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Effect of vaccination on clinical outcomes in COVID-19 positive chronic kidney disease patients on haemodialysis

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19) resulted in high mortality worldwide, with significantly higher mortality among patients with comorbidities including chronic kidney disease (CKD). Vaccines were developed against COVID-19 and it was given emergency approval because of the associated high mortality. There are only few studies on the efficacy of vaccine in CKD patients on haemodialysis. Effect of vaccination on clinical outcomes in COVID-19 positive CKD patients on haemodialysis was studied.

Materials and methods: In this retrospective study on CKD patients on haemodialysis with confirmed COVID-19 infection, comparison was done on the clinical outcomes between the vaccinated and unvaccinated population.

Results: Of the 104 patients, 74 patients were vaccinated against COVID-19 and 30 were unvaccinated. The study population received either covishield (50) or covaxin (24) which were the approved vaccines in India at that time. Among the vaccinated group 15 (20%) needed invasive mechanical ventilation and 16 (53%) in the unvaccinated group (P value 0.001). There were 16 (22%) deaths in the vaccinated group and 15 (50%) in the unvaccinated group with a significantly higher mortality in the unvaccinated group (P value 0.005). 11 (21%) patients on covishiled and 4 (18%) on covaxin needed invasive mechanical ventilation and there were 12 (24%) deaths in the covishield group and 4 (18%) in covaxin group.

Conclusion: Severity of disease and mortality is less in vaccinated CKD patients on haemodialysis compared to unvaccinated reiterating the importance of vaccination against COVID-19 in high risk patients.

Keywords: COVID-19; vaccine; chronic kidney disease; haemodialysis; inflammatory markers; mechanical ventilation

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), accounted for more than 6.5 million deaths worldwide, since it was first identified in Wuhan, China in December 2019 [1].

Patients with comorbidities like systemic hypertension, diabetes mellitus, chronic kidney disease (CKD) are more likely to develop severe disease, increased hospitalisations, intensive care unit (ICU) admissions and death due to COVID-19.

Mortality among CKD patients with COVID-19 infection is significantly higher when compared to CKD patients without COVID-19 [2]. Many CKD patients have other comorbidities including diabetes mellitus, systemic hypertension, coronary artery disease (CAD) which are all independent risk factors associated with increased severity of the disease and mortality [3, 4].

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In addition to the above risk factors due to the underlying disease, the patients on haemodialysis have to travel to receive dialysis care three times per week at hospitals or community-based dialysis centres. This further increases the risk of exposure to infection from these centres, where social distancing maybe difficult.

With no definite treatment available and associated high morbidity and mortality, vaccine was proposed as the only way to control COVID-19. So, there was rapid development of various vaccines and emergency approval for use was given for these vaccines.

Indian drug regulator gave authorisation for emergency use for two vaccines in India namely covishield (ChAdOx1 nCoV-19)- a recombinant, non replicating adenovirus vector carrying recombinant spike protein of SARS-CoV-2 and covaxin (BBV152)- inactivated whole virion vaccine.

Efficiency of vaccines are measured in terms of reduced infection rate, protection against severe disease and death. Varying success rates were claimed by various approved vaccines worldwide. Efficacy of single dose covishield vaccine is 76% and it is 62-67% after two doses [5]. An early interim analysis showed a reduction in hospitalisation by 91% for Pfizer vaccine and 88% for Astra Zeneca vaccine [6]. Immunisation is recommended for all immunosuppressed individuals including those with CKD.

The immune response to COVID-19 vaccine is less adequate in CKD patients compared to general population and so the efficacy of the vaccine is doubtful in this group of patients [7].

Data regarding the efficacy of COVID-19 vaccine in patients with CKD is limited especially in CKD patients undergoing haemodialysis. This study is intended to compare the course of the disease and its clinical outcome between vaccinated and unvaccinated CKD patients on maintenance haemodialysis with COVID-19 infection.

Effect of vaccination on clinical outcomes in COVID -19 positive end stage renal disease patients on maintenance haemodialysis was studied.

Materials and methods

Study design

Retrospective observational study on end stage renal disease patients on haemodialysis with a confirmed COVID-19 infection. The diagnosis of COVID-19 in subjects was confirmed based on the following criteria: identification of SARS-CoV-2 by reverse transcription-polymerase chain reaction (RTPCR), rapid antigen test, COVID-TRUENAT or CBNAAT in nasopharyngeal swab. The study was conducted in a tertiary care centre in Kerala based on records of patients admitted between May 2021 and April 2022. Data was collected from medical records library using a structured questionnaire.

This study was approved by the Institutional Ethics Committee. Informed consent was waived because of the retrospective design.

Inclusion criteria

End stage renal disease patients on haemodialysis above 18 years with confirmed COVID-19 infection were included in the study. COVID-19 was confirmed either by positive reverse transcription-PCR, rapid antigen test, COVID -TRUENAT or CBNAAT in nasopharyngeal swab. Only patients with severe to very severe disease with any of following symptoms or signs-breathlessness, desaturation, chest pain, drowsiness, hypotension, haemoptysis or worsening of CKD were included in the study. Patients were considered as fully vaccinated after 2 weeks of second dose of vaccine and they were considered as unvaccinated if they have not received any vaccine.

Exclusion criteria

Patients with missing or incomplete information, who have taken only single dose of vaccine or within 2 weeks of second dose of COVID-19 vaccination were excluded from the study. Patients [meeting inclusion criteria] referred to other institutions without completing treatment were also excluded.

Data collection

Baseline demographic, laboratory and clinical information along with details of outcome was collected from the medical record databases in the hospital from May 2021 to April 2022.

Key laboratory parameters included random blood sugar, liver function test, renal function test (RFT), complete blood count, C reactive protein (CRP), serum ferritin and D-dimer.

All patients received standard care which included heparin and systemic steroid either methyl prednisolone or dexamethasone according to the protocol for treatment of COVID-19 severe disease in Kerala state. In this study population antiviral drug was not given in view of deranged RFT.

Statistical analysis

All statistical analysis was conducted using SPSS software trial version 25. Normally distributed continuous variables were expressed as mean and standard deviation (SD) and values for categorical variables were expressed as frequency counts and percentages.

Proportions for categorical variables were compared using the Chi-square test. Differences were considered significant if P value was < 0.05.

Results

One hundred and thirty five COVID-19 positive CKD patients on haemodialysis were admitted during the study period in our Institute with severe COVID-19 disease. Out of this, 11 patients had received only single dose of vaccine and 10 patients had taken the second dose of vaccine less than two weeks before present hospitalisation. Ten patients were excluded because of incomplete data availability. Finally, data of 104 patients were available for statistical analysis (Table 1).

Out of these 104 patients, 30 patients had not received any COVID-19 vaccine and 74 patients had received 2 doses of vaccine, either covishield or covaxin which were the vaccines approved then in India. 50 patients had received covishield and 24 patients had received covaxin. The second dose of vaccine was taken more than two weeks before the present illness.

Table 1: Baseline characteristics of the study population.

	Vaccinated (No =74)	*Unvaccinated (No =30)*
Age (Mean ± SD)	58.33 ± 11.70	60.16 ±15.25
Male, n (%)	55 (74.3)	20 (66)
Diabetes mellitus, n (%)	41 (55)	15 (50)
Systemic hypertension, n (%)	36 (48)	16 (53)
Coronary artery disease, n (%)	30 (40.5)	11 (36.6)
Obstructive airway disease, n (%)	24 (32.4)	9 (30)
Chronic liver disease, n (%)	15 (20.3)	7 (23)

Fever was the presenting symptom in 55 patients, 56 patients had cough and 54 patients had breathlessness. These were the most frequent presenting symptoms in these patients and was present in more than 50% of patients. Haemoptysis was present in 28% of patients. Diabetes mellitus was the most common comorbidity followed by systemic hypertension and CAD.

Inflammatory markers at the time of admission were compared between the vaccinated and unvaccinated group (Table 2). The mean of inflammatory markers like ferritin, CRP and D-dimer were higher in the unvaccinated group compared with the vaccinated group of patients, but a statistically significant difference was seen only for D-dimer.

Table 2: Comparison of inflammatory markers between vaccinated and unvaccinated patients.

Inflammatory markers	*Group*	*N*	*Mean*	*SD*	*Independent sample t test*	*p value*
Ferritin (ng/ml)	Vaccinated	74	642.8562	384.75532	1.843	0.068
	Not vaccinated	30	807.1993	473.98970		
CRP (mg/L)	Vaccinated	74	44.70	26.041	0.671	0.504
	Not vaccinated	30	48.63	29.536		
D-dimer (ng/ml)	Vaccinated	74	913.92	696.482	2.560	0.012
	Not vaccinated	30	1361.00	1033.926		

Note: p value was calculated by independent sample t test, p<0.05 considered as statistically significant.

Majority of CKD patients admitted with COVID-19 had desaturation and required supplemental oxygenation (70%). 31 patients needed invasive mechanical ventilation, 15 (20%) in the vaccinated group and 16 (53.3%) in the unvaccinated group showing, a statistically significant increase in the unvaccinated group (Table 3).

There was no statistically significant difference in inflammatory markers between the two groups of vaccine (Table 5). There was also no significant difference in the requirement of invasive mechanical ventilation, discharge or death between the two vaccines in these patients. Eleven patients (21%) who received

Table 3: Comparison of oxygen requirement and invasive mechanical ventilation between vaccinated and unvaccinated patients.

Oxygen requirement	*Vaccination status*		*Chi square test*	*p value*
	Vaccinated (n=74)	*Not vaccinated (n=30)*		
Need of invasive mechanical ventilation	15(20 %)	16(53 %)	23.49	0.001
Room air/ Other modes of oxygen delivery	59(80%)	14 (47%)		

Note: p value was calculated by chi square test, p < 0.05 considered as statistically significant.

covishield needed invasive mechanical ventilation and four patients (18%) on covaxin.38 (76%) patients who received covishield were successfully discharged and 20 (82%) on covaxin. There was no significant difference in death between the two vaccines, 12 (24%) and 4(18%) for covishield and covaxin respectively.

There was a statistically significant increase in death in unvaccinated group (Table 4).

Among the vaccinated CKD patients, 50 patients had received covishield and 24 patients had received covaxin.

Table 4: Comparison of clinical outcome between vaccinated and unvaccinated patients.

Clinical outcome	*Vaccinated (n=74)*	*Unvaccinated (n=30)*	*OR*	*Chi square test*	*p value*
Discharge	58 (78%)	15 (50%)			
Death	16 (22 %)	15 (50.0%)	3.62	17.01	0.005
Total	74	30			

Note: p value was calculated by chi square test, p<0.05 considered as statistically significant.

Table 5: Comparison of inflammatory markers in COVID-19 CKD patients on haemodialysis between covishield and covaxin.

Inflammatory markers	*Group*	*N*	*Mean*	*SD*	*Independent sample t test*	*p value*
S ferritin (ng/ml)	Covishield	50	670.9432	383.11431	0.905	0.368
	Covaxin	24	584.3417	389.70473		
CRP (mg/L)	Covishield	50	47.30	26.377	1.243	0.218
	Covaxin	24	39.29	25.000		
D-dimer (ng/ml)	Covishield	50	924.94	706.248	0.195	0.846
	Covaxin	24	890.96	690.059		

Note: p value was calculated by independent sample t test, p<0.05 considered as statistically significant.

Discussion

Vaccine against COVID-19 became available in India in January 2021 for healthcare workers and other frontline workers, in March 2021 for people above 60 years of age and for those with significant comorbidities including CKD if above 45 years of age [8]. This vaccination drive coincided with the second wave of COVID-19 in India which was associated with high morbidity and mortality. To what extent vaccination provided protection to these high-risk patients was a concern as these vaccines were given emergency use authorisation in view of the prevailing pandemic. Another concern regarding the vaccine was its safety in patients with comorbidities like CKD, as majority of the vaccine trials did not include CKD patients [9]. So, no significant data was available on the safety and efficacy of COVID-19 vaccine in CKD patients. Most of the vaccine studies are based on the effectiveness of the vaccine in preventing infection and hospitalisations. While only few studies are available on the course of the disease in CKD patients requiring hospitalisation with in breakthrough COVID-19 infections.

This study was conducted to assess the efficacy of vaccine in reducing the severity of infection and mortality in breakthrough infection in CKD patients requiring hospitalisation. In this study on CKD patients on haemodialysis, 74 patients were vaccinated and 30 patients were not vaccinated. Since patients with comorbidities received vaccine on a priority basis from March 2021, 2/3rd of our study population was vaccinated. We conducted a case control study to

find the difference in the course of the disease and its outcome between vaccinated and unvaccinated group with COVID-19 infection.

We did not include patients who had received single dose of vaccine or those who had breakthrough infection less than two weeks after the second dose of vaccine as post vaccination immune response to single dose or within two weeks of vaccination is variable.

COVID-19 vaccines were developed to induce immune response by producing neutralising antibodies to the spike protein of the virus [10]. In patients with CKD, the comorbidities might alter the efficacy of covid vaccine and immunosuppressants might alter the adaptive immunity [11]. In addition to that, vitamin D deficiency, uraemia and erythropoietin deficiency which are common in CKD patients may alter the innate immunity in these patients [12-14]. So, whether vaccine will be able to induce an adequate immune response in CKD patients was a concern.

In a study on Pfizer COVID vaccine in CKD patients on haemodialysis, IgG was measured after completion of second dose of vaccine [7]. The humoral response was found to be lower in CKD patients than the control group of non CKD patients. However, 96% of the CKD patients had humoral response, but the antibody titre was lower.

In another study on Moderna vaccine in CKD patients on peritoneal dialysis, the IgG titre for S- spike protein of SARS-COV2 increased after 2 doses of vaccine [15].

Inflammatory markers including CRP, ferritin, IL-6 and D-dimer are commonly seen elevated in COVID-19. But in CKD patients these inflammatory markers are usually elevated even without any other predisposing diseases [16]. The serum levels of D-dimer and CRP were shown to increase with worsening eGFR [17]. An acute phase reactant, serum ferritin is frequently raised in CKD patients irrespective of iron stores. A serum ferritin level above 500ng/ml is common in CKD patients [18]. The level of inflammatory markers in our cohort of patients showed difference between vaccinated and unvaccinated group. D-dimer levels were significantly higher in the unvaccinated group. Ferritin level was also higher in the unvaccinated group, but it was not statistically significant. There was no statistically significant difference in the CRP levels between the vaccinated and unvaccinated group. In another study comparing vaccinated and unvaccinated, the serum levels of ferritin, LDH, and D-dimer were significantly higher in the unvaccinated group compared to fully vaccinated and partially vaccinated group. But no difference was observed in CRP levels [19].

On symptom analysis, fever, cough and breathlessness were the most common presenting symptoms followed by haemoptysis. There was no significant difference in symptomatology between the groups in our study cohort as only patients with severe disease were included. In a previous study, comparison of symptomatology between vaccinated and unvaccinated cohorts in hospitalised patients showed more severe symptoms in unvaccinated [20]. The first community based COVID-19 vaccine studies in Israel showed that majority of vaccinated population were asymptomatic and needed less hospitalisation [21].

Among the unvaccinated patients with COVID-19, more than half of patients had severe disease and required invasive mechanical ventilation compared to only 20% requiring invasive mechanical ventilation among the vaccinated patients. In the post vaccination study done in Israel, vaccination was found to reduce severe and critical disease in the vaccinated population compared to unvaccinated [21].

In a landmark study by Gibertoni et al, conducted in Italy on a cohort of CKD patients, with COVID-19, the crude mortality due to COVID-19 was 44.6 % compared to 4.7% in CKD patients without COVID, showing a 10 times higher mortality in CKD patients with COVID-19 [22]. This study was conducted before the availability of any vaccine against COVID-19. In the open SAFELY project on 17 million COVID positive patients in England on mortality analysis, it was found that dialysis and organ transplantation is associated with adjusted Hazard Ratio (aHR) of 3.69 and 3.53 respectively. The aHR of CKD with eGFR < 30 ml/min/1.73m^2 is 2.52. And these three conditions are among the four comorbidities associated with highest mortality risk among COVID-19 [23].

The higher mortality in end-stage renal disease (ESRD) patients is due to the immunosuppressive status, old age and comorbidities including diabetes mellitus and systemic hypertension. In our study population of CKD patients with severe COVID-19, mortality in the unvaccinated group is 50% and in the vaccinated group it is only 22%. So, any preventive method including vaccination is essential to lower the morbidity and mortality due to COVID-19 among CKD patients. There was no significant difference in the inflammatory markers, need for invasive mechanical ventilation or death between the patients who received covishield and covaxin, indicating that both vaccines are equally

efficacious in protecting against severe form of COVID-19 in CKD patients. Vaccination is known to reduce the severity of symptoms and mortality in general population. Several clinical trials on vaccine have excluded CKD patients on haemodialysis because of expected poor outcome. But our study has clearly demonstrated the effectiveness of vaccine in CKD patients on maintenance haemodialysis in preventing severe disease requiring invasive mechanical ventilation as well as death.

The major limitation of the study is the retrospective design. The study has limited sample size as only CKD patients on haemodialysis with severe disease requiring hospitalisation were included in the study. So the results cannot be generalised to the community and the effect of the vaccine on CKD patients with breakthrough infection in the community may be different. A community-based study on CKD patients with COVID-19 need to be done to find the effectiveness of vaccine in preventing hospitalisation as well as severe disease and death. The study did not consider the comorbidities and the severity of the renal disease itself leading to mortality. Since this was a retrospective study a regression analysis on confounding factors for mechanical ventilation or death could not be done. Assay of IgG antibody against S spike protein of the virus was not done in these patients to ensure the antibody response after vaccination.

Conclusion

COVID-19 pandemic has been a big threat for CKD patients on haemodialysis because of increased morbidity and mortality in this group of patients. It has been found in this study that severity of disease requiring invasive mechanical ventilation and mortality is lower in vaccinated group compared to unvaccinated group of CKD patients on haemodialysis. Based on the above evidence all CKD patients on haemodialysis should receive vaccination against SARS-COV2 and booster doses as per national guidelines to reduce the morbidity and mortality.

Conflicts of interest

Authors declare no conflicts of interest.

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