International Journal of Medicine and Pharmaceutical Science (IJMPS)
ISSN(P): 2250-0049; ISSN(E): 2321-0095
Vol. 6, Issue 4, Aug 2016, 17-26

ROLE OF CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT) IN SEPTIC ACUTE KIDNEY INJURY PATIENTS

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ABSTRACT

Background

The systemic inflammatory response syndrome (SIRS) and sepsis are complex syndromes resulting from an inciting insult that causes systemic inflammation, leading to widespread tissue injury mainly acute kidney injury AKI. It's an overwhelming inflammatory and coagulopathic response to a source of infection, usually from the lung or abdomen. If not recognized early, or not treated properly and aggressively, it is often a lethal outcome. Objectives: To determine the therapeutic efficacy and safety of continuous renal replacement therapy (CRRT) in the treatment of Patients with septic AKI.

Patients and Methods

This is cross sectional study were 43 patients with sepsis & acute kidney injury included and they were undergo management by using (CRRT plus conventional therapy) in intensive care unit (ICU) of Ghazi Al Hariri teaching hospital in a period from August 2014 to April 2015. Results : Our study showed that 23 out of 43 patients with septic AKI who were treated by continuous renal replacement therapy CRRT were improved and 20 patients were not get benefit of treatment (died).

Conclusions

CRRT is an important adjuvant to conventional treatment to reduce mortality in patients with septic AKI.

KEYWORDS: Sepsis, Acute Kidney Injury, Continuous Renal Replacement Therapy

Received: Jul 02, 2016; **Accepted:** Jul 29, 2016; **Published:** Aug 03, 2016; **Paper Id.:** IJMPSAUG20163

Original Article

INTRODUCTION

Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. [1] The American College of Chest Physicians and the Society of Critical Care Medicine determined the nomenclature for disorders related to sepsis. The following terms describe the progression of signs and symptoms of Systemic inflammatory response syndrome (SIRS): [2] characterized by Temperature >38 C or <36 C, Heart rate >90 beats/min, Respiratory rate >20 breaths/min or the need for mechanical ventilation, White blood cell count >12,000 cells/mm3 or <4000 cells/mm3.Sepsis which is defined as a suspected or documented source of

infection plus two or more SIRS criteria. Severe sepsis which is defined as sepsis with acute sepsis-induced organ dysfunction of one or more organ systems. Septic shock which is defined as a subset of severe sepsis syndrome in which the organ dysfunction is cardiovascular, that is, a subset of severe sepsis in which there is cardiovascular dysfunction. Specifically, sepsis-induced hypotension (mean arterial pressure [MAP] <65 mm Hg) that persists despite adequate and aggressive volume resuscitation. Patients will often require vasopressors to keep MAP _65 mm Hg. Multiple organ dysfunction syndrome (MODS): Failure in more than one organ system that requires acute intervention. Once the patient reaches this degree of illness, the chances of making a meaningful recovery can often be quite low. [3] Sepsis, a commonly encountered scenario in an intensive care unit (ICU), often leads to multi-organ dysfunction and the kidney is one of the organs frequently afflicted. Acute kidney injury (AKI) occurs in about 19% patients with moderate sepsis, 23% with severe sepsis and 51% with septic shock, when blood cultures are positive. [4] Continuous Renal Replacement Therapy which is can be defined as any extracorporeal blood purification therapy intended to substitute for impaired renal function over an extended period of time and applied for or aimed at being applied for 24 hours/day.[5] Blood can be purified by running it in an extracorporeal circuit through a device (membrane, sorbent) where solute (uremic toxins, cytokines) and fluid can be removed. In patients with sepsis it may help in two ways: renal replacement therapy and removal of inflammatory mediators, to achieve immune homeostasis. The indications for commencing renal replacement therapy (RRT) in sepsis-induced AKI are by and large similar to other forms of AKI. They are in followings: worsening azotemia, refractory volume overload, severe metabolic acidosis, uremic encephalopathy and severe electrolyte disarray.[6]In patients with sepsis, sustained oliguria or severe metabolic acidosis may be reason enough to start RRT as these patients often do not manifest signs of azotemia. [7] Some also advocate starting continuous renal replacement therapy (CRRT) early, for immunomodulation. The potential benefits include: better fluid management, temperature control, acid - base-electrolyte control, provision of adequate nutrition, cardiac support, protective lung support, brain protection with preservation of cerebral perfusion and decrease of intracranial pressure, bone marrow protection, blood detoxification and liver support. [6,7]

The goal of our study that to analyze the role of continuous renal replacement therapy in septic acute kidney injury patients.

METHODS

A cross sectional study conducted in intensive care unit of Ghazi Al-Hariri Teaching Hospital in medical city teaching complex, in a period from August 2014 to April 2016.The study has been approved by Scientific Council of Anesthesia and Intensive Care / Arabic Board.This study include patients with sepsis induced acute kidney injury were need to be managed by continuous renal replacement therapy CRRT.

We include all patients with full blown picture of sepsis and acute kidney injury.

An exclusion criteria include pediatric aged group, all patients were intubated and on mechanical ventilation .

As a part of the system for managing such cases, Every patient admitted to this unit a complete work up of full investigations including the renal indices, while blood cells (WBC), C- reactive protein, temperature, and proper monitoring including blood pressure & heart rate were done and taken as parameter guidelines for our study pre & post CRRT utilization.

Modality of Treatment

- Continuous renal replacement therapy CRRT in form of Continuous veno-venous hemodifiltration modality with dual predilution (prefilter) and postdilution (postfilter).
- Using AN69 high flux hemofilter for at least 3 days treatment therapy in intensive care unit with total effluent dose 35ml/k/hr. It was initiated within 24 hours after diagnosis established.
- Substitution fluid and dialysate using readymade pack with fixed concentration of electrolytes as prismasol 2,prismasol 4 and phoxilium.
- Prismaflex machine of Gambro/Baxter Sweden/American Company of medical care.

Proper monitoring and required investigation were done to all patients, the required data were collected and studied to assess the effectiveness of CRRT to such patients.

Statistical Analysis

The Statistical Package for Social Science (SPSS) version 20 was used for data entry and analysis. Graphs and tables were used to describe the data and suitable statistical tests were used according to the nature of data, where Independent student T and ANOVA test were used for analyses of continuous variables as well as Chi-Square test and Fisher's Exact Probability test were used to test association between dependent and independent variables in addition correlation test was also used P value < 0.05 was considered significant.

RESULTS

The results showed that 23 out of 43 patients with renal impairment and sepsis who were treated by CRRT dialyses were improved and 20 patients were not get benefit of treatment (died), also the results showed that the mean age of not improved patients was significantly higher than that of improved group (56.1 years±6.2 SD, 47.3 years±7.1 SD) respectively.

Our finding reported no significant association with regard to the sex of the patients between improved and not improved patients, where the females represented 56.2% and males represented 45.5% of improved patients and 43.8%, 54.5% of non-improved respectively(p=0.3) as seen in table 1.

Table 1: Sex Distribution of the Patients

			Groups		P-Value
			Improved(n=23)	Not-Improved(n=20)	
Sex	Female	Count	18	14	0.3
		% within gen	56.2%	43.8%	
	Male	Count	5	6	
		% within gen	45.5%	54.5%	

The results of this study showed that the mean value of all studied parameters of improved patients significantly decreased with time, where on analyses of data by ANOVA test, the results showed significant difference among the days of treatment regarding the mean value of all tested parameters and the significant difference was noted between first day and third day of treatment of some parameters by LSD test as seen in table 2

Table 2: Mean of Studied Parameters with Time Sequence of Improved Patients

Studied Parameters		N	Mean	Std. Deviation	95% Confidence Interval for Mean		p-Value
					Lower Bound	Upper Bound	
Blood urea mg/dl	Day1	23	140.4	51.9	118.0	162.9	0.001
	Day2	23	94.8	32.1	80.9	108.7	
	Day3	23	49.2	13.6	43.3	55.1	
Serum creatinine mg/dl	Day1	23	4.1	1.2	3.6	4.7	0.001
	Day2	23	2.7	0.8	2.4	3.1	
	Day3	23	1.5	0.3	1.3	1.6	
Temperature/c	Day1	23	38.3	1.3	37.8	38.9	0.03
	Day2	23	38.0	1.0	37.5	38.4	
	Day3	23	37.5	0.7	37.2	37.8	
WBC	Day 1	23	16.0	9.2	12.0	20.0	0.04
	Day 2	23	12.9	7.4	9.7	16.2	
	Day 3	23	10.4	6.1	7.7	13.0	
CRP	Day1	23	115.0	18.7	106.9	123.1	0.001
	Day2	23	46.1	17.7	38.4	53.8	
	Day3	23	32.1	9.5	28.0	36.3	
Pulse rate	Day 1	23	100.3	9.5	96.2	104.4	0.001
	Day 2	23	85.9	6.5	83.1	88.7	
	Day 3	23	77.9	4.7	75.8	79.9	

On further analyses of data of improved patients according to the age and the sex of the patients, the results showed that there was no effect with regards to age or sex of the patients on the results of analyses and the same significant difference was reported for all tested parameters($p \leq 0.05$) as seen in table 3.

Table 3: Mean of Studied Parameters of Improved Patients According to Age Category

			Mean	Std. Deviation	95% Confidence Interval for Mean		p-Value
≤40 years N=13	Blood urea	day 1	131.7	60.2	95.3	168.1	0.001
		day 2	94.6	31.0	75.93	113.45	
		day 3	47.6	12.0	40.5	54.88	
	S.creatinine	day 1	3.9	1.5	3.8	4.891	0.001
		day 2	2.8	0.8	2.3	3.2	
		day 3	1.4	0.3	1.2	1.6	
	Temperature	day 1	38.3	1.49	37.3	39.2	0.04
		day 2	37.5	1.1	36.8	38.2	
		day 3	37.1	0.7	36.8	37.7	
	WBC	day 1	19.3	10.4	13.0	25.6	0.01
		day 2	15.1	8.1	10.7	20.9	
		day 3	12.1	7.3	8.1	16.9	
	CRP	day 1	110.0	20.4	97.6	122.3	0.001
		day 2	50.2	19.0	38.7	61.7	
		day 3	33.6	10.8	27.1	40.2	
	Pulse rate	day 1	99.6	7.9	94.8	104.5	0.001
		day 2	85.6	5.0	82.5	88.6	
		day 3	77.3	3.4	75.2	79.4	
>40 years N=10	Blood urea	day 1	151.8	38.8	124.0	179.	0.001
		day 2	95.0	35.2	69.7	120.2	
		day 3	51.3	15.9	39.2	62.6	
	S.creatinine	day 1	4.3	0.9	3.7	5.05	0.002
		day 2	2.7	0.9	2.0	3.3	
		day 3	1.6	.3	1.4	1.8	
	Temperature	day 1	38.5	1.1	37.7	39.4	0.03

		day 2	38.6	.5	38.2	39.2	
		day 3	37.8	.6	37.4	38.7	
	WBC	day 1	11.6	5.0	8.0	15.1	0.01
		day 2	9.4	4.7	6.0	12.8	
		day 3	7.6	2.2	6.0	9.4	
	CRP	day 1	121.6	14.8	110.8	132.2	0.001
		day 2	40.9	15.1	30.0	51.7	
		day 3	30.2	7.6	24.7	35.7	
	Pulse rate	day 1	101.2	11.7	92.8	109.9	0.001
		day 2	86.3	8.3	80.3	92.9	
		day 3	78.7	6.2	74.2	83.5	

The p-value is a function of the observed sample results (a test statistic) relative to a statistical model, which measures how extreme the observation is. The p-value is the probability that the observed result has nothing to do with what one is actually testing for. Specifically, the p-value is defined as the probability of obtaining a result equal to or "more extreme" than what was actually observed, assuming that the model is true

- A small p-value (≤ 0.05) indicates strong evidence against the null hypothesis, so it is rejected.
- A large p-value (> 0.05) indicates weak evidence against the null hypothesis (fail to reject).
- p-values very close to the cutoff (~ 0.05) are considered to be marginal (need attention).

The results of our study revealed where was direct correlation between all tested parameters, where when one parameter decreased the other also decreased and the significant correlation was noted between blood urea and s.creatinine,WBC,CRP and pulse rate(p=0.001 for all)R=(0.6,0.3,0.6 and 0.5)respectively also between S.creatinine and CRP(P=0.001,R=0.7) and S.creatinine and pulse rate(p=0.001,R=0.6),in addition between WBC and pulse rate(p=0.002,R=0.4) and CRP and pulse rate(p=0.001,R=7) as seen in table 4

Table 4: Correlation among Studied Parameters of Improved Patients

		Blood Urea	S. Creatinine	Temperature	WBC	CRP	Pulse Rate
Blood urea	Pearson Correlation	1	0.6	.1	0.3	0.7	0.5
	Sig. (2-tailed)		0.001	0.2	0.01	0.001	0.001
S.creatinine	Pearson Correlation	0.6	1	.219	0.3	0.7	0.6
	Sig. (2-tailed)	0.001		.07	0.01	0.001	0.001
Temperature	Pearson Correlation	0.1	0.2	1	0.04	0.2	0.2
	Sig. (2-tailed)	0.2	0.07		0.7	0.02	0.09
WBC	Pearson Correlation	0.3	0.3	0.04	1	0.3	0.4
	Sig. (2-tailed)	0.01	0.01	0.7		0.01	0.002
CRP	Pearson Correlation	0.7	0.7	0.2	0.3	1	0.7
	Sig. (2-tailed)	0.001	0.001	0.02	0.01		0.001
Pulse rate	Pearson Correlation	0.5	0.7	0.2	0.4	0.7	1
	Sig. (2-tailed)	0.001	0.001	.09	0.002	0.001	

The results of this study reported that the percentage of change of tested parameters between the first and third day of treatment was differed and the highest percentage of change was reported with CRP, temperature and PR (96%, 92% and 91%) respectively as seen in table 5

Table 5: Percentage of Change of Studied Parameters of Improved Patients between First and Third Day of Treatment

% of Change	N	Minimum%	Maximum%	Mean%	Std. Deviation
Blood urea	23	18	77	39.8	14.6
S.creatinine	23	22	58	39.2	11.3
Temp	23	81	92	96.6	3.6
WBC	23	30	88	65.3	16.5
CRP	23	2	96	72.4	20.9
PR	23	84	91	91.1	4.2

Our finding demonstrated that 2 out of 20 patients who were not improved were died on the second day and 13 of them on third day, also the finding revealed that mean value of blood urea increased slightly, other variables changed slightly with time as seen in table 6

Table 6: Mean of Studied Variables of Non- Improved Patients with Time Sequence

		N	Minimum	Maximum	Mean	Std. Deviation
First day	urea	20	34.0	350.0	177.7	103.6
	creatinine	20	2.0	4.6	3.4	0.7
	temp	20	32.0	40.1	36.3	1.9
	wbc	20	9.0	16.7	12.8	1.7
	CPR	20	114.0	122.0	116.9	3.2
	Pulserate	20	80.0	130.0	105.	13.7
Second day	urea	18	50.00	350.0	180.7	84.5
	creatinine	18	2.00	4.30	3.1	0.7
	temp	18	35.00	40.	36.9	1.6
	wbc	18	7.00	16.70	11.9.	2.2
	CPR	18	90.00	122.0	112.6	8.3
	Pulserate	18	84.00	130.0	107.	12.7
Third day	urea	7	120.0	260.0	185.0	51.0
	creatinine	7	3.00	4.30	2.9	0.3
	temp	7	34.00	39.10	37.0	2.0
	wbc	7	8.00	12.0	10.3	1.4
	CPR	7	90.00	105.0	99.8	4.5
	Pulse rate	7	88.00	110.0	95.	7.8

The results of present study revealed that the majority of improved patients have no co morbid illness (87%).only 8% have had hypertension, and 4.3% complain of diabetes mellitus disease, while 45% of those who were not respond to the treatment have had hypertension and diabetes mellitus and 25% had hypertension, diabetes mellitus and ischemic heart disease, just 2% of patients were free from co-morbid illness as seen in table 7.

Table 7: Comorbidity of Improved and Non-Improved Patients

		Co-Morbid Illness									
		NO Co-Morbid Illness		HT		DM		HT,DM		HT,DM,IHD	
		Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %
Patients statues	Not improved (Died) (n=20)	2	10.0%	1	5.0%	3	15.0%	9	45.0%	5	25.0%
	Improved (n=23)	20	87.0%	2	8.7%	1	4.3%	0	0.0%	0	0.0%

HT=hypertension, DM=diabetes mellitus, IHD=ischemic heart disease.

DISCUSSIONS

This observational study that patients septic AKI who were treated by CRRT prismaflex machine in form of continous venovenous hemodiafilteration (CVVHDF) which is new extracorporeal therapies are being designed to provide supportive treatment beyond the classic renal indications in sepsis and AKI patients. The study show that 23 out of 43 patients septic AKI who were treated by CRRT improved and 20 patients who treated of same modality of CVVHDF were not get benefit of treatment (died) .Overall observations there were statistically significant improvement in renal indices as blood urea and serum creatinine from day one of starting CVVHDF modality of CRRT to the day three (p value for both was 0.001).This indicates better short term renal recovery in improved group because of convective and diffusive property of CRRT for removal of small molecular weight uremic toxins.This consistent with Jacka et al study [8] that showed the renal recovery was significantly more frequent among patients initially treated with CRRT (21/24 vs 5/14, P = 0.0003).

Also there were statistically significant improvement in systemic inflammatory mediators as C reactive protein, and white blood cell counts in addition to resolution of tachycardia and fever from day1 to day 3 in intensive care unit of starting CVVHDF modality of (p value = 0.3,0.001,0.001, 0.04 respectively). This consistent with Wang et al study [9] that show significant decrease of CRP in CRRT treated group (P value less than 0.01).This could be explained by the extracorporeal removal of circulating toxic mediators using high permeability haemofiltration, and coupled plasma filtration with adsorption [10].

On analyses of data of improved patients according to the age and the sex of the patients, the results showed that there was no effect with regards to age or sex of the patients on the results of analyses and the same significant difference was reported for all tested parameters $p \leq 0.05$.

This study also revealed that direct correlation between all tested parameters, where when one parameter decreased the other also decreased and the significant correlation was noted between blood urea and s.creatinine, WBC, CRP and pulse rate (p=0.001 for all) R=(0.6,0.3,0.6 and 0.5) respectively also between S.creatinine and CRP (P=0.001,R=0.7) and S.creatinine and pulse rate(p=0.001,R=0.6),in addition between WBC and pulse rate (p=0.002,R=0.4) and CRP and pulse rate (p=0.001,R=0.7). That could explained by directed relationship with acute kidney injury and systemic inflammatory response with pro-inflammatory cytokines and sepsis itself in critical care patients [24.[

Also the study reported that the percentage of change of tested parameters between the first and third day of treatment was difference and the highest percentage of change was reported with CRP, temperature and PR (96%, 92% and 91% respectively).

The results of present study revealed that the majority of improved patients have no co morbid illness (87%). The only 8% have had hypertension, and 4.3% complain of diabetes mellitus disease, while 45% of those who were not respond to the treatment have had hypertension and diabetes mellitus and 25% had hypertension, diabetes mellitus and ischemic heart disease, just 2% of patients were free from co-morbid illness.

CONCLUSIONS

- Early initiation of CRRT in modality form of CVVHDF had better short term renal recovery
- Significant improvement in systemic inflammatory mediators as, C reactive protein, and white blood cell counts in addition to resolution of tachycardia and fever when using CVVHDF modality.
- Our study show CRRT is safe & effective in decreasing mortality rate

ACKNOWLEDGEMENTS

Our great thanks to all staffs in the Department of Intensive Care, Ghazi Al-Hariri Teaching Hospital, Medical City Teaching Complex, Baghdad, Iraq. Then, last but not least, thanks for every one support us in this work.

DISCLOSURES

There is no disclosure.

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