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Original Article

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Daily Versus Conventional Dialysis for COVID-19 Patients: A Randomized Controlled Trial

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Abstract

Background: Hemodialysis patients have high mortality and morbidity in COVID-19 due to different causes, thus the current study evaluates the difference between the effect of conventional and daily hemodialysis on mortality in End-Stage Renal Disease (ESRD) patients with COVID-19.

Methods: This study was designed as a single-center, parallel, randomized and un-blinded clinical trial that chronic hemodialysis patients with confirmed COVID-19 infection enrolled. The study group was dialyzed daily for a week and the control group was on three sessions per week of dialysis. The primary outcome was estimation of mortality rate and secondary outcome was considered as ICU admission rate during hospitalization.

Results: A total of 47 patients with the diagnosis of ESRD were included. The mean age of the included patients was 57.1±14.2 years in daily hemodialysis and 58.8±17.4 years in the conventional hemodialysis, and 36(76.6%) were male. From the 47 included patients, 18(38.3%) were admitted to the ICU, and 12(25.5%) were deceased during their hospital stay. The prevalence of the two main outcomes of the study, ICU admission and mortality, was not different between the two groups of the study.

Conclusion: In this study, daily hemodialysis was beneficial in reducing mortality in COVID-19 infected patients, but this difference was not statistically significant. Studies with higher sample sizes may show this difference significantly.

Keywords: COVID-19, Renal dialysis, Renal insufficiency

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Introduction

The COVID-19 virus first emerged from Wuhan in 2019 and then became a global pandemic that, by May 2022, had more than 500 million documented cases and left more than 6 million deaths. One of the high-risk populations for COVID-19 is patients with Chronic Kidney Disease (CKD) and End Stage Renal Disease (ESRD). They have higher mortality and morbidity due to various causes, such as a higher prevalence of diabetes, hypertension, cardiovascular disease, and immune insufficiency due to uremia (1). The most common cause of mortality in hemodialysis patients is cardiovascular disease and inadequate dialysis (2). Three times a week, is a standard hemodialysis method. A rationale for this hemodialysis is the combination of physiological experiments, patient acceptance, feasibility, logistics, and costs (3).

Despite all the advancement in management of ESRD patients, the mortality rate was reported up to 47% (4). However, studies have shown that the mortality rate of patients in daily hemodialysis is less than the conventional ones (5). Therefore, the present study was conducted in two groups of patients with conventional three times a week hemodialysis and daily hemodialysis to evaluate the efficacy of daily hemodialysis in reducing mortality, ICU hospitalization, and inflammatory factors.

Materials and Methods

Study design

This study was designed as a single-center, parallel, randomized, and un-blinded clinical trial conducted in Masih Daneshvari Hospital -a teaching hospital-, Tehran, Iran. The study was approved by ethics committee of Shahid-Beheshti University of Medical Sciences (SBMU), Tehran, Iran. The trial is registered at clinicaltrials.gov with identifier: NCT05212675.

Patients

In this study, chronic hemodialysis patients with confirmed COVID-19 infection based on positive nasopharyngeal real-Time Reverse Transcription-Polymerase Chain Reaction (rRT-PCR) assay from May 2021to September 2021 were included. Criteria for selecting the subjects were age>18 years, over three months on dialysis, and willingness to participate in the study. Informed consent was obtained from all the patients before enrollment on the study.

Study groups

The study group was dialyzed daily for a week (2 hours per session and UF rate of 300 *ml/hour* for seven days), and the control group was on three sessions per week of dialysis (4 hours per session, UF rate of 400 *ml/hour*). Lab tests including bun, electrolytes, and VBG were checked daily from the patients, and in case of electrolyte disorders including hypokalemia, the patients were given drug treatment. Also, in daily hemodialysis, the amount of ultrafiltration was considered lower than conventional, and the time of hemodialysis was reduced to two hours daily to minimize the mentioned side effects.

Data collection

All the data was extracted using research-made checklist from medical records by a trained medical staff. The research-made checklist included the demographic and clinical information such as underlying diseases, medication history, vital signs on admission, laboratory data during first 24 hours after admission and echocardiography results during hospitalization.

Randomization

The patients were randomly allocated to intervention and control groups using an electronic platform with allocation ratio of 1:1. Patients' random allocation in two groups was done using simple randomization method and generating the random numbers using Excel software functions.

Sample size

We designed this study as a pilot and considered 30 patients in each group based on expert opinion and total number of eligible patients. Finally, 47 patients with informed consent and eligibility of inclusion criteria were recruited and randomly assigned to two groups.

Outcomes

The primary outcome was estimation of mortality rate and secondary outcome considered as ICU admission rate during hospitalization.

Statistical analysis

In this study, normality of continuous variables was assessed using Shapiro-Wilk test and Q-Q plot. Continuous variables with normal and skewed distributions were expressed as mean ±SD (standard deviation) and median and interquartile range (IQR: 25th and 75th percentile), respectively. Baseline data regarding the categorical variables are presented as frequency (percentages). For comparing the mean of continuous variables between two groups student's

Table 1. Patient's baseline demographics and related clinical characteristics

Characteristics		Daily dialysis (n=22)	Conventional dialysis (n=25)	p-value
Age, year		57.1±14.2①	58.8±17.4	0.731
Gender, male (%)		18(81.8)	18(72.0)	0.428
Diabetes mellitus (%)		13(59.1)	10(40.0)	0.191
History of heart failure (%)		9(40.9)	5(20.0)	0.118
Medication history	Angiotensin receptor blocker (%)	14(63.6)	14(56.0)	0.595
	Atorvastatin (%)	19(86.4)	17(68.0)	0.138
	Aspirin (%)	14(66.7)	21(84.0)	0.170
Vital signs on admission	Systolic blood pressure (*mmHg*)	134.4±29.2	138.6±19.1	0.570
	Diastolic blood pressure (*mmHg*)	74.5±15.3	78.6±8.3	0.278
	Heart rate (beats/min)	86.7±13.3	84.5±8.4	0.507
	O_2 saturation	87.50±7.01	88.72±4.92	0.097
	Respiratory rate (breath/min)	22.1±5.2	23.0±3.7	0.491
	Fever (>37^0C)	9(40.9)	5(20.0)	0.118
Laboratory parameters	WBC	7450(4700-9675)②	7200(5300-9050)	0.966
	Lymph	690(545-1025)	940(850-1150)	0.024
	Hb	10.0±1.9	10.2±1.6	0.630
	Plt	141000(118000-200500)	166000(131000-191000)	0.586
	Alb	3.2±0.5	3.1±0.5	0.587
	LDH	555(463.7-687.7)	560(375.5-832)	0.915
	CPK	134(85.5-300)	102(46-295)	0.360
	Ca	7.8±0.6	7.8±0.9	0.986
	P	5.3±2.1	5.5±1.2	0.768
	Ferritin	1084(800-1380)	702(518.2-1025)	0.011
	25-OH Vit D	14(10.5-19)	20(15-22)	0.044
	Iron	44.9±18.6	43.1±16.7	0.769
	IL6	12(8-16.2)	21(8.5-55.2)	0.117
	D-dimer	950(750-2658.5)	662(460-1470)	0.134
	CRP (*mg/dL*)	32.0±17.0	34.7±13.4	0.556
	ESR (*sec*)	78.3±32.9	52.5±18.6	0.003
	Positive Troponin	6(27.3)	8(34.8)	0.586

1. Mean±SD (Standard deviation)
2. Median and interquartile range

t-test or Mann-Whitney U test was used. Also, for comparing the categorical variables between groups were used from chi-squared or Fisher's exact test was used.

Moreover, logistic regression models were used to evaluate associations between patient characteristics and study's outcomes. Statistical analysis was carried out using the SPSS 20.0 software (IBM Corp., Armonk, NY, USA). The significance level was set at $p< 0.05$. All the methods were carried out in accordance with the relevant guidelines and regulations.

Results

In this clinical trial, a total of 47 patients with the diagnosis of ESRD were included. The mean age of the included patients was 58.00±15.87 years, and 36 (76.6%) were male. Diabetes was reported in 23 (48.9 %) patients, and 14 (29.8%) had a history of heart failure with reduced ejection fraction. Considering the baseline demographics and clinical characteristics (Table 1), no significant differences were observed. Laboratory data revealed that patients on daily dialysis had lower lymphocyte count compared to the

Table 2. Outcomes of the included patients

Outcome	Daily dialysis (n=22)	3 times weekly dialysis (n=25)	p-value
ICU admission (%)	9(40.9)	9(36.0)	0.730
Mortality (%)	5(22.7)	7(28.0)	0.679

Table 3. Patient's characteristic according to ICU admission

Patient characteristics	Not admitted to ICU (n=29)	Admitted to ICU (n=18)	p-value
Age, year	57.9±13.8	58.1±19.1	0.970
Gender, male (%)	23(79.3)	13(72.2)	0.726
Diabetes mellitus (%)	13(44.8)	10(55.6)	0.474
EF<40% (%)	6(21.7)	9(50)	0.036
Tachy/Brady arrhythmia (%)	11(37.9)	13(72.2)	0.022
3 time a week dialysis (%)	16(55.2)	9(50.0)	0.730
WBC	7300(5350-9325)	6650(4275-10050)	0.654
Lymph	860(600-1200)	895.5(600-1025)	0.983
LDH	520(449-640.5)	753(487.5-900.5)	0.039
Ferritin	850(541-1200)	1000(748-1435)	0.267
25-OH Vit D	20(14-25)	13(7.5-18)	0.017
IL-6	12(8-24)	16.2(9.5-26.5)	0.347
D-dimer	662(460-1200)	1335(800-2858.5)	0.010
CRP (*mg/dL*)	29.0±14.0	39.9±14.8	0.017
ESR	62.7±31.8	68.1±24.9	0.562
Troponin	6(22.2)	8(44.4)	0.115

Table 4. Logistic regression analysis of predictors of ICU admission and mortality

Variables	Univariable OR (%95 CI)	p-value	Multivariable OR (%95 CI)	p-value
ICU admission				
Dialysis program	1.23(0.38-4.0)	0.730		
Age, year	1.00(0.96-1.04)	0.970		
Gender	1.47(0.37-5.79)	0.578		
EF<40%	0.26(0.07-0.95)	0.041	0.2(0.03-3.85)	0.373
Tachy-, Brady arrhythmia	4.25(1.19-15.23)	0.026	2.42(0.16-36.88)	0.525
LDH	1.00(1.00-1.01)	0.034	1.00(1.00-1.01)	0.054
25-OH Vit D	0.83(0.71-0.98)	0.027	0.85(0.65-1.11)	0.235
D-dimer	1.00(1.00-1.00)	0.042	1.00(0.99-1.00)	0.357
CRP	1.05(1.01-1.10)	0.024	1.09(0.97-1.22)	0.155
Mortality				
D-dimer	1.00(1.00-1.00)	0.025	1.00(0.99-1.00)	0.081
CRP	0.93(0.89-0.98)	0.012	0.94(0.89-1.00)	0.052

other group (p=0.024). Furthermore, higher ferritin level and ESR were observed in daily dialysis group (p=0.011, p=0.044, respectively). Besides, lower serum 25-OH Vit D levels were observed in the daily dialysis group (p=0.044). There were no significant differences between the groups regarding other laboratory markers.

From the 47 included patients, 18 (38.3%) were admitted to the ICU, and 12 (25.5%) were deceased during their hospital stay. The prevalence of the two main outcomes of the study, ICU admission and mortality, was not different between the two groups of the study (Table 2). Regarding the patients admitted to the ICU, the prevalence of baseline low EF (*i.e.*<40%) and tachy or brady arrhythmia were significantly higher (p=0.036 and p=0.022, respectively). Furthermore, higher baseline inflammatory markers, including LDH, D-dimer, and CRP were observed in daily dialysis group. Table 3 represents the clinical characteristics of the patients based on admission to ICU.

Non-survivors had a higher level of IL-6, D-dimer, and CRP at baseline (p=0.018, p=0.008, p=0.006, respectively). Other parameters were the same between the two groups.

Based on the logistic regression model, associated factors to ICU admission and mortality were examined. The results of the logistic regression model are represented in table 4. The univariable analysis demonstrated the association of the factors including EF<40%, tachy-, Brady arrhythmia, LDH, 25-OH Vitamin D, D-dimer, and CRP to ICU admission. In the multivariable analysis, no significant association was observed between any of the factors and outcomes.

Discussion

As of April 2022, over 6 million deaths from COVID-19 were reported, which is 1.22% of the total population mortality compared to all the Covid 19 cases. In the current study, 12 out of 47 patients died, which is equal to 25.5%, indicating a higher mortality of COVID-19 in patients with CKD undergoing hemodialysis as in a review study of 125 articles, the mortality rate of COVID-19 in hemodialysis patients was reported to be up to 47% (4). To our knowledge, this is the first study comparing the COVID-19 clinical outcomes in patients with daily and conventional hemodialysis. Cardiovascular disease and infections are associated with altered immune responses that

cause a high prevalence of morbidity and mortality and generate 70% of deaths in patients with chronic kidney disease. The inability of the immune system to respond generally in these patients predisposes them to infections and a reduced response to vaccines, as well as increasing the production of inflammatory cytokines and decreasing their renal clearance (6).

In this study, it was found that patients who received daily dialysis had a lower mortality rate than dialysis three times a week. Although the daily hemodialysis group showed more severe COVID-19 involvement, the mortality was lower than conventional hemodialysis, albeit by a nonsignificant percentage (p-value=0.679). Further studies with more sample size may show a significant difference. In a survey by Ayus *et al*, the effects of daily and conventional hemodialysis on inflammatory factors and left ventricular hypertrophy were performed. Improved fluid volume management and reductions in the left ventricular mass index and inflammatory markers, as well as urea reduction ratio and calcium × phosphorus, which seems that daily hemodialysis can reduce morbidity and mortality in the patients (7).

A comparison of daily and conventional hemodialysis has been studied in ESRD patients. Patients with daily hemodialysis had two to three times less mortality than hemodialysis three times a week, which may be due to less fluctuation in body chemistry and fluid volume. Fluid overload, blood pressure, and left ventricular hypertrophy decrease, and levels of brain natriuretic peptide normalize; pulmonary fluid overload disappears, and cardiac ejection fraction increases. Also, daily hemodialysis improves with metabolic markers that increase mortality, such as high homocysteine, dyslipidemia, hypoalbuminemia, and vascular calcification (5).

Previous studies have concluded that low levels of vitamin D, as well as high levels of D-Dimer and ferritin, lead to an increase in ICU admission and mortality rate (8,9). In the present study, levels of vitamin D, ESR, ferritin, and D-Dimer were higher in daily hemodialysis patients. Despite randomization, the patients appeared to have more inflammation and worse prognosis than patients with hemodialysis three times a week. The rate of ICU admission in patients on daily hemodialysis was also higher than those on conventional method (40.9 *vs.* 36%). This seems to be the reason for the lack of statistical significance of mortality between the two groups and it seems that daily hemodialysis has been able to be effective in improving patients.

Among the hemodialysis patients with COVID-19, 38% were admitted to the ICU and had a worse cardiovascular status than those admitted to the ward, with significantly lower ejection fraction, higher rate of tachycardia and bradycardia, positive D-Dimer and positive troponin. This indicates that the cardiovascular conditions of these patients were worse than patients admitted to the ward. As an acute-phase protein, CRP is commonly known as a systemic inflammatory phase reactor and is used as a predictor of COVID-19 progression. High levels of CRP are associated with the overproduction of inflammatory cytokines, especially in ICU patients. IL6- is also used as a biomarker for disease progression and response to treatment in patients, which has a higher level in ICU patients such as CRP, and an increase in LDH indicates the destruction of tissue and cells (10). In this study, inflammatory factors that increase due to COVID-19, such as CRP and LDH, were significantly higher in patients admitted to the ICU, and other inflammatory factors such as ferritin, ESR, and IL-6 were higher in these patients but not statically significant.

In a study conducted by Sevinc *et al*, hemodialysis patients with COVID-19 were compared between two groups of patients admitted to the ward and ICU that congestive heart failure in patients admitted to the ICU had a higher incidence but was not statistically significant, while D-Dimer was significantly higher in the ICU patients. LDH, CRP, and ferritin were also significantly higher in the ICU patients (11).

Regarding mortality outcomes, similar ICU outcomes were obtained for inflammatory factors such as LDH, CRP, IL-6, and D-Dimer, which were statistically significantly higher in the group hospitalized in ICU, which is due to the higher severity of the disease. In another study, 123 hemodialysis patients with COVID-19 were compared into the two groups; the dead and the survivors. Inflammatory factors such as LDH, CRP, and ferritin were significantly higher in the group of the dead. D-Dimer was also statistically significantly higher in the deceased group (12).

Conclusion

In our study, daily hemodialysis was beneficial in reducing mortality in COVID-19 infected patients, but this difference was not statistically significant. Studies with higher sample sizes may show this difference significantly.

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Conflict of Interest

There was no conflict of interest in this manuscript.

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