ROLE OF EARLY CONTINUOUS VENO-VENOUS HEMODIAFILTERATION IN SEPTIC SHOCK AND MULTI-ORGAN FAILURE

Thesis Submitted by

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ABSTRACT

INTRODUCTION: We conducted a prospective observational study from august 2007 to august 2008 to evaluate early continuous veno-venous haemodiafiltration (**CVVHDF**), in patients with refractory septic shock and multi-organ failure upon mortality & morbidity in the ICU.

Methods: **CVVHDF** was implemented at less than 6–12 hours of maximal haemodynamic support. Metabolic acidosis, serum lactate & serum procalcitonin level (**PCT**) before & after **CVVHDF** at day 5 were the monitoring used to evaluate the improvement achieved.40 patients included in the study were chosen randomly, 20 underwent **CVVHDF** (group I) & 20 were control group (group II) treated using traditional guidelines. **APACHE II** & **Delta-SOFA** scoring systems were used before & after **CVVHDF** at day 5.

RESULTS: Compared to group II, pts of group I had lower mortality (55% vs 70%). Group I patients showed a non significant delta **SOFA** (5.95±4.39 vs 6.2±3.3 in group I & II respectively & P=0.66), regarding **APACHE II** scores, group I also showed statistically non-significant lower figures than group II (on admission **APACHE II** scores were 39.35±10.65 vs 41.85±10 in group I & II respectively & P=0.45) while on day 5 **APACHE II** scores were (34.8±10.6 vs 36.1±10.9 in group I & II respectively & P=0.41). Group I patients showed lower **PCT** on admission & day 5 than group II patients (on admission **PCT** level was 0.64±0.18 vs 0.68±0.17 in group I & II respectively & P=0.5) while day 5 **PCT** level was (0.51±0.15 vs 0.52±0.17 in group I & II respectively & P=0.83). Indicators of improvement showed statistically significant difference between survivors & non-survivors regarding **Serum lactate level** at day 5 (P<0.001), while other indicators as **Fever**, **Renal profile, WBC count, Metabolic acidosis, Serum lactate level** on admission & **Platlets count** were statistically insignificant (on admission **P-value**=0.2, 0.55, 0.45, 0.41, 0.65, 0.55 for each indicator respectively & on day 5 **P-value**=0.37, 0.94, 0.71, 0.5, <0.001, 0.88 for each indicator respectively).

Conclusion: Early **CVVHDF** may improve the prognosis of sepsis-related multiple organ failure, Failure to correct metabolic acidosis rapidly during **CVVHDF** is a strong predictor of mortality as it was more evident in non-survivors.Continous rising of serum lactate level despite **CVVHDF** is associated with increased mortality rate. Of all scoring systems used **SOFA** maximum, **Delta-SOFA** and **APACHE II** day 5 were the most accurate prognostic indicators for mortality .More than 4 organs failure showed 100% mortality, while less than 4 organs failure showed no mortality in our study.**PCT** level was higher in non-survivors but with insignificant statistical difference between the 2 groups.

KEYWORDS: continuous veno-venous hemodiafiltration, lactate, procalcitonin, delta-sofa, APACHE II

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Abbreviations

ABP	**Arterial Blood Pressure**
APACHE II	**Acute Physiology and Chronic Health Evaluation II**
APACHE III	**Acute Physiology and Chronic Health Evaluation III**
aPTT	**Activated Partial Thromboplastin Time**
ARDS	**Adult Respiratory Distress Syndrome**
ARF	**Acute Renal Failure**
AT	**Anti-Thrombin**
BAL	**Bronco-Alveolar Lavage**
Bcl-2 gene	**B-cell Leukemia/lymphoma-2 genes**
C3a	**Activated Complement 3**
CD 46,256	**Cell of Differentiation 46,256**
CHFD	**Continuous High-Flux Dialysis**
CO	**Cardiac Output**
CPFA	**Continuous Plasma Filtration Adsorption**
CRP	**C-Reactive Protein**
CRRT	**Continuous Renal Replacement Therapies**
CVP	**Central Venous Pressure**
CVVH	**Continuous Veno-Venous Hemofiltration**
CVVHDF	**Continuous Veno-Venous Hemodiafiltration**
DIC	**Disseminated Intravascular Coagulation**
DNA	**Deoxyribo Nucleic acid**
DO2	**Oxygen Delivery**
ED	**Emergency Department**
EGDT	**Early Goal-Directed Therapy**
ESKD	**End Stage Kidney Disease**
FIO2	**Fraction of Inspired Oxygen**
FISH	**Fluorescent Insitu Hybridization**
FIX	**Factor 9**
FVa	**activated Factor 5**
FVIIa	**activated factor 7**
FVIIIa	**activated factor 8**
FX	**factor 10**
FXa	**activated factor 10**
GCS	**Glasgow Coma Scoring**
G-CSF	**Granulocyte Colony-Stimulating Factor**
HLA-DR	**Human Leukocytic Antigen- type DR**
HR	**Heart Rate**
HVHF	**High Volume Hemo-Filtration**
ICU	**Intensive Care Unit**
IFN-g	**Interferon-Gamma**

IHD	**Intermittent Hemodialysis**
IL-1,2,4,6,8,10	**Interleukin-1,2,4,6,8,10**
INR	**International Normalized Ratio**
LPS	**Lipopolysaccharide**
MAP	**Mean Arterial blood Pressure**
mHLA-DR	**Monocyte Human Leukocytic Antigen type DR**
MODS	**Multi-Organ Dysfunction Syndrome**
MOF	**Multi-Organ Failure**
mRNA	**Messenger Ribonucleic Acid**
MRSA	**Methicillin Resistant Staphylococcus Aureus**
NFkB	**Nuclear Factor- Kappa B**
NO	**Nitric Oxide**
PACO2	**Partial Pressure of Carbon Dioxide in the Arterial blood**
PAI-1	**Plasminogen Activator Inhibitor-1**
PAO2	**Partial Pressure of Oxygen in the Arterial blood**
PARs	**Protease Activated Receptors**
PCR	**Polymerase Chain Reaction**
PCT	**Pro-calcitonin**
RCT	**Randomized Controlled Trials**
RNA	**RiboNucleic Acid**
RR	**Respiratory Rate**
rRNA	**Ribosomal Ribonucleic Acid**
SBP	**Systolic Blood Pressure**
SC tissue	**Subcutaneous Tissue**
SD	**Standard Deviation**
SIRS	**Systemic Inflammatory Response Syndrome**
SOFA	**Sequential Organ Failure Assessment**
sPLA2	**Secretory Phospholipase A2**
ScVo2	**Central venous oxygen saturation**
SVO2	**Mixed Venous Oxygen Saturation**
T-cells	**Thymus Cells**
TF- VIIa	**Activated Tissue Factor 7**
TFPI	**Tissue Factor Pathway Inhibitor**
TGF-b	**Transforming Growth Factor-b**
Th1	**Type 1T-helper cells**
Th2	**Type 2 T-helper cells**
TLC	**Total Leukocytic Count**
TNF-a	**Tumor Necrotic Factor alpha**
VO2	**Oxygen Consumption**
WBC	**White Blood Cell**

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INTRODUCTION
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INTRODUCTION

Sepsis constitutes a significant consumption of intensive care resources and remains an ever-present problem in the intensive care unit. It has been estimated that between 400,000 and 500,000 patients are so affected each year in both the **USA** and Europe. Morbidity and mortality have remained high despite improvements in both supportive and anti-microbial therapies. Mortality rates vary from 40% for uncomplicated sepsis to 80% in those suffering from septic shock and multi-organ dysfunction. [1]

Severe sepsis and septic shock are common, accounting for about 2.9% of hospital admissions and 10% of admissions into the intensive care unit (**ICU**). The mortality rates for these 2 conditions exceed 30 %.[2] Patients admitted and treated for sepsis in the **ICU** are often transferred from general medical/surgical practice units, operating rooms, Emergency Departments, long-term care facilities and other hospitals. The diagnosis and treatment of these patients may be sub-optimal, even among those who were admitted to general medical or surgical practice units or the **ICU**. [3]

Delays in the identification, transfer and management of critically ill patients during the first 6 hours after **ICU** admission have been associated with higher mortality rates[4] and increased utilization of hospital resources.[2] Within the last 5 years, advances in the treatment of severe sepsis and septic shock have provided new therapies to treat this disease.

Although these studies were **ICU**-based, the timelines of treatment became a more important issue when Rivers and colleagues [5] were able

to show a significant mortality benefit when hemodynamic optimization was provided within the first few hours of disease presentation.

This "***golden hour***" and "***silver day***"[(6)] perspective of early resuscitation, which traditionally has been applied to trauma, can now be applied to severe sepsis and septic shock. Early diagnosis and rapid intervention became synonymous with improved outcomes for trauma patients, which inspired the concept of the "golden hour."[(7)]

In turn, the "silver day" represented the first day's remaining hours, during which aggressive correction of shock and organ dysfunction was found to decrease health-care resource utilization [(8)] and improve outcomes, these ideals have been incorporated into the Surviving Sepsis Campaign, a multinational initiative, which recommends a 24-hour sepsis pathway that includes a critical 6-hour course of action. [(9)]

The conventional treatment in septic shock is the use of antibiotics, and fluid replacement. Once they do not respond promptly to fluid replacement to prevent development of septic shock, the patient is worsening into a more severe condition, necessitating intensive care treatment, including vasopressor support, besides respiratory aid and dialysis. [(10, 11)]

Septic shock is usually accompanied by acute renal injury, heralded by a drop in diuresis. However, when standard intermittent hemodialysis (**IHD**) is used to treat renal failure, the initiation of renal replacement therapy is often delayed by concerns about haemodynamic tolerance. With the availability of continuous veno-venous hemofiltration (**CVVHF**), a safe procedure in haemodynamically unstable patients [(12)], there is no reason to delay renal replacement therapy [(13)].

Hemofiltration has been reported to improve cardio-pulmonary function in septic patients, even if they are not oliguric [(14)]. In hemodynamically stable patients with acute renal failure, continuous veno-venous hemofiltration and intermittent hemodialysis are equally effective. In hemodynamically unstable patients, continuous hemofiltration provides easier management of fluid balance. [(15)]

The incidence of renal failure requiring dialysis is low in sepsis patients (<5%); however, the risk of mortality in sepsis patients with acute renal failure (**ARF**) exceeds 50% [(9)]. Renal replacement therapies in critically ill patients are primarily limited to intermittent renal replacement therapy (**IRRT**) and continuous renal replacement therapy (**CRRT**). Considerable debate surrounds the management of **ARF** patients and whether or not the more costly **CRRT** should be adopted. A recent meta-analysis suggested that **CRRT** was associated with a significant mortality reduction when adjustments were made for study quality and severity of illness [(16)].

AIM OF THE WORK

The aim of the presented study is to:

- Evaluation of the effect of early continuous veno-venous hemodiafiltration therapy in septic shock regarding mortality & morbidity in **ICU**.

- Evaluating **Delta-SOFA** & **APACHE II** scoring systems in critically ill patients due to septic shock.

- Evaluating **PCT** level in association to mortality