

Effectiveness of 4 doses of COVID-19 vaccine in patients on maintenance hemodialysis in 5th wave of COVID-19 infection in Myanmar: Do we need 5 doses?

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ABSTRACT

Background: Patients on maintenance hemodialysis (MHD) are at high risk of contracting SARS-CoV-2 and developing severe COVID-19 infection because they have low innate immunity as well as poor antibody response to COVID-19 vaccine. This study aimed to assess the effectiveness of 4 doses of COVID-19 vaccine in preventing 5th wave of COVID-19 infections in patients on maintenance hemodialysis in Myanmar.

Methods: A hospital-based descriptive study was conducted in July 2022 to November 2022 among patients on MHD who received COVID-19 vaccine 4 doses; last dose was 2 weeks ago. Data were collected by using standardized forms and analysis was done.

Results: A total of 61 patients on maintenance hemodialysis (MHD) who had 4 doses of COVID-19 vaccination more than 2 weeks were included. Nasopharyngeal swab PCR was taken twice a week to all patients (if they did not have symptoms) and it was repeated if they had symptoms suggestive of COVID-19 infection or they had history of contact with patients having COVID-19 infection. Their signs and symptoms were analyzed; chest radiograph and blood tests were taken if indicated. Then, the severity of COVID-19 infection was determined according to WHO criteria and they were given treatment according to hospital guideline. They were followed up till 28 days.

The base line characteristics were as follows: mean age was 51.15 ± 12.85 years; male to female ratio was 4:6; mean BMI was 19.93 ± 2.83 kg/m²; 16.4% (10/61) had diabetic nephropathy; 9.8% (6/61) had cerebrovascular accident; 24.6% (15/61) had coronary heart disease; and one fifth of them were current smokers. Sixty six percent had past history of COVID-19 infection; duration from last infection was 404 days. Thirty three percent of cases had shortest duration of hemodialysis (6 months) and 23% were over 3 years. Mean duration from last vaccination was 39 days. Thirty six percent (22/61) had confirmed COVID-19 infection and 64% (39/61) of them were not infected till the end of 5th wave. All infected cases were mild form according to WHO criteria; none of them required oxygen therapy. One case having multiple comorbidities (lymphoma, coronary heart disease, hypertension and malignant cachexia) had sudden death due to pulmonary embolism.

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Conclusions: The protection rate of four doses of COVID-19 vaccine in patients on MHD was not good as 36% of them were infected in the 5th wave of epidemic in Myanmar. However, all the infected cases were mild form and they did not need oxygen therapy showing that booster vaccination prevented morbidity and mortality. Therefore, the protection rate of four doses of COVID-19 vaccine in patients on MHD was nearly 65%; it reduced the severe form of infection and death. Fifth dose of COVID-19 vaccine is necessary along with personnel protective measures.

KEYWORDS: COVID-19 infection, vaccination, effectiveness, maintenance hemodialysis (MHD)

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BACKGROUND

Vaccine program has been launched in Myanmar since January 2021; Covaxin and Covishield are the only two main vaccines available initially. Later, Sinopharm, Sinovax, Sputnik, Pfizer, Moderna, Johnson and Johnson has been accessible. Patients with end stage renal disease on maintenance hemodialysis (ESRD on MHD) are in priority group for immunization as their immunity is low. First, two doses of vaccine were given with the interval of 4-6 weeks; first dose in January/February 2021 and second dose in March/April 2021. Third and fourth doses were given in December 2021 and June 2022 respectively. In August 2022, 50% of total population of Myanmar got two doses of COVID vaccine (MOHS, 2021). The Omicron variant infection from Myanmar was reported in January 2022; the 4th wave of COVID-19 infection (Pyar, 2022).

Vaccine stimulates the individual to produce protective antibody level. It begins few days after vaccination; then, the level continues to rise till 6 months. Vaccination elicits robust SARS-CoV-2-specific immune memory regardless of prior infection. The protective antibody response, both quantity and quality, was better in vaccinated individuals than that of natural infection (Yu et al., 2022). The combination of a previous SARS-CoV-2 infection and vaccination, hybrid immunity, had the greatest protection against SARS-CoV-2 infections (Pilz et al., 2022) (Goldberg et al., 2022) as well as the longest duration of protectivity (Hall et al., 2022) (Bates et al., 2022).

Both anemia and bone marrow suppression in uremia step down the immune system; impaired renal function was reported as independent risk factor for acquiring severe COVID-19 infection and mortality (Pyar, Kyaw, et al., 2022). Mortality rate of patients on MHD was high as they had other comorbid conditions: older age, diabetes mellitus, anemia, hypertension, coronary heart disease and cerebrovascular accident (Rincon-Arevalo et al., 2021) (Pyar, Kyaw, et al., 2022). In addition, they were vulnerable to COVID-19 infection because they had to travel to the dialysis center two to three times per week; they exposed to patients with asymptomatic COVID-19 infection and health care workers. Not only the immunity but also the antibody response was related with renal function; those with chronic kidney disease stage 5 (ESRD) had poorer response than those with stage 4 (Matsunami et al., 2022). The immune response following

COVID-19 vaccine in patients on MHD was interesting; it was generally comparable to healthy population in some studies (Sanders et al., 2022) (Park et al., 2022). Nonetheless, lower immune response was found in others (Akpolat, 2022). Reported clinical predictors of antibody positive response toward COVID-19 vaccination were age, previous infection (Aoun et al., 2022), immunosuppressive therapy, body mass index, iron deficiency anemia (Drakesmith et al., 2021) (Preston et al., 2021) and serum albumin level (Aoun et al., 2022). Longer vintage of end-stage kidney disease, and lower pre-vaccination serum albumin were related with response to vaccine in patients on MHD (Anand et al., 2021). In addition, the antibody response related with the time of day of vaccination (Nobis et al., 2019), vaccine type, age, sex, and days post-vaccination (Wang et al., 2019); antibody level was higher in those who received vaccine in the afternoon than those who were vaccinated in the morning (Wang et al., 2019). It may vary among different race and ethnic group. Mortality of COVID-19 infection was high in patients on MHD (Kocak et al., 2021)

The study from Canada suggested that compared with a third dose of mRNA covid-19 vaccine, a fourth dose improved protection against infection, symptomatic infection, and severe outcomes in elderly (Grewal et al., 2022). As the Omicron variant had high transmissibility and the protective efficacy on the Omicron variant and its subvariant was debatable. Both the BNT162b2 vaccine and previous infection produced immunity against omicron infection and protection against hospitalization and death (Lin et al., 2022). Most of the findings on efficacy of COVID-19 vaccine was positive; it prevented severe infection (Šmíd et al., 2022). The study from Canada found that the Omicron reinfection risk was limited in twice-vaccinated individuals with prior non-Omicron SARS-CoV-2 infection after a third dose of mRNA vaccine (Carazo et al., 2022). Moreover, the researchers from Netherland supported Canadian study; “vaccine- or infection-induced immunity against SARS-CoV-2 infections was less effective against the Omicron than the Delta variant” (Eggink et al., 2022). Reported COVID-19 vaccine break through infections after 2 doses in Myanmar were 25% among healthy physicians in 2021 (Pyar, 2022); the similar result was noted among health care workers with same vaccine- Covaxin and Covishield in India (Malhotra et al., 2022). The data on vaccine efficacy with 4 doses was required in Myanmar.

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Therefore, this study aimed to assess the effectiveness of 4 doses of COVID-19 vaccine among patients on MHD in Yangon, Myanmar.

METHODS

Study Design and Population

A hospital based descriptive study was conducted in July 2022 to November 2022 among patients on MHD who received COVID-19 vaccine 4 doses; last dose was 2 weeks ago. Nasopharyngeal swab PCR was taken once a week to all patients (if they did not have symptoms) and it was repeated if they had symptoms suggestive of COVID-19 infection or if they exposed to COVID-19 cases. This study was approved by the Hospital Research and Ethics Committee of No.(1) Defence Services General Hospital (1000-Bedded) Mingaladon, Yangon.

Data Collection and Procedure

A total of 61 patients on maintenance hemodialysis (MHD) who had 4 doses of COVID-19 vaccination more than 2 weeks were included. Nasopharyngeal swab PCR was taken once a week to all patients (if they did not have symptoms) and it was repeated if they had symptoms suggestive of COVID-19 infection or they had history of contact with patients having COVID-19 infection. The signs and symptoms were analyzed; chest radiograph and blood tests were taken if indicated. Then, the severity of COVID-19 infection was determined according to WHO criteria. They were given treatment as per hospital protocol and they were followed up till 28 days.

Demographic characteristics (sex, age, height, dry weight, smoking status, duration of MHD, comorbidity (hypertension, diabetes mellitus) and vaccine related factors like the name of each COVID-19 vaccine, date of each vaccination, timing of the day of vaccination of the last dose, timing of SARS-CoV-2 infection and duration of HD were recorded. The data were checked by two medical officers and then, supervision, completeness, and consistency of collected data were performed by the principle investigator. Data were collected by using standardized forms and analysis was done.

Working Definition

Body mass index (BMI) was a person's weight in kilograms divided by the square of height in meters, an indicator of body fatness. BMI was categorized as underweight ($< 18.5 \text{ kg/m}^2$), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2) and ($\geq 30.0 \text{ kg/m}^2$) obese. Dry body weight was taken for calculation of BMI. Comorbidity was a presence of one or more additional medical conditions or diseases diagnosed by physicians..

Smoking status was classified into smoker and non-smoker. Smoker was defined if patient was still smoking at the time of estimation of blood test irrespective of duration of smoking. Nonsmoker was defined if patient stopped smoking

at the time of estimation of blood test irrespective of duration of quitting.

Based on WHO severity score, the severity of COVID-19 was classified as mild, moderate, severe disease and critical disease. Mild disease was symptomatic patients without evidence of viral pneumonia in CXR or hypoxia. Moderate disease was confirmed patients with clinical signs of pneumonia (fever, cough, dyspnea, and fast breathing), CXR showed pneumonia and SaO_2 on air is $\geq 95\%$. Severe disease was confirmed patient with clinical signs of pneumonia (fever, cough, dyspnea, and fast breathing) adding one of the following: respiratory rate > 30 breaths per min, severe respiratory distress and $\text{SpO}_2 < 90\%$ on room air. Critical disease was confirmed COVID-19 patient with one or more of the followings: ARDS, sepsis, septic shock and acute thrombosis (pulmonary embolism, acute coronary syndrome, acute stroke).

History of COVID-19 infection was defined if patient had signs and symptoms of COVID-19 infection with positive nasopharyngeal swab tests either with rapid test or PCR method.

Duration of maintenance hemodialysis was defined as total duration since first HD.

Statistical Analysis

Statistical analysis was done by IBM® SPSS® version 26. All continuous data were done normality test by histogram as well as by Shapiro-Wilk test. If there was non-normal distribution, data were expressed as Median (IQR) and if normal distribution, expressed as mean \pm SD. The categorical data were expressed as frequency (percentage).

RESULTS

Thirty-six percent (22/61) had confirmed COVID-19 infection and 64% (39/61) of them were not infected. All infected cases were mild form according to WHO criteria; none of them required oxygen therapy. Table (1) shows clinical characteristics. The base line characteristics were as follows: mean age was 49.77 ± 11.58 years; male to female ratio was 4:6; mean BMI was $19.75 \pm 3.00 \text{ kg/m}^2$; 16.4%(10/61) had diabetic nephropathy; 9.8%(6/61) had cerebrovascular accident; 24.6%(15/61) had coronary heart disease; and one fifth of them were current smokers. Sixty four percent had past history of COVID-19 infection. Thirty-three percent of cases had shortest duration of hemodialysis (6 months) and 23% were over 3 years. Mean duration from last vaccination was 37.64 ± 2.22 days. Past history of COVID-19 infection was seen in 64% (14/22) of infected cases. One case having multiple comorbidities (lymphoma, coronary heart disease, hypertension and malignant cachexia) had sudden death due to pulmonary embolism.

DISCUSSION

Patients on MHD attending hemodialysis unit in public hospital twice a week were closely followed up for 5 months;

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those who received COVID-19 vaccine 4 doses at least 2 weeks ago were included. They had total 4 doses of Covaxin/Sinopharm/Covishield/Sinovax. Nasopharyngeal swab PCR was taken once a week to all patients and extra swab was done either development of COVID-19 symptoms or contact exposure. Thirty-six percent (22/61) had confirmed COVID-19 infection and 64% (39/61) of them were not infected. According to Salerno et al, male sex, having comorbidities such as diabetes mellitus and cardiac diseases were associated with high risks of COVID-19 (Salerno et al., 2021).

Two third (64%) of them were not infected showing the effectiveness of vaccine 4 doses to some extent. Reported COVID-19 vaccine break through infections after 2 doses in Myanmar were 25% among healthy physicians in 2021 (Pyar, 2022); the similar result was noted among health care workers with same vaccine- Covaxin and Covishield in India (Malhotra et al., 2022). It gave another evidence for Canadian study done in elderly population which pointed out efficacy of fourth dose; better prevention of COVID-19 infection and reduction of severity of infection (Grewal et al., 2022). Therefore, close follow up and observation to patients on MHD was extremely important as they have poor response to vaccine as well as low immunity (Demiray et al., 2022).

The infected cases were having mild form and did not require oxygenation in this study. It supported other findings “vaccination may yield a protective effect against severe forms of COVID-19 in dialysis patients, despite altered immunologic vaccine responses” (El Karoui et al., 2022) and study from United Kingdom; a multicenter observational study of the London hemodialysis population undergoing surveillance PCR testing during the period of vaccine rollout with BNT162b2 and AZD1222 demonstrated a substantially lower risk of severe COVID-19 after vaccination in patients on dialysis who become infected with SARS-CoV-2 (Ashby et al., 2022).

Surge of SARS CoV-2 infections due to the Omicron variant began in January 2022 in Yangon, Myanmar (Pyar, Wunna, et al., 2022); then, the Omicron subvariant were reported in neighboring countries (Joung et al., 2022) (Chu et al., 2022) (Thakur & Ratho, 2022). This study was conducted in July 2022 to November 2022; therefore, the protective efficacy of COVID-19 vaccine 4 doses to the Omicron variant was 64%. Moreover, it prevented severe form of COVID-19 infection in patients on MHD- immunodeficient patients. It pointed out former report that 4 doses of COVID-19 vaccine prevented severe form of infection- the Omicron and its subvariant despite altered immunologic vaccine responses (Šmíd et al., 2022) (El Karoui et al., 2022).

Although the Omicron and its subvariant had high transmissibility, four doses of vaccine had relatively good efficacy on both prevention of infection and reduction of morbidity and mortality. The study done in Turkey pointed out the importance of early case detection “early screening of

both symptomatic and asymptomatic patients was shown to be highly important” (Islam et al., 2021). In this study, nasopharyngeal swab PCR was taken once a week to all patients (if they did not have symptoms) and it was repeated if they had symptoms suggestive of COVID-19 infection or they had history of contact with patients having COVID-19 infection. Having non-severe cases in this study may be due to early detection of cases or vaccine effect or virus itself. The Omicron variant seemed to result in less severe disease in patients on MHD compared with other variants (Spensley et al., 2022) (Pyar K P et al, 2022). Chimon et al suggested the importance of surveillance and continuous protection measures to limit SARS-CoV-2 infection to patients on MHD high risk of severe forms of infection compared to non-HD population (Chimon et al., 2022).

Combination of the BNT162b2 vaccine and previous infection produced immunity against omicron infection and protection against hospitalization and death (Lin et al., 2022). In this study, nearly 67% (26/39) percent of non-infected cases and sixty four percent (14/22) of infected cases had past COVID-19 infection; 36% of infected cases did not have past COVID-19 infection. It was hard to support the fact that the Omicron reinfection risk was limited in twice-vaccinated individuals with prior non-Omicron SARS-CoV-2 infection after a third dose of mRNA vaccine (Carazo et al., 2022)(Malhotra et al., 2022). The time of the day of vaccination determined antibody response because of circadian clocks in the adaptive immune response (Nobis et al., 2019).

CONCLUSIONS

The protection rate of four doses of COVID-19 vaccine in patients on MHD was not good as 36% of them get infection in the 5th wave of epidemic in Myanmar. However, those who acquired COVID-19 infection in the 5th wave were mild form and they did not need oxygen therapy showing that it prevented morbidity and mortality.

LIMITATION OF STUDY

There are several limitations in this study. The number of patients was not large in this study as it was conducted in one HD center. The variant and subtype of the Omicron variant should be done to get better information on vaccine efficacy. Further research on both humoral and cellular response to booster vaccination on patients on MHD should be done.

RECOMMENDATION

Because 4 doses of COVID-19 vaccination in patients on MHD is not enough for protection of 5th wave, another dose should be given for prevention of 6th wave. Patients on MHD should be still in priority group for vaccination as all studies proved high prevalence of COVID-19 infection and severity in this particular group. Personnel protective measures like wearing mask, gloves, cap are important not only to patients

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but also to their close attendants and health care workers. Surveillance is very important; regular screening of both symptomatic and asymptomatic patients on MHD as early detection will lower mortality.

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DECLARATION OF CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to authorship and publication of this article.

ETHICAL APPROVAL

This study was approved by Hospital Research and Ethic Committee from Defence Services General Hospital (1000-Bedded) Mingaladon, Myanmar. Informed consent was also taken from each patients on MHD.

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Table -Base line characteristics of patients on MHD (n = 61)

Variables	Frequency (%)	Mean ± SD	Median (IQR)
Age		51.15 ± 12.85	
Age groups			
≤ 50 years	32 (52.5)		
> 50 years	29 (47.5)		
BMI (kg/m ²)		19.93 ± 2.83	
BMI groups			
Underweight	15 (24.6)		
Normal weight	44 (72.1)		
Overweight	2 (3.3)		
Sex			
Male	26 (42.6)		
Female	35 (57.4)		
History of COVID-19 infection	40 (65.6)		
Diabetic Nephropathy	10 (16.4)		
Cerebrovascular Accident	6 (9.8)		
Coronary heart disease	15 (24.6)		
Current Smoker	12 (19.7)		
Duration from last infection (days)			404 (151)
Duration from last vaccine (days)			39 (3)
HD Duration			
< 6 months	20 (32.8)		
6 months to 1 year	8 (13.1)		
1 to 2 years	12 (19.7)		
2 to 3 years	7 (11.5)		
3 to 4 years	13 (21.3)		
> 4 years	1 (1.6)		