LAMPIRAN A

A Pilot Randomized Control Study Comparing Sustained Low Efficiency Daily Dialysis (SLEDD) with Sustained Low Efficiency Daily Diafiltration (SLEDD-f) for the treatment of Acute Kidney Injury (AKI) in critical care areas at HUSM: Effect on Renal Outcome.

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Introduction: Acute kidney injury in critically ill patients requiring dialysis remains to be a burden to the population in terms of mortality and renal recovery. Renal recovery is important as dialysis dependant patient leads to chronic hemodialysis which is a major burden for patients, their families, and healthcare systems, and is associated with higher long-term mortality. Emerging modalities as an alternative such as sustained low efficiency daily dialysis (SLEDD) and sustained low efficiency daily diafiltration (SLEDD-f) have shown similar outcome in terms of renal recovery and mortality with shorter duration of dialysis. These two therapies have not been directly compared.

Methodology: This is a pilot randomized control study comparing two dialysis modalities (SLEDD vs SLEDD-f) for the treatment of AKI in the critical patients at HUSM. Duration of study is from 1st May 2014 till 1st November 2014 and a total of 12 patients were selected. Primary outcome measures were renal recovery at 42 days either complete, partial or no recovery. Secondary outcome measures all-cause mortality rate after 60 days of randomization.

Results: Baseline characteristics of 12 patients randomized into two groups of 6 patients each were similar. Sepsis represented the major cause of acute kidney injury, 83.33% causes. The overall renal recovery for either SLEDD or SLEDD-f was 33.33%. In the SLEDD group, 20.0% of study subjects had complete renal recovery, while 80% were dialysis dependant. In the SLEDD-f group 50% of patients had complete renal recovery while the rest were dialysis dependant. There were no significant differences in the renal recovery outcome for both modalities (odds ratio, 4.00; 95% CI 0.27 to 6.33; p=0.317).

Mortality within 60 days were observed in two of the six patients (33.3%) in the SLEDD group, and one of the six patients (16.7%) under SLEDD-f group (odds ratio, 0.40; 95% CI 0.03 to 6.18; p=0.512). The overall mortality rate was 25%.

Conclusion: SLEDD-f used in critically ill patients with acute kidney injury did not show any difference between SLEDD with regards to all-cause mortality and renal recovery. Thus SLEDD-f may be used as an alternative for patients in critical care settings.

Dr. Azreen Syazril Adnan: Supervisor

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LIST OF ABBREVIATIONS

AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
APACHE II score	Acute physiology and chronic health evaluation score
AUC	Area under the receiver operating curve
BMI	Body mass index
CKD	Chronic Kidney Disease
CI	Confidence interval
CRRT	Continuous renal replacement therapy
CRP	C-reactive protein
CVVH	Continuous venovenous haemoflitration
CVVHDf	Continuous venovenous hemodiafiltration
ESRD	End stage renal disease
eGFR	Estimated glomerular filtration rate
HUSM	Hospital Universiti Sains Malaysia
ICU	Intensive Care Unit
IHD	Intermittent Hemodialysis

KQIGO	Kidney Disease Improving Global Outcomes
NPV	Negative predictive value
OR	Odd ratio
PIRRT	Prolonged intermittent renal replacement therapy
RIFLE	Risk, injury, failure, loss, end stage
RRT	Renal replacement therapy
SAPS II score	Simplified Acute Physiology Score
SOFA	Sequential Organ Failure Assessment
SD	Standard deviation
SLEDD	Sustained low efficiency daily dialysis
SLEDD-f	Sustained low efficiency daily diafiltration
SPSS	Statistical Package for the Social Sciences
UK	United Kingdom
US	United States
USM HREC	USM Human Research Ethics Committee

A Pilot Randomized Control Study Comparing Sustained Low Efficiency Daily Dialysis (SLEDD) with Sustained Low Efficiency Daily Diafiltration (SLEDD-f) for the treatment of Acute Kidney Injury (AKI) in critical care areas at HUSM: Effect on Renal Outcome.

Abstract

Introduction: Acute kidney injury in critically ill patients requiring dialysis remains to be a burden to the population in terms of mortality and renal recovery. Renal recovery is important as dialysis dependant patient leads to chronic hemodialysis which is a major burden for patients, their families, and healthcare systems, and is associated with higher long-term mortality. The standard renal replacement therapy used worldwide is continuous renal replacement therapy i.e. continuous veno-venous hemofiltration or intermittent hemodialysis. Emerging modalities as an alternative such as sustained low efficiency daily dialysis (SLEDD) and sustained low efficiency daily diafiltration (SLEDD-f) have shown similar outcome in terms of renal recovery and mortality with shorter duration of dialysis. These two therapies have not been directly compared.

Methodology: This is a pilot randomized control study comparing two dialysis modalities (SLEDD vs SLEDD-f) for the treatment of AKI in the critical patients at HUSM. Duration of study is from 1st May 2014 till 1st November 2014 and a total of 12 patients were selected. Primary outcome measures were renal recovery at 42 days either complete, partial or no recovery. Secondary outcome measures all-cause mortality rate after 60 days of randomization.

Results: Baseline characteristics of 12 patients randomized into two groups of 6 patients each were similar. Sepsis represented the major cause of acute kidney injury, 83.33% causes. The overall renal recovery for either SLEDD or SLEDD-f was 33.33%. In the SLEDD group, 20.0% of study subjects had complete renal recovery, while 80% were dialysis dependant. In the SLEDD-f group 50% of patients had complete renal recovery while the rest were dialysis dependant. There were no significant differences in the renal recovery outcome for both modalities (odds ratio, 4.00; 95% CI 0.27 to 6.33; p=0.317).

Mortality within 60 days were observed in two of the six patients (33.3%) in the SLEDD group, and one of the six patients (16.7%) under SLEDD-f group (odds ratio, 0.40; 95% CI 0.03 to 6.18; p=0.512). The overall mortality rate was 25%.

The risk factors associated for renal recovery include estimated glomerular filtration rate, etiology of acute kidney injury and serum creatinine level prior to the initiation of dialysis were found not significant by using logistic regression.

Conclusion: SLEDD-f used in critically ill patients with acute kidney injury did not show any difference between SLEDD with regards to all-cause mortality and renal recovery. Thus SLEDD-f may be used as an alternative for patients in critical care settings.

Kajian Rambang Secara Kaedah Pilot "Sustained Low Efficiency Daily Dialysis" (SLEDD) dengan "Sustained Low Efficiency Daily Diafiltration" (SLEDD-f) dalam pesakit yang mengalami kegagalan buah pinggang akut di kawasan kritikal: Kesan ke atas fungsi buah pingggang.

Pengenalan: Kecederaan buah pinggang akut kepada pesakit yang memerlukan dialisis tetap menjadi beban kepada penduduk dari segi kematian dan pemulihan buah pinggang. Terapi penggantian buah pinggang adalah penyokong utama bagi rawatan sokongan pesakit dengan kecederaan buah pinggang akut yang teruk. Terapi penggantian buah pinggang standard yang digunakan di seluruh dunia adalah terapi penggantian buah pinggang berterusan iaitu berterusan "continous veno-vena hemodiafiltration" (CVVH) atau "intermittent hemodialisis" (IHD). Kaedah baru muncul sebagai alternatif seperti "Sustained Low Efficiency Daily Dialysis" (SLEDD) dan "Sustained Low Efficiency Daily Diafiltration" (SLEDD-f) telah menunjukkan hasil yang sama dari segi pemulihan buah pinggang dan kadar kematian dengan tempoh dialysis yang lebih pendek bebanding dialysis konventional. Kedua-dua terapi ini belum pernah dibandingkan keberkesanan mereka.

Metodologi: Ini adalah kajian pilot rawak kawalan membandingkan dua kaedah dialisis (SLEDD vs SLEDD-f) untuk rawatan AKI dalam penjagaan kritikal kawasan di HUSM. Tempoh pengajian adalah dari 1 Mei 2014 hingga 1 November 2014 dan sebanyak 12 pesakit telah dipilih. Tujuan utama kajian ini adalah untuk melihat pemulihan buah pinggang pada 42 hari sama ada lengkap, separa atau tiada pemulihan. Tujuan kedua kajian ialah melihat kematian dari apa-apa sebab pada hari ke 60 bermula hari pertama dipilih untuk dialisis.

Keputusan: Ciri-ciri asas daripada 12 pesakit dalam kedua-dua kumpulan adalah sama termasuk markah meramalkan kematian iaitu APACHE II, SOFA dan SAPS II. Sebab utama kecederaan buah pinggang akut adalah disebabkan oleh sepsis (83,33%). Pemulihan buah

pinggang sepenuhnya untuk pesakit dengan AKI yang menjalani dialisis sama ada SLEDD atau SLEDD-f adalah 33.33%. Satu daripada enam pesakit (20.0%) dalam kumpulan SLEDD telah berjaya mengalami pemulihan buah pinggang sepenuhnya, manakala baki pesakit iaitu 80% mengalami kegagalan buah pinggang berterusan dan memerlukan dialysis sepanjang hayat, berbanding tiga daripada enam pesakit (50%) mengalami pemulihan buah pinggang sepenuhnya dalam kumpulan SLEED-f tetapi tiga daripada enam pesakit (50.0%) telah mengalami kegagalan berterusan. Tiada perbezaan yang signifikan bagi pemulihan hasil buah pinggang di antara kedua-dua kaedah (nisbah kemungkinan, 4.00; 95% CI 0,27-60,33; p = 0,317).

Dua daripada enam pesakit (33.3%) dalam kumpulan SLEDD yang meninggal dunia dalam masa 60 hari selepas rawak, berbanding dengan hanya satu daripada enam pesakit (16.7%) di bawah kumpulan SLEDD-f (nisbah kemungkinan, 0.40; 95% CI 0.03 untuk 6.18; p = 0.512). Kematian adalah sama antara kedua-dua kaedah rawatan. Kadar kematian keseluruhan adalah 25%.

Faktor-faktor risiko yang berkaitan untuk pemulihan renal diuji termasuk eGFR, sebab-sebab kecederaan buah pinggang akut dan “serum creatinine” setelah bermulanya dialisis tidak menunjukkan perbezaan yang signifikan dengan menggunakan regresi logistic.

Rumusan: SLEDD-f yang digunakan untuk pesakit yang dengan kecederaan buah pinggang akut tidak menunjukkan apa-apa perbezaan dengan kaedah SLEDD dari segi kematian dan pemulihan buah pinggang. Oleh itu SLEDD-f boleh digunakan sebagai alternatif untuk pesakit yang dirawat di bahagian kritikal.

CHAPTER ONE

Introduction

1.1 Study Background

1.1.1 Acute Kidney Injury (AKI)

Acute kidney injury (formerly known as acute renal failure) is characterised by rapid loss of the kidney's excretory function and diagnosed by accumulation of nitrogen end metabolism products (urea and creatinine) or decreased in urine output, or both. It is the clinical manifestation of several disorders that affect the kidney acutely (Rewa and Bagshaw 2014).

The described notions have led to a consensus definition of acute kidney injury by the Acute Dialysis Quality Initiative. These RIFLE (risk, injury, failure, loss, end stage) criteria (Table 1.2) have been broadly supported with minor modifications by the Acute Kidney Injury Network (AKIN) (Table 1.1) and both definitions have now been validated in thousands of patients. A new consensus definition combining RIFLE criteria and the AKIN definition has emerged from the Kidney Disease: Improving Global Outcomes (K-DIGO) group (KDIGO 2012).

AKI is common in our population especially in the severely ill patients under critical care management, as such carrying important diagnostic and therapeutic challenges for clinicians.

The incidence varies between definitions and populations, from more than 5000 cases per million people per year for non-dialysis-requiring acute kidney injury, to 295 cases per million people per year for dialysis requiring disease (Hsu, McCulloch et al. 2007).

Most clinicians are familiar with two key ideas related to acute kidney injury—namely, acute tubular necrosis and prerenal azotaemia. Acute tubular necrosis describes a form of intrinsic acute kidney injury that results from severe and persistent hypoperfusion of the kidneys (ie, prerenal acute kidney injury)(Bellomo, Kellum et al. 2012).

1.1.2 Burden of Acute Kidney Injury (AKI)

Until recently, an absence of consensus had resulted in several different definitions of acute renal failure in standard use. As such a wide variation existed in estimates of disease prevalence (1–25%) and mortality (15–60%)(Uchino, Kellum et al. 2005).

The reported incidence varies, which can be as high as 65% in some ICU populations, depending on the definition used. AKI is associated with mortality rates of approximately 50%,and early management with renal replacement therapy (RRT) is considered an essential intervention(Jamal, Mat-Nor et al. 2014).

Acute kidney injury is associated with several complications, including fluid overload, electrolyte abnormalities, and coagulopathy. Fluid overload is associated with increased risks of death,(Bouchard, Soroko et al. 2009) and this association too might reflect the severity of illness.

Acute kidney injury requiring dialysis in critically ill patients is associated with 40–70% mortality and is an independent risk factor for death(Bouchard, Soroko et al. 2009).

Recent hospital studies in developed world countries reported AKI in 3.2–9.6% of admissions, with overall mortality 20%, and 50% in ICU patients. There is increased long-term mortality in AKI patients surviving hospitalization, with adjusted mortality risk of 1.4, and augmented with increasing severity of AKI(Fang, Ding et al. 2010). It is estimated that 2 million people die of AKI every year(Uchino, Kellum et al. 2005, Murugan and Kellum 2011). AKI survivors have a higher risk for later development of CKD (Coca, Singanamala et al. 2011).

1.2 AKI in critical care

Patients with AKI require critical care management as they are usually associated with multi-organ failures which subsequently lead to death.

Recently, a web-based data collection survey conducted in 10 Italian intensive care units (ICU) found that absolute AKI incidence is high (more than one third of all admissions) with 30%, 20% and 50% of these patients stratified across the three AKI severity classes, risk, injury and failure, respectively. Almost two thirds of AKI cases were diagnosed within 24 hours of ICU admission. AKI is associated with a crude ICU mortality (28.8% vs. non-AKI 8.1%) and longer ICU length of stay (median 7 days vs. non-AKI 3 days). (Garzotto, Piccinni et al. 2011)

In Malaysia the reported incidence of AKI within 24 h of ICU admission is approximately 14%, while 15% of all the critically ill receive RRT at some point. RRT commencement for critically ill AKI patients is variable and frequent in some region (more than 60% of AKI cases). AKI is associated with in-hospital mortality rate of 41.4%, and encountered up to 80% of patients presenting with severe sepsis and multi-organ failure (MRIC Annual Report 2012).

1.2.1 Management of AKI in critical care

There have been no definitive criteria or specific timing to subject an AKI patient for initiation of renal replacement therapy. Nephrologists usually decide based upon, factors like potassium, serum creatinine , and urea levels, fluid status; acid–base status; urine output; and the overall prognosis of the patient in addition to their pre-existing complication(Bellomo, Kellum et al. 2012).

The appropriate timing for renal replacement therapy initiation is controversial as studies linking time and outcome were mostly observational (Bagshaw, Bellomo et al. 2010). Three forms of renal replacement therapy are available in intensive care setting: continuous, intermittent (either as intermittent haemodialysis (IHD) or slow low efficiency dialysis), and peritoneal dialysis. Continuous renal replacement therapy may consist of filtration alone (eg, continuous venous–venous haemofiltration) or diffusion alone (eg, continuous veno–venous haemodialysis), or both (eg, continuous veno–venous haemodiafiltration)(Bellomo, Kellum et al. 2012).

Two large multicentre randomized controlled studies published in 2009 (the randomized evaluation of normal versus augmented level (RENAL) replacement therapy study(Bellomo, Cass et al. 2009) and the VA/NIH Acute Renal Failure Trial Network (ATN) study finally clarified the concept of optimal dialysis dose. The RENAL and ATN studies were designed to compare ‘normal’ or ‘less intensive’ renal support to an ‘augmented’ or ‘intensive’ therapy: in particular, the RENAL study compared 25 ml/kg per continuous venovenous haemodiafiltration (CVVHDF) to 40 ml/kg per h; the ATN study compared 20 ml/kg per h CVVHDF or thrice weekly intermittent dialysis to 35 ml/kg/h CVVHDF or daily

intermittent dialysis. Surprisingly, both studies showed that increasing the intensity of the RRT dose did not improve overall patient outcomes, essentially confuting a large body of evidence coming from previous smaller trials(Network 2008).

Controversy exists as to which is the optimal RRT modality for patients with AKI. In current clinical practice, the choice of the initial modality for RRT is primarily based on the availability of, and experience with, a specific treatment and on the patient's hemodynamic status. Transitions between CRRT and IHD are also frequent, mostly determined by the hemodynamic status of the patient or coagulation problems(KDIGO 2012).

As the mortality of AKI in critical care have reached almost 50%, the importance of renal replacement therapy either being early or late must be given the utmost priority to be initiated in order to reduce the mortality rate. RRT modalities have evolved over time, in parallel with technological advances, to offer better patient tolerability and solute removal. However, 'ideal' RRT settings remain controversial, and delivery of a standard RRT prescription globally is unlikely(Jamal, Mat-Nor et al. 2014).

1.2.2 Outcomes of AKI in critical care

Acute kidney injury (AKI) is a common complication in the intensive care unit (ICU) (De Mendonça, Vincent et al. 2000, Uchino, Kellum et al. 2005). Renal replacement therapy (RRT) is the major supportive treatment of AKI. Despite progress in RRT management, mortality remains high(Ympa, Sakr et al. 2005), and the timing of its initiation remains open to debate(Palevsky 2013). Randomized studies focused on RRT modalities, and none has shown a real benefit of one technique over the other.

Conversely, only few studies focused on when is the best time to initiate RRT, however conflicting results were reported. Then, consensus conferences and expert opinions

acknowledge that apart from obvious indications (life threatening hyperkalemia and volume overload pulmonary edema), precise criteria for initiating RRT in ICU patients with AKI are lacking(Brochard, Abroug et al. 2010, KDIGO 2012).

When RRT becomes necessary in an AKI patient, it is possible that (critically ill) patient has a clinical picture of multiple organ failure and the probability of survival further decreases: a correct dialysis prescription and delivery, avoidance of dialysis under dosing and prevention of harmful complications (such as hypotension and bleeding) are currently recommended to target "standard of care". AKI survivors have to be followed up as progression to chronic renal failure is currently increasing(Ricci 2013).

1.3 Justification and Rationale

The future of AKI management is still unsettled and remains uncertain, more work are required on diagnosis and prevention. Unfortunately the morbidity and mortality of critically ill patients associated with AKI remains high (about 50%). Despite a short episode of AKI may contribute to long-term organ complications. Thus, this complex syndrome should be aggressively treated.

As previously mentioned there are many modalities in renal replacement therapy; however the superiority between the modalities in terms of outcome i.e. renal recovery and mortality has never been proven.

With the wide availability of CRRT machines and the increasing complexity of critically ill patients, it is likely to remain one of the preferred modalities of renal replacement in the ICU. Hybrid therapies like SLEDD and extended daily dialysis have been shown to be safe and effective in critically ill patients. Sustained low efficiency diafiltration (SLEDD-f) by

combining SLEDD with ultrafiltration has been shown to provide stable renal replacement therapy(Marshall, Ma et al. 2004).

Thus the rationale of carrying out this pilot study is to compare SLEDD with SLEDD-f with regards to the renal recovery and mortality in patients with AKI patient in critical care areas. With this comparison, SLEDD-f can be used as an alternative therapy other than the conventional SLEDD. SLEDD-f in this study focuses on a shorter duration of 4 hours as compared to SLEDD of 6 hours. With the additional diffusion SLEDD-f is seen to be able to clear larger molecules mainly in patients with sepsis however no studies have performed SLEDD-f in 4 hours. The ultimate aim in shortening dialysis treatment without compromising the outcome of patients is to optimize dialysis cost and human resources. However in this study we are unable to compare the treatment cost between both modalities, this can be determined in the near future study.

CHAPTER TWO

Literature Review

2.1 Renal Replacement Therapy (RRT) in Acute Kidney Injury

RRT modalities have evolved over time, in parallel with technological advances, to offer better patient tolerability and solute removal. However, 'ideal' RRT settings remain controversial, and the delivery of a standard RRT prescription globally is unlikely. This is due, in part, to the high costs and need for specialized staffs that are unlikely to be sustainable in resource-limited settings. RRT can be given intermittently, lasting approximately 4 hours per session, such as occurs with conventional intermittent haemodialysis (IHD)(Jamal, Mat-Nor et al. 2014). Prolonged intermittent RRT (PIRRT) adapted from both intermittent and continuous modalities, has a longer duration of treatment, lasting up to 18 hours(Lonnemann, Floege et al. 2000).

Continuous RRT (CRRT) is perhaps most common in the ICU, and is given over 24h. Generally, the aims of treatment are to control fluid volume, correct acid-base abnormalities, improve uraemia, promote renal recovery and improve mortality without causing complications(O'Reilly and Tolwani 2005).

RRT modalities are categorized by mechanisms of fluid and solute removal and by the intermittent vs. continuous nature of treatment. Given the lack of definitive outcome data for RRT modality in Acute Kidney Injury (AKI), current practice is largely dictated by the modalities that are available at a given hospital and the personal experience of attending nephrologist(Riviello and Christopher 2006).

Main principles in renal replacement therapy for acute kidney injury patients are fluids removal and solute removal. Fluid removal is accomplished through ultrafiltration (UF) in majority of RRT methods with the exception of peritoneal dialysis. UF uses a pressure gradient to drive fluids across a semipermeable membrane. Solute removal involves 2 primary mechanism of solute removal involves diffusion and convection. In hemodialysis, solutes are cleared by diffusion. Diffusion is the movement of solute from a higher to lower concentration across a semipermeable membrane. Diffusion is most effective with small molecular weight molecules (<500 daltons). The dialysate fluids, generally contains sodium, bicarbonate, chloride, magnesium, and calcium, runs counter-currently to blood flow, thus maximizing the concentration gradient.

Convection, the primary mechanism of solute clearance in hemofiltration, occurs when solutes are “dragged” with water during ultrafiltration. Solutes eliminated by convection include both small molecular weight molecules, such as potassium, phosphates, creatinine, and blood urea nitrogen (BUN), as well as medium molecular-weight molecules up to 40,000 daltons. Solute clearance is primarily dependent on the ultrafiltration rate, the ultrafiltration coefficient of the membrane, and the sieving coefficient of the solute that is inversely proportional to the molecular weight.

2.1.1 Continuous renal replacement therapy (CRRT)

CRRT includes a variety of modalities that use ultrafiltration and may use convection, diffusion, or both. Treatment is 24 hours per day with a blood flow of 100-200 ml/min, and a dialysate flow of 17-34 ml/min in the case of diffusive technologies(O'Reilly and Tolwani 2005).

The advantages of CRRT stem from its continuous nature: both fluid and solutes shift more slowly, allowing for better hemodynamic stability and more precise solute

concentration control. The gradual nature of solute removal in CRRT makes it less likely to cause cerebral oedema(Bellomo and Ronco 1999). CRRT has greater cumulative solute removal than IHD due to the longer treatment time. It has been postulated that the removal of middle molecular weight (MMW) molecules, including pro-inflammatory molecules with CRRT may be advantageous in sepsis; however, CRRT may also remove anti-inflammatory molecules. Therefore, the net effect is dependent on the balance of pro-inflammatory and anti-inflammatory molecules that are removed. The benefit of removing inflammatory molecules via CRRT has not been demonstrated(Kellum, Bellomo et al. 2008).

Replacement solution replaces the ultrafiltration continuously removed by hemofiltration and hemodiafiltration. Buffers used in the replacement solution include lactate, bicarbonate, or citrate. Lactate and citrate are metabolized by the liver and muscles to produce bicarbonate, which is easily tolerated, but can be unstable in solution. Lactate is stable in replacement solution; however, it may contribute to an existing lactic acidosis in patients with sepsis or liver failure(Riviello and Christopher 2006).

Disadvantages of CVVH include time consuming in the preparation and setting of the machine this could however delay the initiation of dialysis. Others include worsening of bleeding disorders due to prolong use of anti-coagulation, patient's mobility is restricted as the CVVH would run up to 46 hours per session, loss of nutrients(John and Eckardt 2006) and requiring specialized and qualified staffs to monitor closely during the dialysis sessions.

2.2 Hybrid therapies

Hybrid techniques have arrived during the last years as a feasible compromise solution to the dispute of CVVH versus IHD comparison thus bringing both of good qualities from each modalities. SLEDD is a hybrid therapy, offering advantages of both CRRT and IHD(Vanholder, Van Biesen et al. 2011), combining protracted treatment with an intermittent

time scheme, usually applying IRRT machines, and representing a high-tech return to the roots of dialysis as applied in the early days by Kolf(Vanholder, Van Biesen et al. 2011). Other than SLED, sustained low-efficiency dialysis, prolonged daily intermittent RRT(Naka, Baldwin et al. 2004), extended daily dialysis(Kumar, Craig et al. 2000), or simply extended dialysis(Kielstein, Kretschmer et al. 2004), depending on variations in schedule and type of solute removal (convective or diffusive) which is also known as SLEDD-f. Theoretically speaking, the purpose of such therapy would be the optimization of the advantages offered by either CRRT or IHD, including efficient solute removal with minimum solute disequilibrium; reduced ultrafiltration rate with hemodynamic stability, an optimized delivered to prescribed ratio, low anticoagulant needs, diminished cost of therapy delivery, efficiency of resource use, and improved patient mobility. These initial case series have shown the feasibility and high clearances potentially associated with such approaches. A single short-term, single-center trial comparing hybrid therapies to CRRT has shown satisfying results in terms of dose delivery and hemodynamic stability(Baldwin, Naka et al. 2007). Dr. Baldwin and colleagues randomized 16 patients to 3 consecutive days of treatment with either CVVH(Ricci, Bellomo et al. 2006) or extended daily dialysis with filtration(Ricci, Bellomo et al. 2006)and compared smallsolute, electrolyte, and acid-base control. They did not find significant differences between the two therapies for urea or creatinine levels over 3 days. All electrolyte derangements before treatment were corrected as a result of treatment, except for one patient in the CVVH group who developed hypophosphatemia (0.54 mmol/L) at 72 hrs. After 3 days of treatment, there was a mild but persistent metabolic acidosis in the extended daily dialysis with filtration group compared with the CVVH group. However to date there has been no single study comparing between the hybrid therapies.

2.2.1 Sustained Low Efficiency Daily Dialysis (SLEDD)

SLEDD uses the same hemodialysis machines as IHD, but runs for longer periods at slower rates. A usual treatment runs for 6-12 hours, with blood flow rate of 200 ml/min and dialysate flow rate of 300 ml/min. It combines many of the advantages of IHD and CRRT. It is relatively low cost and low complexity since it uses the same technology as IHD; however, it also has the advantages of gradual fluid and solute removal and high total solute removal. In addition, because it is lengthy, but not continuous, it allows for scheduling of other diagnostic and therapeutic procedures between treatments. Although the beginnings of dialysis are rooted in SLED, its regular use in the ICU is a relatively new phenomenon. Some small studies have indicated that it is a safe and effective alternative to CRRT in the setting of AKI in the ICU,(Marshall, Ma et al. 2004) but large randomized trials comparing its outcomes to IHD and CRRT have not been performed.

2.2.2 Sustained Low Efficiency Daily Diafiltration (SLEDD-f)

Variations on SLED have been tried, including nocturnal therapy to maximize time for other therapeutic and diagnostic procedures, and sustained low efficiency diafiltration (SLEDD-f), which combines diffusion and convection. SLEDD-f contains both diffusion and convection principles which has been postulated to be able to clear larger molecules and still keeping the haemodynamically stability shown by CVVH. Marshall et al. demonstrate that SLEDD-f can provide small solute clearance comparable to that provided by a regimen of CRRT with substitution fluid rate. SLEDD-f can provide excellent clinical and metabolic outcomes in critically ill AKI patient mainly due to sepsis(Marshall, Ma et al. 2004). Small solute clearance is adequate by available standards and large solute clearance significant. SLEDD-f can be delivered autonomously in ICU by dialysis nurse or ICU personnel in similar manner to CRRT.

It is difficult to predict the role of SLEDD-f in ICU's however the results of upcoming appropriately designed and powered clinical studies will better determine the clinical role and benefit of SLEDD and SLEDD-f in relation to other modalities or improvement of these hybrid therapies.

2.3 Renal replacement modalities and outcome

Data comparing the outcomes of different modalities in AKI continues to be inconclusive, although the available data points to similar survival rates for IHD and CRRT. Previous studies suffer from inadequate study designs and the use of older technologies, including the types of vascular access.

In 2001, Mehta et al performed a multicenter, randomized, controlled trial comparing IHD with CRRT in 166 ICU patients. The study revealed no survival advantage for CRRT over IHD; however, unexpected differences in the randomized arms precluded a meaningful direct analysis(Mehta, Mcdonald et al. 2001).

An extensive meta-analysis by Kellum et al in 2002 revealed no differences in mortality for CRRT vs. IHD after examining 13 studies comprising 1400 patients (RR 0.93; CI, 0.79-1.09, p=0.29). However, when controlling for disease severity and study quality, there was a survival advantage with CRRT (RR 0.72; CI, 0.60-0.87, p<0.01). The authors concluded that the data were insufficient to make strong recommendations for CRRT in AKI(Kellum, Angus et al. 2002).

A meta-analysis in 2002 found no differences in mortality between IHD and CRRT (IHD vs. CRRT, RR 0.96; CI, 0.85. 1.08; p =0.50)(Tonelli, Manns et al. 2002).

Trials conducted since these meta-analyses were performed fail to definitively answer the question of whether dialysis modality affects mortality and renal recovery outcomes.

Small retrospective studies and recent small randomized prospective trials have all failed to show any survival advantage with the use of CRRT(Uehlinger, Jakob et al. 2005).

Overall, these studies suggest a lack of survival improvement with CRRT versus IHD, with a possibility of improvement with CRRT in the most severely ill AKI patients. While studies have failed to show a survival advantage for any of the modalities, there are specific conditions where a particular RRT method is preferred over another.

It is now possible to generate ultrapure replacement fluid and administer it in the ICU with a lower cost than CRRT, in greater amounts and for shorter periods of time. Hemofiltration may be combined with diffusion, or pure diffusion can be selected at any chosen clearance for a period of time that can encompass the day shift with its maximum staff availability or the night shift. Thus, the choices are now almost limitless: 3 or 4 hour of IHD with standard settings or CRRT at 35 mL/kg/hr of effluent flow rate can be selected. SLED at blood and dialysate flow rates of 150 mL/min for 8 hrs during the day or SLED for 12 hours overnight can be considered as an alternative(Ricci and Ronco 2008).

Mortality from acute kidney injury remains high, particularly in critically ill patients, in whom mortality was 53% in the ATN trial and 44·7% in the RENAL trial. Several large epidemiological studies have linked acute kidney injury with the later development of chronic kidney disease, end-stage kidney disease, and mortality. These results suggest that even a short episode of acute illness might contribute to long-term morbidity and mortality. Thus, the cost to the patient and to society of acute kidney injury might be greater than was postulated earlier.

Whether this increased risk of chronic kidney disease shows the effect of acute kidney injury itself, or whether acute disease is a marker that identifies vulnerable patients, is unclear

and requires further studies. Thus preventing mortality and improving renal recovery in patients suffering from acute kidney injury remains the mainstay of many clinical trials. Critical renal replacement therapies may need to be modified to achieve this objectives keeping with the accessibility and convenience of the therapies to ensure patients received the optimal dialysis therapy.

The consequences of AKI are severe and characterized by increased risk of short-term and long-term mortality, incident CKD and accelerated progression to end-stage renal disease. AKI-associated mortality is decreasing, but remains unacceptably high. Moreover, the absolute number of patients dying as a result of AKI is increasing as the incidence of the disorder increases, and few proven effective preventative or therapeutic interventions exist. Survivors of AKI, particularly those who remain on renal replacement therapy, often have reduced quality of life and consume substantially greater health-care resources than the general population as a result of longer hospitalizations, unplanned intensive care unit admissions and rehospitalisation(Rewa and Bagshaw 2014).

CHAPTER THREE

Objectives

3.1 Primary End Point

To determine the renal recovery* between patients with acute kidney injury (AKI) receiving either Sustained Low Efficiency Daily Dailysis (SLEDD or Sustained Low Efficiency Daily Dialfiltration (SLEDD-f).

(*renal recovery in this study will be described in detail under the methodology section)

3.2 Secondary End Point

To compare the mortality rate of AKI patients receiving either SLEDD or SLEDD-f.

3.3 Research Questions

1) What is the difference of renal recovery outcome between AKI patients receiving SLEDD or SLEDD-f

2) What is the difference of mortality rate between patients with AKI receiving SLEDD or SLEDD-f

3) Are factors like (length of hospital stay, stage of chronic kidney disease and creatinine level prior to initiation of dialysis) significantly associated with renal recovery in patient with AKI

4) Are factors like (APACHE II score, SOFA score, eGFR before admission or creatinine level prior to initiation of dialysis) significantly associated with the mortality rate.

5) What is the overall renal recovery rate in patients with AKI in HUSM.

6) What is the overall mortality rate in patients with AKI in HUSM.

3.4 Research hypothesis

1) Null hypothesis: There are no significant differences in renal recovery and morbidity among critically ill patient with acute kidney injury receiving SLEDD or SLEDD-f.

2) Alternative hypothesis: There are significant differences in renal recovery and morbidity among critically ill patients with acute kidney injury receiving SLEDD or SLEDD-f.

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CHAPTER FOUR

4.1 Study Design

This is a pilot randomized controlled study with intention to treat comparing patient with acute kidney injury (AKI) in critical care setting receiving SLEDD or SLEDD-f.

4.2 Study Period

Patients with AKI in critical care setting from 1st May 2014 until 1st October 2014 were randomly selected

4.3 Study Area

This study was conducted in critical care setting involving intensive care unit (ICU), coronary care unit (CCU) and medical high dependency unit (HDU) at Hospital Universiti Sains Malaysia (HUSM).

4.4 Reference Population

Patients with AKI in critical care setting at HUSM

4.5 Sampling frame

All patients with AKI based on Acute Kidney Injury Network(AKIN) 2 Staging that have fulfills eligibility criteria (inclusion and exclusion criteria) will be randomized to receive either SLEDD or SLEDD-f.

4.6 Eligibility Criteria

4.6.1 Inclusion criteria

i) Age 18 between 65 years

ii) Patients in critical care setting with acute kidney injury defined as AKI Stage 2(KDIGO 2012)

iii) Mean arterial pressure (MAP) > 70 mmHg prior to starting hemodialysis

iv) Patients or relatives agreeing for dialysis

4.6.2 Exclusion criteria

i) End stage renal disease patients

ii) Chronic Liver Disease with liver cirrhosis

iii) Chronic Hepatitis B/C

iv) Retroviral positive

v) Advanced malignancy (Stage III/IV)

vi) Chronic Heart Failure (Ejection fraction < 30%)

vii) Pregnancy

viii) Recent neurosurgery <6 weeks

viiii) Recent myocardial infarction (STEMI/NSTEMI) < 6 weeks

4.7 Sampling Method

All eligible patients in critical care setting with AKI were included in the study using convenient sampling and randomized to modalities of treatment.

4.8 Randomization

Randomization was done using coding envelopes which was assigned to either SLEDD or SLEDD-f. The envelopes will then be mixed up with no specific order by the hemodialysis staff nurse. Once patient has been identified the hemodialysis nurse in charge will select envelope on the most top and follow the instructions as per given in the envelope.

4.9 Sample size determination

As this is a pilot randomize control study there was no sample size calculation however for the purpose of future studies the calculated the sample size using G*Power software as follows.

<u>Statistical test used difference between two independent means (two groups)</u>

Tails – Two

Effect size d – 0.8

α err prob – 0.05

Power (1 – β err prob) - 0.80

Allocation ratio N2/N1 – 1

<u>Output parameters</u>