Original article

CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

Severity of COVID-19 in bacillus Calmette-Guérin vaccinated population

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Purpose: Considering the cross-protection reported for bacillus Calmette-Guérin (BCG) vaccination on viral respiratory infections, it has been proposed that it could reduce the severity of coronavirus disease 2019 (COVID-19). The objective of the current study is to investigate the association between the severity of COVID-19 with prior BCG vaccination in adult patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Materials and Methods: Adult patients (18 years or above) with positive SARS-CoV-2 polymerase chain reaction admitted in July 2020 were included in this cross-sectional study. Patients were classified into non-severe, severe, and critical diseases. History of prior BCG vaccination and the presence of a BCG vaccination scar were recorded.

Results: Out of 103 patients, 64 patients with prior history of BCG vaccinations were compared with 39 patients without BCG vaccination in childhood. The median age was 55 years and 64 years in BCG vaccinated & non-BCG vaccinated patients (p-value=0.002). There was male predominance in both groups and frequent comorbid illnesses were hypertension and diabetes mellitus. Severe COVID-19 was found in 91 patients (88.3%) followed by non-severe disease and critical diseases i.e., 7 (6.8%) and 5 (4.9%) patients, respectively. No association of prior BCG vaccination with disease severity of COVID-19 was found in this study and mortality was 8.7%. Out of nine patients who expired only 2 (22.2%) had a prior history of BCG vaccination (p-value=0.01). Secondary infections were present in 26 patients and the majority had pneumonia.

Conclusion: The BCG vaccine has no impact on the severity of COVID-19 but could have a protective role with a low mortality rate in already infected patients.

Keywords: COVID-19, BCG vaccine, SARS-CoV-2

Introduction

Bacillus Calmette-Guérin (BCG), although a collective name for a family of live attenuated strains of *Mycobacterium bovis*, is being used widely for the prevention of *Mycobacterium tuberculosis* infection in the endemic areas and up to 80% protection is documented in various studies [1,2]. BCG is the most common vaccine with more than 120 million vaccines administered worldwide every year and is one of the key vaccines given at birth [3]. Non-specific protection offered by the BCG vaccine has been demonstrated in the published literature [4-6].

The existing literature is not conclusive about the protective role of BCG vaccination against coronavirus disease 2019 (COVID-19) since China, the epicenter of this deadly

pandemic, still has BCG vaccination in the routine schedule. Furthermore, Egypt and Iran, with BCG coverage rates of 95% and 99%, respectively, are included in the list of the countries with a high burden of COVID-19 [7,8]. There is a difference in case positivity (172.4 versus 1,043.9), infectivity (8.53% versus 11.2%), and mortality (4.3 versus 48.9) in those countries that still have universal BCG vaccination policy in comparison to countries with no BCG vaccine in their immunization program. The higher protection against morbidity and mortality secondary to COVID-19 reported in the countries that still have BCG in their Expanded Program on Immunization (EPI) program may be attributed to nonspecific and cross-protective immune responses elicited by the BCG vaccine [9,10]. The protective effect of BCG against viral infections can be explained by trained immunity. BCG vaccination leads to epigenetic programming of the monocytes, possibly at the bone marrow level and this is considered as a weak primary response. Subsequently, there is a secondary trained response when an individual already vaccinated with BCG gets infected with a specific virus that leads to increased gene transcription and improved host defense [11].

While COVID-19 vaccination has already started in some of the countries, long-term immunity is still a matter of debate. Different measures have been proposed to prevent the spread of the disease and similarly, different therapeutic options have been studied but none of them has given promising results. There was no study on the protective effects of BCG vaccination against COVID-19 severity to date.

Along with the constant struggle to find new interventions, existing tools should be evaluated for their potential preventive role to overcome the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Understanding the role of prior BCG vaccination with COVID-19 diseases severity may help in planning new interventions, such as revaccination or introduction of the vaccine to the adult population, risk stratification of patients, and so forth. The aim of this study is to evaluate the association of past BCG vaccination on the severity of COVID-19 so that it can be used as a cost-effective tool to reduce mortality and morbidity of this global health challenge.

Materials and Methods

We conducted a cross-sectional observational study of all adult patients admitted with polymerase chain reaction confirmed COVID-19 disease between the period of 1st July to 31st July 2021 at the tertiary care hospital of Karachi, Pakistan. Demographic, comorbid illnesses, history of BCG vaccination in childhood, clinical characteristics, and outcomes along with the severity of illness were recorded on a structured proforma. All adult patients (18 years of age and above) who gave consent to participate were included in the study. Patients with active tuberculosis and pregnant females were excluded. The severity of COVID-19 was classified according to national guidelines for the management of COVID-19. The presence or absence of the vaccination was evaluated using the presence of a scar as a proxy of BCG vaccination. The BCG scar was examined in the deltoid region. A verbal history regarding vaccination was also taken from the patients after taking informed consent.

Ethical approval

The study was approved by the ethical review committee of Aga Khan University with reference number 2020-5366-14052.

Statistical analysis

Continuous variables were reported as mean±standard deviation and frequencies (%) were computed for categorical variables for the characteristics of participating subjects. The patient baseline characteristics were analyzed based on the presence or absence of the BCG vaccine using an independent t-test for continuous variables or a chi-square test for categorical variables. A difference with a p-value of <0.05 was considered statistically significant. All analysis was performed using IBM SPSS ver. 19.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 103 patients with COVID-19 were included in the study. Sixty-four patients had a prior history of BCG vaccinations and they were compared with 39 patients who did not receive BCG vaccination in childhood. The median age was 55 years in BCG vaccinated and 64 years in non-BCG vaccinated patients (p-value=0.002). There was male predominance in both groups. The most frequent comorbid illnesses were hypertension and diabetes. History of cerebrovascular accident was only reported in non-vaccinated group as compared to vaccinated one (5 versus 0, p-value=0.07). Fever was the most frequent symptom followed by dyspnea and cough. Severe COVID-19 was found in 91 (88.3%) patients followed

by the non-severe disease and critical diseases, i.e., 7 (6.8%) and 5 (4.9%) patients, respectively (Table 1). Although the majority of patients in both groups were admitted with severe disease, however, four out of five patients with critical illness were from the non-vaccinated group. There was no association of prior BCG vaccination with the severity of COVID-19 found in the current study.

Secondary infections were present in 26 patients and the majority, i.e., 16 had pneumonia. Microorganisms isolated from respiratory specimens were *Stenotrophomonas maltophilia*, *Acinetobacter, Pseudomonas* spp., *Klebsiella* spp., *MRSA*, and *Aspergillus* spp.

The majority of patients were discharged home in stable conditions 94 (91.3%), and the mortality rate was 8.7%. Out of nine patients who died, only 2 (22.2%) had a prior history of BCG vaccination (p-value=0.01). The patients with prior BCG vaccination had lower mortality (3% versus 17.9%).

Discussion

The BCG, a live attenuated vaccine, is derived from an isolate of *M. bovis* and is the most widely used vaccine worldwide. Even though the vaccine offers protection against miliary tuberculosis, tuberculosis meningitis, as well as the dissemi-

Table 1. Descriptive characteristics of study population

Characteristic	Total (n=103)	BCG vaccination		p-value
		Yes	No	
Age (yr)	58.6±14.3 (60 [48–69])	55.3±12.6	64.0±15.3	0.002
Gender				0.22
Male	72 (69.9)	42 (65.6)	30 (76.9)	
Female	31 (30.1)	22 (34.4)	9 (23.1)	
Comorbid illnesses				
Diabetes mellitus	55 (53.4)	34 (53.1)	21 (53.8)	0.99
Hypertension	61 (59.2)	38 (59.4)	23 (59.0)	0.99
Ischemic heart disease	19 (18.4)	10 (15.6)	9 (23.1)	0.43
Asthma	5 (4.9)	3 (4.7)	2 (5.1)	0.99
Chronic kidney disease	6 (5.8)	2 (5.1)	4 (6.3)	0.99
History of tuberculosis	2 (1.9)	2 (3.1)	0	0.52
Malignancy	6 (5.8)	5 (7.8)	1 (2.6)	0.4
Cerebrovascular accident	5 (4.9)	0	5 (12.8)	0.007
Symptoms				
Fever	85 (82.5)	53 (82.8)	32 (82.1)	0.99
Abdominal pain	1 (1.0)	0	1 (2.6)	0.37
Myalgia	7 (6.8)	5 (7.8)	2 (5.1)	0.7
Sore throat	6 (5.8)	5 (7.8)	1 (2.6)	0.4
Diarrhea	5 (4.9)	3 (4.7)	2 (5.1)	0.99
Shortness of breath	72 (69.9)	47 (73.4)	25 (64.1)	0.37
Confusion	3 (2.9)	0	3 (7.7)	0.052
Cough	50 (48.5)	33 (51.6)	17 (43.6)	0.54
Nausea	2 (1.9)	1 (1.6)	1 (2.6)	0.99
Vomiting	4 (3.9)	3 (4.7)	1 (2.6)	0.99
Severity of COVID-19				0.12
Non severe	7 (6.8)	4 (6.3)	3 (7.7)	
Severe	91 (88.3)	59 (92.2)	32 (82.1)	
Critical	5 (4.9)	1 (1.6)	4 (10.3)	
Outcome				0.01
Expired	9 (8.7)	2 (3.1)	7 (17.9)	
Discharge	94 (91.3)	62 (96.9)	32 (82.1)	

Values are presented as mean±standard deviation (median [interquartile range]) or number (%).
BCG, bacillus Calmette-Guérin; COVID-19, coronavirus disease 2019.

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nated form of tuberculosis in children, its protective role against tuberculosis in adult populations is uncertain [12,13]. Randomized control trials have proven the efficacy of the BCG vaccine against other bacterial and viral infections as reflected by a major decline in overall infections related to neonatal and infant mortality rates in previous studies [14,15].

BCG vaccination modulates the immune response to infections caused by other pathogens. It induces the heterologous lymphocyte responses that lead to increased macrophage activation, cytokine, and antibodies production, hence confer protection against viral and other organisms. Another mechanism by which BCG vaccines induce protective effects against various pathogens is through activation of innate immunity especially monocytes, macrophages, and natural killer cells, a mechanism independent of B cell and T cell immune response. This is known as "trained immunity", a phenomenon of enhanced non-specific response to infections secondary to different microorganisms and mediated by innate immunity [16,17].

The severity and mortality of COVID-19 are variable in different countries that also differ in their health policies. A number of epidemiological studies have suggested a negative association between incidence as well as mortality of COVID-19 and national BCG vaccination policy. A study by Escobar et al. [18] found a 10.4% reduction in mortality from COVID-19 with every 10% increase in BCG index which reflects the extent of the country's BCG vaccination status. There is also a high mortality rate observed in those countries with delayed initiation or no BCG vaccine uptake. Epidemiological researches support that countrywide BCG vaccination policies are believed to be linked to decrease in numbers of cases and death related to COVID-19 [10,19,20]. A recent study on seroprevalence of anti–SARS-CoV-2 antibodies among healthcare workers found that prior history of BCG vaccination is associated with decreased SARS-CoV-2 immunoglobulin G seroconversion and lower incidence of self-reported COVID-19 related symptoms [21].

We did not find any association between the severity of COVID-19 with childhood BCG vaccination in our study which is in accordance with a few prior published literature [22,23]. A study by Hensel et al. [24] was not able to demonstrate any correlation between BCG vaccination policy with the spread of SARS-CoV-2 and associated mortality after taking care of confounding variables especially testing rate. The efficacy of the BCG vaccine declines with time and vaccine effectiveness declines to 49% at age 40 years and older [25,26]. Among all the pediatric age groups affected by COVID-19, the majority are between 9 and 19 years, sparing the first few years of life [27]. The prior infection with endemic coronaviruses or universal BCG vaccination policy might have protected children against severe COVID-19 [28]. This relatively less incidence of COVID-19 in the early years of the life of children might be attributed to the effect of the BCG vaccine and can form the base for the initiation of the BCG vaccine in adults as one of the protective strategies against COVID-19.

Our study also found that despite mandatory BCG vaccination policy at birth, only 64% of the study population had received BCG vaccine as part of routine EPI in the country. This finding is in accordance with a recent survey which also found that only 58% of children under 2 years of age have received all basic vaccines in our country [29]. Although immunization coverage has improved at the national level in the last few decades, there is a variation between provinces as well as between urban and rural populations [30].

The mortality rate is 8.7% in this study with more patients in the group who didn't receive BCG vaccine, although this difference did not reach statistical significance. The severity and mortality of COVID-19 are low in countries with universal BCG vaccination policy as compared to some countries in which either there is no universal childhood immunization program or it has been stopped at the government level earlier [31]. Considering the waning effect of immunity with time, the BCG vaccine, like other vaccines might require booster doses in an individual who has already been vaccinated in childhood, a fact yet to be known.

The protective effects of the BCG vaccine on viral infections including COVID-19 can be appreciated by the fact that the positivity rate of the population in the younger age group especially below 9 years of age is very low in countries with universal BCG vaccination policy. This fact will further support the idea of re-introducing the BCG vaccine in the adult population to assess its protective effect. It is important especially for low resources countries where the availability of COVID-19 vaccine will be a great challenge.

Limitations

This is a single-center study with a small sample size. Ideally larger population-based study is required to validate our findings. Several clinical trials are in progress, recruiting participants including healthcare workers to see whether the effect of the BCG vaccine has any protective role against SARS-CoV-2.

Conclusions

The enormous impact of COVID-19 worldwide has led researchers to explore different therapeutic agents as well as vaccines to combat the alarming increase of SARS-CoV-2 infection. Along with the development of hundreds of new vaccines against COVID-19, old vaccines like BCG can be utilized considering its non-specific protection against viral infection. In the current study, prior BCG vaccination has no impact on the severity of COVID-19 but could have a protective role with the low mortality rate in already infected patients. Prospective clinical trials are mandatory to evaluate the role of the BCG vaccine as a possible hope for protection against SARS-CoV-2. The immunity elicit by the BCG vaccine might be beneficial in the current pandemic especially in the current situation of the emergence of SARS-CoV-2 variants where the efficacy of vaccines is questionable. Vaccines such as BCG that elicited trained immunity may improve the impact of evolving pathogens in future pandemics. Administration of BCG vaccine as protection against COVID-19 should only be done in the context of a clinical trial.

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