magnetic resonance angiography are impractical and expensive to perform in the surveillance program. Thus, current recommendations favor the use of indirect Qa measurement techniques, the most extensively validated and most precisely standardized method of which is the ultrasound dilution technique (UDT)[4-6] (Figure 1A). However, the UDT requires a specific instrument and, thus, is available in limited hemodialysis centers.

Recently, ionic dialysance has been introduced as a new dialysate side method of dialyzer clearance determination[7]. In standard diffusive HD mode, this ionic dialysance method which is based on conductivity variation could provide an accurate urea dialyzer clearance when compared with blood-side urea clearance[8, 9]. Besides, recent studies have demonstrated that measurements of ionic dialysance in normal and reversed positions of the blood lines could be used to determine the Qa [10-12]. The difference between both values of ionic dialysance depends on the recirculation rate caused by reversal of the blood lines. This recirculation rate is inversely proportional to the Qa.

In online HDF (OL-HDF), a new model for the measurement of ionic dialysance was recently reported for Online Clearance Monitor (OCM) in Fresenius HDF machine and could determine accurate urea dialyzer clearance when compared with blood-side urea clearance[13]. There are no available studies utilizing this ionic dialysance measurement for Qa determination in OL-HDF.

bubble trap before ultrasound dilution sensor, mixed with the blood flow in the extracorporeal circuit (Qb), then passed to the arterial access, and was detected by arterial sensor[6].

Online Clearance Monitor (OCM) technique

To determine the Q_a by the OCMT, the OCM mode must be enabled. In a recent study and according to the manufacturer information, this OCM mode could measure ionic dialysance in pre-dilution OL-HDF with approximately 6% S.D. of difference when compared with blood-side urea clearance[13]. The BFR was set up at 300 mL/min and ultrafiltration was set up with constant rate. First, online clearance value (K) was determined in normal position of blood line (Figure 2A). This value would come out around 20 minutes after the OCM mode started measuring and was defined as K_{norm} for further Qa calculation. After that, the blood pump was stopped and the tubing was reversed by arterial tubing connected to venous needle whereas venous tubing was connected to arterial needle. The blood pump was restarted at 300 mL/min and K_{rev} was measured taking for another 22 minutes (Figure2B). At the end of the test procedure which took approximately 50 minutes, the blood pump was stopped and the tubing was aligned back into the regular non-reversed position. Then, the blood pump flow rate, ultrafiltration, and the left over HDF time were then reprogrammed.

The Qa_{OCMT} was calculated according to the following equation[11]:

$$Qa_{OCMT} = \frac{[(K_{norm} - Q_{UF}) \times K_{rev}]}{K_{norm} - K_{rev}}$$

Where, Qa_{OCMT} = vascular access blood flow (mL/min)

K_{norm} = the effective ionic dialysance with normal tubing postion

K_{rev} = the effective ionic dialysance with reversed tubing postion

Q_{UF} = ultrafiltration rate

glomerulonephritis (n=5), hypertensive nephropathy (n=4), obstructive uropathy (n=2), chronic tubulointerstitial nephropathy (n=1), and unknown (n=12).

The mean arterial blood pressure values before measuring Qa were comparable between the OCMT and UDT groups (98.5 ± 15.2 vs. 94.9 ± 9.8 mmHg, NS).

Vascular access flow rate

The values of the standard Qa_{UDT} were derived from the average of the duplicated measurement which demonstrated a good repeatability (coefficient of variation, CV=4.73%). The values of the standard Qa_{UDT} were 800.5 ± 910.3 mL/min and were utilized as the reference values. The values of the first measurement of Qa_{OCMT} were 794.6 ± 895.4 mL/min. In all 32 patients, there were no significant differences in the mean values of the standard Qa_{UDT} and Qa_{OCMT} (p=0.75) with the mean absolute difference of -5.84 ± 103.79 mL/min. Importantly, the values of the first Qa_{OCMT} were highly significantly correlated with the Qa_{UDT} ($r = 0.95$, $p < 0.01$). By regression analysis, the regression equation was Qa_{UDT} = [1.03 x Qa_{OCMT}] -17.64 (Figure 3). Of note, the AVG group provided higher correlation than the AVF group (r=0.99 and 0.89, respectively and $p < 0.01$ for both).A Bland-Altman plot comparing the Qa_{OCMT} and Qa_{UDT} that displayed in figure 4 showed a good agreement.

However, the second measurement of Qa_{OCMT} showed the CV of 31.6% which did not offer the good repeatability. The second and mean Qa_{OCMT} measurement did not provide as good correlation with the Qa_{UDT} as the first measurement (r= 0.88 and 0.93, respectively).

DISCUSSION

Growing evidence has shown that OL-HDF, which combines convection and diffusion in a single therapy, is superior to high-flux HD, which mainly provides diffusion therapy, in various respects including enhanced middle-molecule clearance, better

caused intravascular volume reduction and this might affect the access flow value. Therefore, only single measurement at the beginning of HDF session was recommended for Qa_{OCMT} determination.

The advantages of the Qa_{OCMT} over other indicator dilution techniques are no need for an injected indicator, no need for a precise measurement of blood flow rate, and no need for an extra supply that would refer to no additional expense for each measurement. Few minor inconveniences still exist such as the requirement for the reversal of the blood lines which also remains the main disadvantage of all other indicator dilution techniques including the standard UDT. Other inconveniences are time consuming and slight reduction of session clearance from low blood flow rate and reversed blood line-induced recirculation during the study period.

In the present study, all pitfalls of indicator dilution method were considerably prevented. Ultrafiltration was kept off during the measurement by the standard UDT to ensure that the blood flow is identical in the circuit. In the case that the ultrafiltration could not be kept off during OCMT to avoid the risk of compensated enhancing ultrafiltration rate after OCMT measurement, it was kept constant and the value of ultrafiltration rate was considered into the formula calculation. Insertion of the venous or return needle in the direction opposite to access flow, placing the two needles at least 3 cm apart, and setting BFR at 300 mL/min also facilitated mixing. Since Qa is influenced by the blood pressure which usually falls during hemodialysis, this error was minimized by performing OCMT and standard UDT as early as possible, during the first 60 minutes of dialysis session.

In standard diffusive HD, there are several other practical methods to determine the Qa. Some of these techniques utilize other online sensors that are integrated in the HD machine and, thus, do not require additional indicator injection. These include ultrafiltration method[15], thermodilution[16], and temperature gradient method (TGM)[17] conductivity dilution

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FIGURE LEGENDS

Figure 1 Pre-dilutional Online Hemodiafiltration circuit during vascular access flow rate measurement by the Transonic HD03 machine. The HD circuit was reversed and arterial/venous line sensors were placed as picture.

Figure 2 Step by step during vascular access flow rate measurement by the online clearance monitor technique (OCMT). The OCM mode was turned on. Then, the BFR was set up at 300 mL/min and ultrafiltration rate was set up at zero. **(A)** First, online clearance value (K) was determined in normal position of blood line (K_{norm}). **(B)** Connection between needles A and V, and blood lines A and V was set in a reversed position. Then, the blood pump was restarted at 300 mL/min (BFR). The K_{rev} was measured after all.

Qa = vascular access flow rate

BFR = blood pump setting flow rate (mL/min)

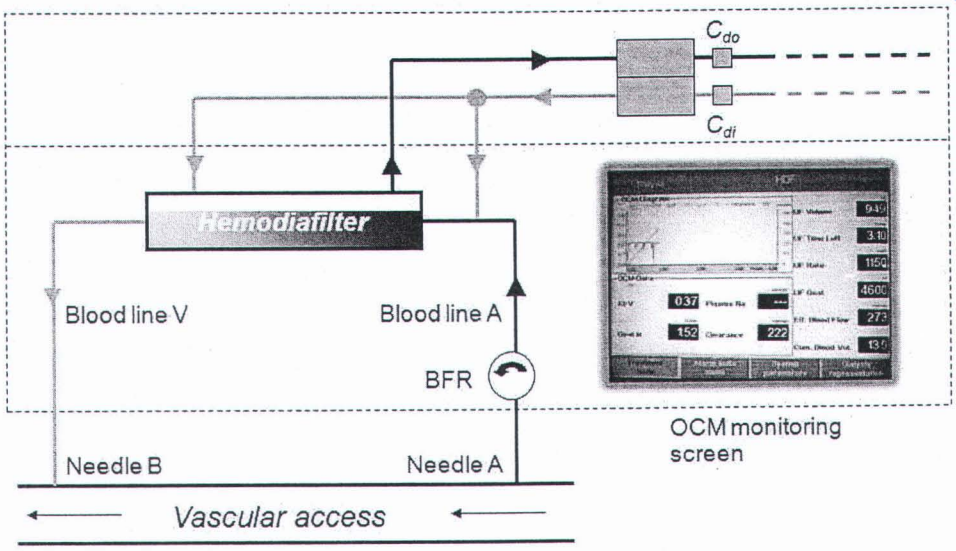
C_{di} = dialysate inlet conductivity

C_{do} = dialysate outlet conductivity

OCM = online clearance monitor

Figure 3 Correlation between the transonic HD03 ultrasound dilution technique (UDT) and the online clearance monitor technique (OCMT).

Figure 4 Bland-Altman OCMT/UDT. Qa = vascular access flow rate; OCMT = online clearance monitor technique; UDT = transonic HD03 ultrasound dilution technique.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OCM monitoring screen

A

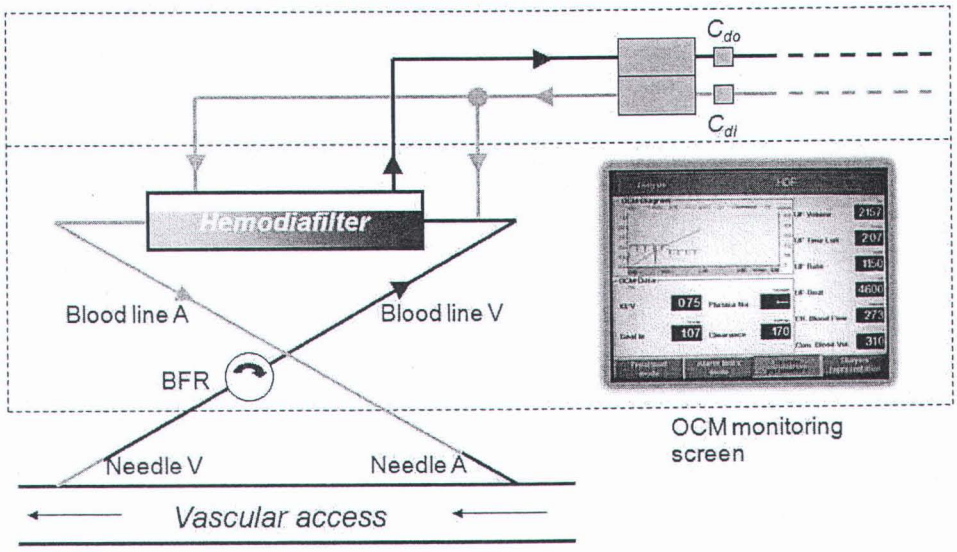
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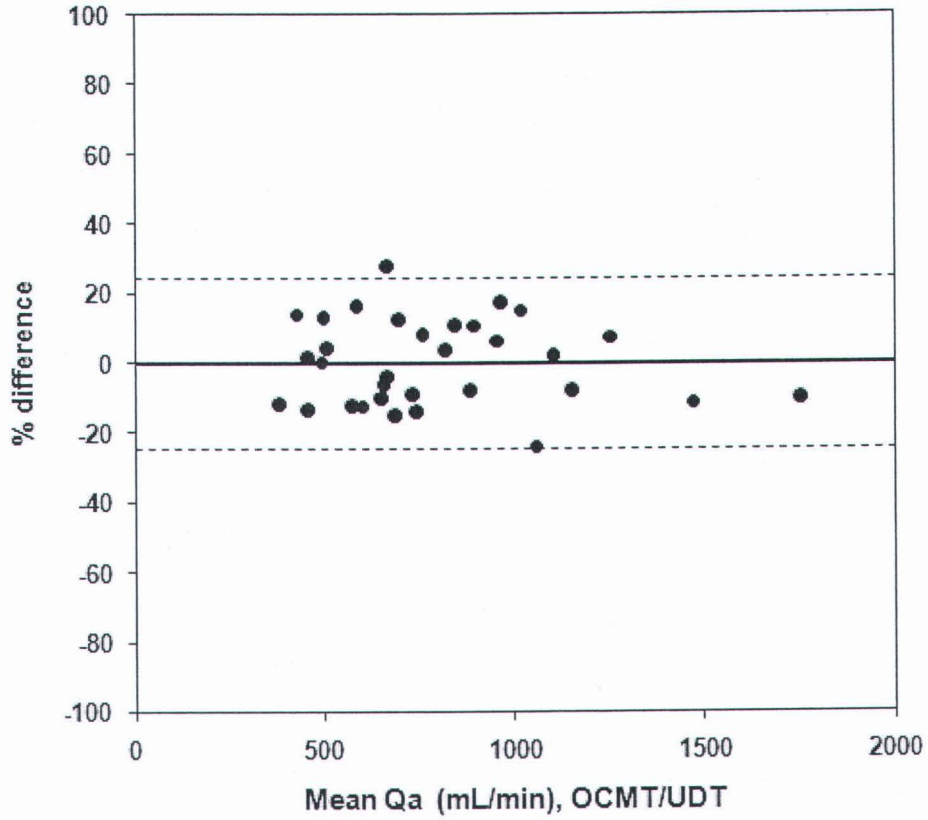
Figure 2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Mean Qa (mL/min), OCMT/UDT

Figure 4

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Manuscript Draft

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Title: Regional Citrate Anticoagulation Reduces Polymorphonuclear Cell Degranulation and Inflammatory Cytokines in Critically Ill Patients Treated with Continuous Veno-venous Hemofiltration (CVVH): A Randomized Controlled Trial

Article Type: Clinical Investigation

Keywords: CVVH; regional citrate anticoagulation; myeloperoxidase; cytokines

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Abstract: Objective: Citrate which chelates ionized calcium can be used as regional anticoagulation in continuous venovenous hemofiltration (CVVH). This is the first study conducted to examine the potentially additive benefit effect of regional citrate anticoagulation (RCA) on polymorphonuclear (PMN) cell degranulation and cytokines production in patients with critically acute kidney injury (AKI) undergoing CVVH treatment.

Design: Prospective single-center randomized controlled trial.

Setting: Intensive care units of a university hospital

Patients: Adult patients with critically AKI undergoing CVVH treatment.

Interventions: The patients were randomized into regional citrate group (n=10) and heparin group (n=10).

Measurements and Main Results: The levels of pre-filter and post-filter MPO as well as inflammatory and anti-inflammatory cytokines were measured at baseline, 6, and 24 hour after initiating CVVH. In the heparin group, the pre-filter serum MPO levels were significantly increased at 6 hr (40.5 ± 21.3 to 66.0 ± 63.5, $p < 0.01$) and the post-filter serum MPO levels were also significantly higher than the pre-filter (76.7 ± 69.8 vs 66.0 ± 63.5 ng/mL, $p<0.05$). There were no significant differences between pre- and post-dialyzer MPO levels in the citrate group. At 6 hr, citrate could significantly decrease pre-filter serum MPO levels (56.7 ± 51.0 vs. 27.7 ± 34.6 ng/mL, $p<0.01$) as well as TNF-α and IL-8 levels ($p<0.05$) whereas heparin provided only significant TNF-α reduction ($p<0.05$). The mean CVVH circuit survival in the citrate group was longer than the heparin group.

Regional Citrate Anticoagulation Reduces Polymorphonuclear Cell Degranulation and Inflammatory Cytokines in Critically Ill Patients Treated with Continuous Veno-venous Hemofiltration (CVVH): A Randomized Controlled Trial

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Short title: Regional citrate anticoagulation, oxidative stress, and inflammation in CVVH

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ABSTRACT

Objective: Citrate which chelates ionized calcium can be used as regional anticoagulation in continuous venovenous hemofiltration (CVVH). This is the first study conducted to examine the potentially additive benefit effect of regional citrate anticoagulation (RCA) on polymorphonuclear (PMN) cell degranulation and cytokines production in patients with critically acute kidney injury (AKI) undergoing CVVH treatment.

Design: Prospective single-center randomized controlled trial.

Setting: Intensive care units of a university hospital

Patients: Adult patients with critically AKI undergoing CVVH treatment.

Interventions: The patients were randomized into regional citrate group (n=10) and heparin group (n=10).

Measurements and Main Results: The levels of pre-filter and post-filter MPO as well as inflammatory and anti-inflammatory cytokines were measured at baseline, 6, and 24 hour after initiating CVVH. In the heparin group, the pre-filter serum MPO levels were significantly increased at 6 hr (40.5 ± 21.3 to 66.0 ± 63.5, $p < 0.01$) and the post-filter serum MPO levels were also significantly higher than the pre-filter (76.7 ± 69.8 vs 66.0 ± 63.5 ng/mL, $p<0.05$). There were no significant differences between pre- and post-dialyzer MPO levels in the citrate group. At 6 hr, citrate could significantly decrease pre-filter serum MPO levels (56.7 ± 51.0 vs. 27.7 ± 34.6 ng/mL, $p<0.01$) as well as TNF-α and IL-8 levels ($p<0.05$) whereas heparin provided only significant TNF-α reduction ($p<0.05$). The mean CVVH circuit survival in the citrate group was longer than the heparin group.

Conclusions: Citrate, utilized as regional anticoagulant in CVVH, can reduce both membrane bioincompatibility-induced as well as systemic oxidative stress and inflammation, and can prolong CVVH circuit survival time.

Keywords: CVVH, regional citrate anticoagulation, MPO, cytokines

INTRODUCTION

Continuous venovenous hemofiltration (CVVH) is currently a standard continuous renal replacement therapy (CRRT) for critically ill patients with acute kidney injury (AKI)[1]. However, some undesirable effects of CRRT, including the risks of systemic anticoagulant-induced bleeding and membrane bioincompaibility, might affect the patient outcome. To prevent the clotting of the extracorporeal circuit of CRRT, heparin is the most commonly used anticoagulant but can cause bleeding in up to 30% of the treatment[2]. Growing evidence has shown that regional citrate anticoagulation (RCA) which chelates calcium, an essential element of the coagulation cascade, could reduce the incidence of bleeding and could lengthen the patency of the CRRT circuit[3].

Two components of membrane bioincompatibility are activated during RRT and these comprise 1) the cellular elements containing polymorphonuclear (PMN) cells, monocytes, lymphocytes, and platelets[4] and 2) the humoral elements, such as coagulation and complement cascades. Regarding PMN cells, various granule products including myeloperoxidase (MPO) are released into the circulation shortly after the start of intermittent hemodialysis, resulting in enhanced oxidative stress and endothelial dysfunction that could potentiate acute systemic proinflammatory process in AKI[4, 5]. The activation of monocyte/macrophage from membrane bioincompatibility also enhances various cytokine releases such as TNF-α and IL-8. With the longer duration of treatment, the magnitude of the humoral and cellular components of membrane bioincompatibility developing in CRRT would be greater than intermittent hemodialysis.

Of interest, PMN cell degranulation process requires an inflowing of ionized calcium as a key mediator[6-8]. Thus, RCA could abolish PMN degranulation[6-9] and lower the monocyte IL-1β release[10] during the 4-hour hemodialysis in stable end stage renal disease (ESRD) patients. The role of citrate in attenuating oxidative stress and alteration of inflammatory

were used (Figure 1). Blood flow rate was120 mL/min and pre-dilution replacement fluid rate was 1,300 mL/hr. Net ultrafiltration loss rates were 0–100 mL/hr according to individual needs and were kept constant throughout the study period as long as hemodynamics were stable. The patent CVVH circuit was routinely changed at 72 hrs.

Heparin group

The circuit was primed with 1 L of normal saline containing 5,000 IU of heparin followed by a second prime with normal saline 1 L. After priming, heparin was given as a bolus of 1,000 IU and a continuous infusion of 500 IU/hr to keep aPTT value of 1.5X (Figure 1A). Pre-filter replacement fluid regimen included 0.45 % NaCl 900 mL+ 3% NaCl 55 mL + 7.5 % $NaHCO_3$ 45 mL (Na^+ 137 mEq/L, HCO_3^- 40 mEq/L). Initial calcium replacement was 10% Ca gluconate 200 mL/d (46.5 mmol/d) and, then, was adjusted to keep the prefilter iCa^{2+} in the range of 0.9-1.2 mmol/L.

RCA group

The pre-dilution isotonic citrate-base replacement technique which required only one extra calcium infusion pump was used for CVVH in this study (Figure 1B). The circuit was primed with 2 L of normal saline. After priming, citrate was used in the replacement fluid as anticoagulant. Pre-filter replacement fluid regimen comprised 4 % trisodium citrate 100 mL + 3% NaCl 60 mL + 0.45% NaCl 840 mL (Na 136.3 mEq/L, citrate 13.6 mmol/L which equivalent to HCO_3^- 40.8 mEq/L after in-body conversion). The citrate that entered the systemic circulation would be later converted to bicarbonate mainly by the liver. Initial calcium replacement was 10% Ca gluconate 240 mL/d (55.8 mmol/d) then was adjusted to keep prefilter iCa^{2+} ranging 0.9-1.2 mmol/L.

Sample collection

Blood samples were taken from pre-filter and post-filter sampling ports at start, 6 hr, and 24 hr. The pre-filter point was the afferent line proximal to the heparin or citrate infusion

RESULTS

1. Patient demographic data

The average age of the patients was 66±19 (18-87) years. The etiologies of AKI were sepsis (n=11), acute myocardial infarction (n=3), post coronary artery bypass graft (n=4), post aneurysmectomy (n=1), and congestive heart failure (n=1).The average APACHE II score was 22.0±.3.7. Fourteen patients were on inotropic drugs while 13 patients were on ventilator. These basic patient characteristics in both groups were presented in Table 1. The mean age of patients, the etiology of AKI, severity of illness including APACHE II and percentages of inotropic drug were not different between the two groups. The percentages of ventilator usage were 50% and 80% in heparin and citrate groups, respectively. The serum BUN, creatinine, total calcium, ionized calcium, and electrolyte in the two groups were comparable. The baseline serum C-reactive protein (CRP) and MPO levels between both groups were also not significantly different (Table 1). However, some of the baseline cytokine levels including TNF-α and IL-8 were significantly higher in the citrate group (Table 1).

2. Systemic and membrane biocompatibility-induced oxidative stress

Regarding systemic oxidative stress, the prefilter MPO levels in the heparin group at 6 hr. were significantly increased from baseline ($p<0.01$) and returned to baseline levels at 24 hrs (Table 2). In contradistinction, the prefilter MPO levels at 6 hr in the citrate group were significantly lower than baseline values ($p<0.01$) and were persistently low at 24 hr. As seen in figure 2, the values of MPO change from baseline at 6 hr in the citrate group were significantly different from the heparin group ($p<0.05$).

Regarding membrane bioincompatibility-induced oxidative stress, the post-filter MPO levels in the heparin group were significantly greater than the pre-filter levels at 6 hr ($p<0.05$)

DISCUSSION

Acute kidney injury (AKI) requiring RRT is a strong independent mortality risk factor in critically ill patients [12]. Oxidative stress and inflammation from loss of immune system homeostasis play an important role in the pathophysiology including initiation and extension phases of AKI. Moreover, growing evidences demonstrate the roles of oxidative stress and inflammation in causing adverse distant-organ injury after AKI[13]. The heightened oxidative stress and inflammation may be caused by the AKI process, the CVVH treatment, and the medications used in the patients such as heparin. Regarding AKI process, the very early inflammatory response is innate immune system that includes activations of PMN cells and macrophages, leading to PMN cell degranulation and macrophage production of pro-inflammatory cytokine. The adherence of PMN cells to the vascular endothelium is the first step in the extravasation of these cells into the injured tissue. After adherence and chemotaxis, the infiltrating PMN cells can release reactive oxygen species that can damage the tubular cells[14]. Both pro-inflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α, and anti-inflammatory cytokines including IL-10 and TGF-β appear to be significantly increased in AKI. These would further injure kidney and also result in systemic organ effects once are released into the circulation[13].

Although a recent meta-analysis study suggested that early initiation of RRT might be associated with improved outcomes in patients with AKI[15], this advantage might be impaired by bioincompatiblity which can enhance the release of various granule products including MPO from activated PMN cells during HD[16, 17]. This might potentiate the oxidative stress injury in AKI patients.

The present study demonstrated that citrate could diminish both bioincompatibility-induced as well as systemic oxidative stress. Regarding the former, the post-filter serum

with both citrate and heparin anticoagulant could significantly reduce TNF-α which plays an important role in AKI and sepsis (Figure 3B). TNF-α is released from activated macrophages and can cause fever, hypotension, myocardial depression, and neutrophil and endothelial cell activations. Of interest, citrate could significantly reduce IL-8 while heparin did not provide this beneficial effect (Figure 3C). IL-8 was another important proinflammatory cytokine in AKI and sepsis. It is produced from activated macrophages like TNF-α and has a role in chemotactic process for PMN and T-cell. IL-6 in both groups did not significantly change during CVVH treatment. Regarding anti-inflammatory cytokine, IL-10 was not significantly altered during CVVH treatment in both groups. As such, the present study is the first to demonstrate that RCA could potentially provide more beneficial effects on systemic inflammation than heparin in CVVH treatment. This occurred even the baseline inflammatory state than the citrate group seemed to be higher than the heparin group (Table 1). Indeed, a previous study in 4-hour hemodialysis in ESRD also demonstrated the lower IL-1β secretion in RCA than heparin groups[10]. It might be hypothesized that calcium chelating ability of citrate could downregulate inflammation [20, 21] not only from membrane-induced but also systemic inflammation. Another possible explanation is the fact that the ready availability of citrate, which is a crucial regulator of the citric acid cycle in mitochondria, might maintain the redox state of the cell [22].

A recent interesting study demonstrated that RCA reduced mortality when compared with heparin anticoagulant in CVVH[23]. This reduction in bioincompatibility-induced and systemic oxidative stress and inflammation, demonstrated in the current study, might be an explanation of the increased patient survival. In the present study, the patient survival was slightly, although not significantly, better in the citrate group (Figure 4B). This might be caused by the quite small number of patient in each group. The patient survival benefit of citrate needs to be confirmed in the larger RCT study.

the clinical advantages including renal recovery and patient survival in acute kidney injury are to be established.

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TABLES

Table 1 Baseline clinical and demographic features of patients

	Heparin group (n=10)	Citrate group (n=10)	*p* value
Sex (M/F)	7/3	5/5	
Age (yrs)	66.3 ± 24.8	66.0 ± 13.5	NS
The etiology of AKI			
Sepsis (%)	60	50	
Myocardial infarction (%)	10	20	
Post CABG (%)	20	20	
Post aneurysmectomy (%)	0	10	
Congestive heart failure (%)	10	0	
APACHE II score	22.2 ± 4.5	21.8 ± 3.0	NS
On inotropic drugs (%)	70	70	
On ventilator (%)	50	80	
Blood urea nitrogen (mg/dL)	87.2 ± 18.7	74.1 ± 28.8	NS
Creatinine (mg/dL)	4.3 ± 1.5	3.9 ± 1.9	NS
Total calcium (mg/dL)	9.4 ± 1.0	9.2 ± 0.8	NS
Ionized calcium (mmol/L)	1.1 ± 0.1	1.1 ± 0.1	NS
Albumin (gm/dL)	2.8 ± 0.5	2.7 ± 0.6	NS
Sodium (mEq/L)	133.3 ± 3.5	136.8 ± 4.1	NS

Table 2. Comparison of prefilter and postfilter MPO concentrations during heparin and citrate CVVH

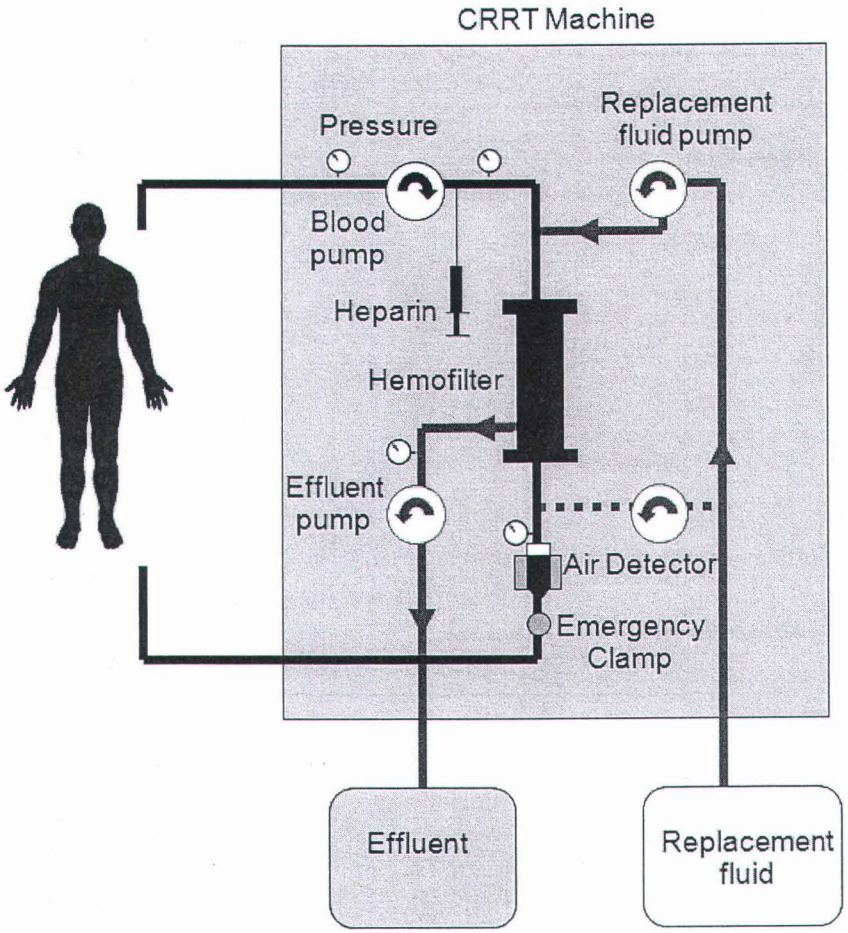
	Prefilter MPO (ng/mL)	Postfilter MPO (ng/mL)
Heparin group		
At start (n=10)	40.5 ± 21.3	39.7 ± 20.1
At 6 hr (n=10)	66.0 ± 63.5*	76.7 ± 69.8**
At 24 hr (n= 4)	40.3 ± 13.1	35.8 ± 19.7
Citrate group		
At start (n=10)	56.7 ± 51.0	59.5 ± 51.0
At 6 hr (n=10)	27.7 ± 34.6*	28.2 ± 33.5
At 24 hr (n= 8)	28.9 ± 50.0	23.2 ± 34.8

* $p<0.01$ when compared with baseline

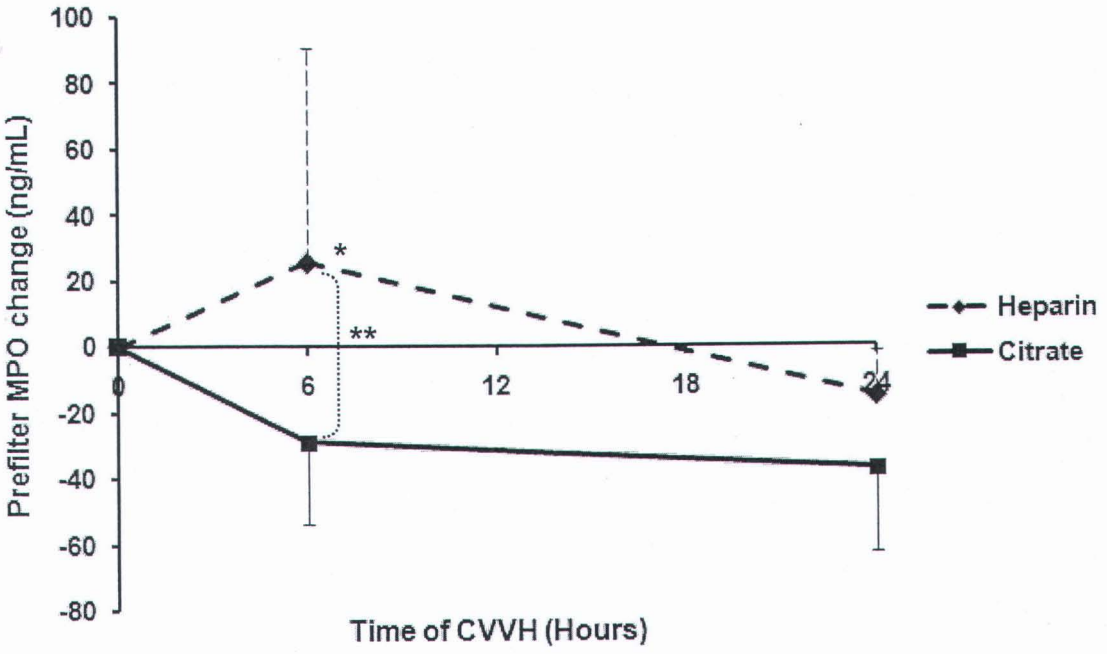
** $p<0.05$ when compared between postfilter and prefilter MPO levels in the same group

Figure

FIGURES



A.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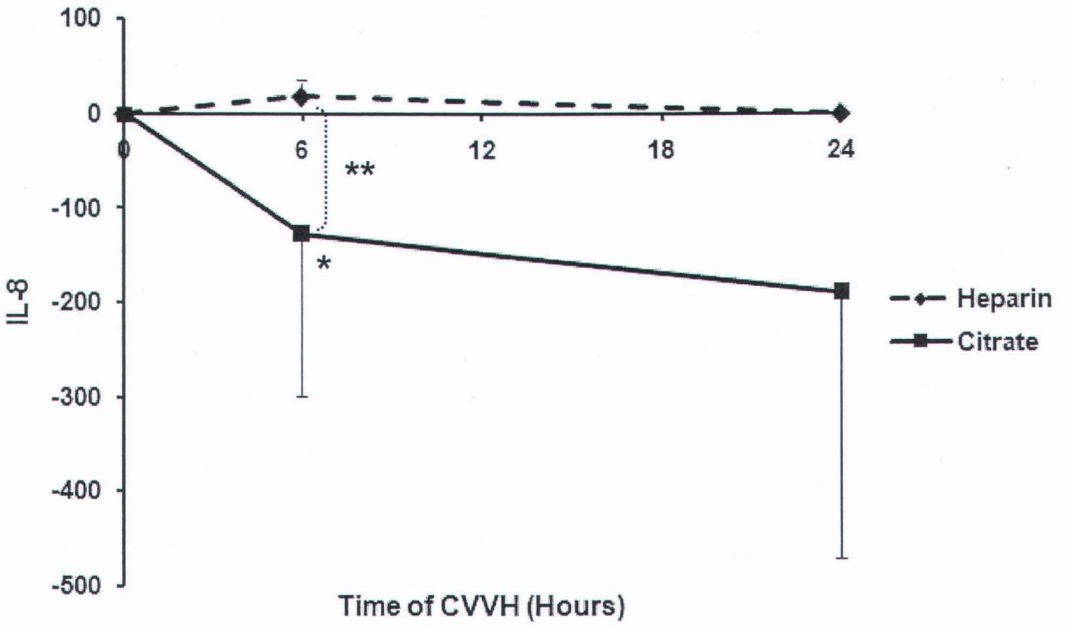
80
60
40
20
0
-20
-40
-60
-80
Prefilter MPO change (ng/mL)
0
6
12
18
24
Time of CVVH (Hours)
*
**
Heparin
Citrate

Figure 2.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-200
-300
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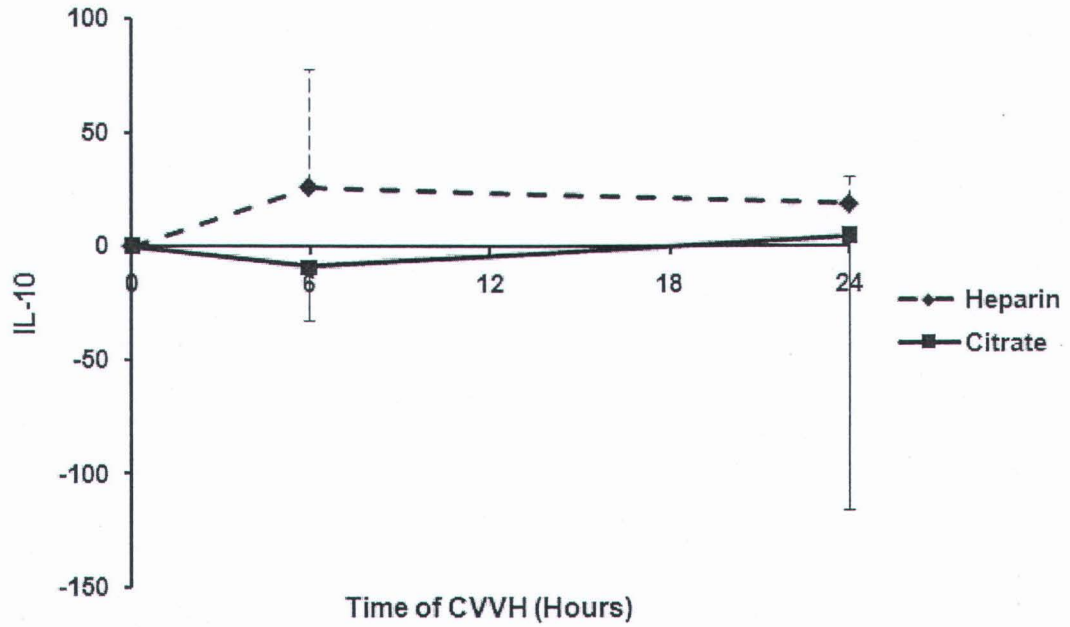
Heparin
Citrate
Time of CVVH (Hours)

C.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50
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-50
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Heparin
Citrate
Time of CVVH (Hours)

D.

Figure 3.