EVALUATION OF BCG SCAR AND TUBERCULOSIS SKIN TESTS IN HEALTH CARE WORKERS WITH AND WITHOUT COVID-19

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ABSTRACT

Introduction*: The prevalence, morbidity and mortality of novel coronavirus infection is reported to be lower in countries with routine Bacille Calmette-Guérin (BCG) vaccination schedule. But it is not clear yet whether BCG vaccination has a protective effect on COVID-19 infection on groups under risk such as healthcare workers (HCW) and elderly. In this study we evaluated the relation of BCG vaccination, tuberculosis skin test (TST) result and COVID-19 in HCW.*

Materials and methods*: The study was designed as retrospective, case control study in the health care personnel working in pandemics clinics. The whole cases were divided to two groups as COVID-19 group (with a history of SARS CoV-2 infection) and control group (who did not suffer from COVID-19). Demographic data, TST, BCG scar and history for SARS CoV-2 infection were collected from hospital staff working in pandemics clinics between March 15, 2020 and November 15, 2020. In the cases suffered from COVID-19 the clinical and laboratory features and radiological severity of pneumonia -if present- and time for polymerase chain reaction (PCR) conversion in nasopharyngeal swab were recorded. All parameters were compared between two groups.*

Results*: 148 HCW were included to the study. COVID-19 group included 68 (66.7%) females and 34 (33.3%) males (mean age: 36±9 years) and control group included 23 (50%) females and 23 (50%) males (mean age: 35±8 years). The mean value of TST for whole group was 6.3±7.6 mm and similar between groups. The number of cases with BCG scars were significantly more in COVID-19 group (p=0.04). In COVID-19 group 29 (28.4%) of the cases were hospitalized while only 1(1%) suffered from severe disease. None of the cases were died. No relation was found between TST value, positivity and presence of BCG scar with the laboratory parameters, clinical features, radiological severity and hospitalization rate (p>0.05). The mean PCR conversion time was 10±3.7 days and similar in BCG and TST positive and negative cases(p>0.05).*

Conclusion*: BCG vaccination or a positive TST doesn't have an effect on the susceptibility to and clinical course of COVID-19 in health care workers.*

Keywords: *Health care workers, COVID-19, severity, BCG vaccine, tuberculosis skin test.*

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Introduction

It was reported that the prevalence, morbidity and mortality of novel coronavirus infection is lower in countries with national Bacille Calmette-Guérin (BCG) vaccination policy[(1-4)] including our country. Health care workers (HCW) are under increased risk for SARS CoV-2 infection compared to general population[(5-7)]. As there are several factors effecting the prevalence and clinical course of the disease, whether the BCG vaccination have a protective effect on COVID-19 is still not clear[(1)]. There are several ongoing clinical trials investigating the protective effect of BCG vaccination on HCW and population under risk for COVID-19 infection[(8-10)].

In this study we evaluated the BCG vaccination and tuberculosis skin test (TST) result in HCW with and without COVID-19 to assess if immunity against tuberculosis decreased the susceptibility to SARS CoV-2 infection.Besides we searched if the severity and clinical course of the disease differed in HCW with BCG scar and positive TST results.

Materials and methods

The study was designed as retrospective, case control study in the health care personnel working in 2. Sultan Abdülhamid Han Training and Research Hospital pandemics clinics between March 15, 2020 and November 15, 2020 were included to the study. The study was approved by local ethics committee (280/June 25, 2020). TST was performed to all cases except one and BCG scars were recorded. TST was measured as induration at the site of an intradermal injection of peptide extract from mycobacterial culture filtrate and recorded in both millimeters and a scale as follows: 0-4 mm: negative, 5-9 mm: weakly positive, 10-14 mm: positive and >15 mm: strongly positive. The HCW with COVID-19 was defined as having PCR positivity in nasopharyngeal swab. Demographic data and information for history of COVID-19, fever, hospitalization, duration of hospital stay, radiological severity on chest computerized tomography (CT), lowest number of lymphocytes during SARS CoV-2 infection and time for polymerase chain reaction (PCR) for SARS CoV-2 conversion in nasopharyngeal swab were obtained from medical records. Radiological manifestations on chest CT in cases with pneumonia was degreed by modifying the radiological scoring system by Bernheim A. et al.[11].

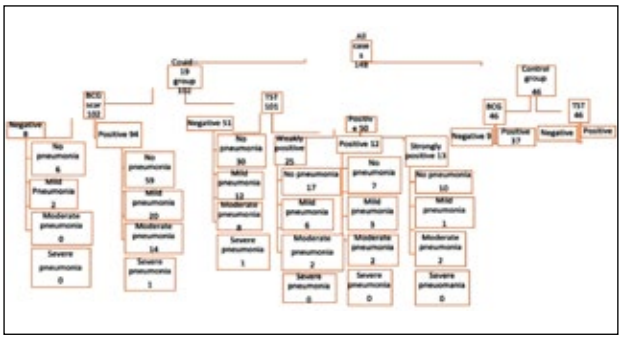

Fig. 1. Flowchart of the study based on outcomes.

The whole cases were divided into two groups as COVID-19 group (with a history of SARS CoV-2 infection) and control group (who did not suffer from COVID-19). The demographic data, BCG and TST values were compared between two groups. COVID-19 group was divided to subgroups according to BCG scar and TST positivity scale. The clinical, radiological and laboratory parameters and time for PCR conversion were compared between the subgroups (Figure 1).

Statistical analysis

Patient data collected in the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 21.0 package program (Statistical Package for the Social Sciences, Chicago, IL, USA). Discrete data were given as frequency and percentage. The mean ±Standard deviation for continuous data was given as a descriptive value. "Chi-Square Test" was used to compare two categorical groups. The “Pearson Correlation Analysis” was used to assess the relation between continuous variables. The results were considered statistically significant when the p-value was less than 0.05.

Results

The demographic and clinical features of the COVID-19 and control group are shown in Table 1.

		Total (n=148) n (%) or mean±SD	COVID-19 group(n=102) n (%) or mean ±SD	Control group (n=46) n (%) or mean±SD	p value
Sex	Female	91 (61.5)	68 (66.7)	23 (50.0)	0.068
	Male	57 (38.5)	34 (33.3)	23 (50.0)	
Age (years)		35±9	36±9	35±8	0.482
TST value (mm)		6.3±7.6	5.5±6.52	7.9±9.40	0.119
BCG scar	No	17 (11.5)	8 (7.8)	9 (19.6)	0.040
	Yes	131 (88.5)	94 (92.2)	37 (80.4)	

Table 1: Demographic, BCG and TST features of groups.

A total of 148 HCW consisting of 91(61.5%) female and 57 (38.5%) male with a mean age of 35±9 years) were included to the study. COVID-19 group included 68 (66.7%) female and 34 (33.3%) male (mean age= 36±9 years) and control group included 23 (50%) female and 23 (50%) male (mean age=35±8 years). The mean value of TST in millimeters for whole group was 6.3±7.6 and similar between groups(p>0.05). The number of cases with BCG scars were significantly more in COVID-19 group (p=0,04). The TST results of COVID-19 group were shown in Table 2. 29 (28.4%) cases in COVID-19 group were hospitalized while only 1(1%) suffered from severe disease. None of the cases were died. The COVID-19 group was divided into subgroups according to presence of BCG scar and TST result. No relation was found between TST value, positivity and presence of BCG scar with the laboratory parameters, clinical features, radiological severity and hospitalization rate (p>0.05). The mean PCR conversion time was 10±3.7 days and similar in BCG and TST subgroups (Table 3).Evaluation of radiological severity of COVID-19 in TST and BCG subgroupswas shown in Table 4. There was no difference between TST and BCG subgroups according to radiological severity(p=0,921, and p=0.683 respectively).

		n (%)	TST value (mm) mean ± SD	p value
Sex	Female	67 (65.7)	5.6±6.9	0.886
	Male	35 (34.3)	5.4±5.9	
Hospitalization	No	70 (68.6)	6.2±6.9	0.153
	Yes	32 (31.3)	4.1±5.5	
Degree of radiological severity on CT	No pneumonia	64 (62.7)	6.1±6.9	0.376
	Mild	22 (21.6)	4.6±5.6	
	Moderate	13 (12.7)	4.46±6.553	

Table 2: Evaluation of TST values of COVID-19 group.

	TST, n (%)	mean ± SD	p value	BCG scar, n (%)	mean ± SD	p value
The lowest number of lymphocytes /ml	Negative 51(50.5)	1758.8±728.1	0,092	No 8(7.8)	1612.5±640.2	0.542
	Weakly positive 25(24.7)	1686.4±663.2				
	Positive 12(11.9)	1456.7±596.7		Yes 94(92.2)	1767.8±692.7	
	Strongly Positive 13(12.9)	2133.1±546.6				
Hospital stay, days	Negative 51(50.5)	2.5±3.9	0.391	No 8(7.8)	1±4	0.564
	Weakly positive 25(24.7)	1.4±2.9				
	Positive 12(11.9)	1.8±2.9		Yes 94(92.2)	2±3	
	Strongly Positive 13(12.9)	1.0±2.5				
Time for PCR conversion, days	Negative 51(50.5)	10.5±4.0	0.262	No 8(7.8)	11±4.03	0.429
	Weakly positive 25(24.7)	9.1±2.3				
	Positive 12(11.9)	11.0±4.7		Yes 94(92.2)	9.9±3.68	
	Strongly Positive 13(12.9)	9.1±3.6				

Table 3: Evaluation of the relation of TST results, BCG scar and hospital stay time and lowest number of lymphocytes in COVID-19 group.

Degree of radiological severity on CT	TST, n (%)				BCG scar, n (%)	
	Negative	Weakly positive	Positive	Strongly Positive	No	Yes
No pneumonia	30 (58.8)	17 (68.0)	7 (58.3)	10 (76.9)	6(75)	59(62.8)
Mild	12 (23.5)	6 (24.0)	3 (25.0)	1 (7.7)	2(25)	20(21.3)
Moderate	8 (15.7)	2 (8.0)	2 (16.7)	2 (15.4)	0(0)	14(14.9)
Severe	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0(0)	1(1.1)
Total	51 (100.0)	25 (100.0)	12 (100.0)	13 (100.0)	8(100)	94(100)

Table 4: Evaluation of radiological severity of COVID-19 in TST and BCG subgroups.

Discussion

The initial observations about COVID-19 pandemics revealed that in the countries that do not perform childhood BCG vaccination including the United States and European countries such as Italy, Spain, and France, the prevalence and mortality were more than the countries that provide BCG vaccination[1-2]. So, it was speculated that BCG vaccine might have a nonspecific and cross-protective immunity on COVID-19[12-16]. The HCW are under increased risk for SARS CoV-2 infection[5-7]. In this study our aim was to investigate the relation between BCG, TST with the rate and clinical course of COVID-19 infection in HCW. The positive TST may reflect latent tuberculosis (TB) infection but may also result from prior BCG vaccination. BCG vaccination is included in routine childhood vaccination schedule and performed in infancy and repeated at age of 7 years in our country. Previous studies revealed that BCG vaccine has a protective effect on TB by enhancing cellular immunity, also it provides a long-term immune response and provides protection against respiratory tract infections and viral infections like influenza A and H1N1 resulting in a decrease in all-cause morbidity and mortality[10,12-16]. The authors speculated that BCG could have a nonspecific protective effect on COVID-19 via stimulation of immune system[16,18,19]. However, the difference between countries in terms of COVID-19 prevalence, morbidity and mortality may be due to several other factors such as age, comorbidities and national differences[1]. The protective effect of BCG vaccination is decreased by time. In a study from Norway it was reported that the effectiveness of BCG against pulmonary TB was decreasing with age and found 40% for 30-40 years[17]. The mean age of HCW in our study was 35±9 years. So, we can suggest that the BCG vaccination may have a protective effect on nearly the half of the group. 94 of 102 cases in COVID group had a BCG scar while 51 had a positive TST. The mean value of TST in millimeters was similar between groups (p>0.05) but the number of cases with BCG scar were significantly more in COVID group (p=0,04). This suggests that BCG vaccination did not have a decreasing effect on susceptibility to SARS CoV-2 infection. 29 cases were hospitalized for COVID-19 and only 1 (1%) suffered from severe disease. This case had a BCG scar but a negative TST. The laboratory parameters, clinical features and radiological severity were similar in COVID group when compared for presence of BCG and TST positivity(p>0.05). There was no mortality among 102 cases. In a study from Germany and Malaysia including 6927 cases the COVID-19 mortality rate in HCW was 0.2% to 0.5%[6]. Our study group was smaller but as there was no cases died we suggested that the BCG vaccination may have a protective effect on COVID-19 mortality.

There are several studies evaluating the relation between COVID-19 infection, BCG vaccination and TB in general population[20-23]. In a previous study from our country the general population was evaluated for developing COVID-19 pneumonia and it was reported that BCG vaccination was not associated with disease severity while age and low income were found as risk factors for developing severe COVID-19 pneumonia[20].

In a study from United States it was reported that patients suffering from COVID-19 with BCG vaccination were reported to require nearly four times less hospital admission[22].

The finding from our study also suggests the potential preventive effect of BCG from severe COVID-19.

In case of coinfection of TB and COVID-19 studies report contradictory results. Gao et al.[23] reported that TB was associated with a 2.10-fold increased risk of severe COVID-19 disease, although the difference was not statistically significant. The authors attributed this increased risk to impaired lung function and decreased resistance to viruses because of active TB. They concluded that TB may be a risk factor for progressive disease but not associated with an increased risk of COVID-19 mortality. On the other hand, Stochino et al.[21] reported that patients with TB and COVID-19 coinfection had a rather benign clinical course, TB lesions at chest X-ray were not aggravated and four over 20 patients developed COVID-19 pneumonia and only one of them died. This finding supports that the immunity against mycobacterium tuberculosis via vaccination or active infection may have a protective effect on COVID-19. Koeken et al showed that the concentrations of proinflammatory proteins in the circulation of healthy volunteers were decreased and this finding reveals that BCG vaccination downregulates the systemic inflammation at the same time[24]. So, immunity against mycobacterium tuberculosis may protect from exaggerated immune response and prevents from cytokine storm which results in severe disease and mortality due to COVID-19. This may be the cause why the COVID-19 disease had a relatively benign course in patients with tuberculosis.

Several countries started clinical trials on HCW and population with older age to investigate if the BCG vaccination decreased the susceptibility and protected from severe COVID-19[5-7]. In the randomized clinical trials ongoing in Holland, HCW are administered either the BCG vaccine or a placebo saline injection to assess if BCG vaccination in adults enables a protection from COVID-19[5]. These clinical trials were not finished yet and there is not enough data about this subject.

Conclusion

In our study there was no relation between BCG vaccination and a positive TST with the clinical course of COVID-19 infection but there was no mortality so we concluded that the immunity against tuberculosis is not related with a decreased susceptibility to COVID-19 infection but it may protect from severe disease and mortality. Our study includes a small group and we believe that the results of ongoing clinical trials and other studies will enlighten this topic in the future.

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