DOI: 10.4274/terh.galenos.2022.61214
J Tepecik Educ Res Hosp 2022;32(1):147-50

CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Intracavitary Bacillus Calmette-Guérin Treatment for Bladder Cancer: Is it Protective Against COVID-19?

Mesane Kanserinde İntrakaviter Bacillus Calmette-Guérin Tedavisi: COVID-19'a Karşı Koruyucu mu?

Mehmet Zeynel Keskin[1], Mert Hamza Özbilen[1], Kenan Teker[2]

[1]University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Clinic of Urology, İzmir, Turkey
[2]University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Clinic of General Surgery, İzmir, Turkey

Cite as: Keskin MZ, Özbilen MH, Teker K. Intracavitary BCG Treatment for Bladder Cancer: Is it Protective Against COVID-19? J Tepecik Educ Res Hosp 2022;32(1):147-50

Abstract

Objective: To investigate whether the intravesical Bacillus Calmette-Guérin (BCG) administered to non-muscle invasive bladder cancer (NMIBC) patients has a protective effect against Coronavirus disease-2019 (COVID-19).

Methods: Six hundred and ninety-nine patients with NMIBC were enrolled in the study. The patients were divided into 2x2 groups based on the conditions of having received BCG treatment and having had a COVID-19 infection. The normality of the distribution was analyzed using the Shapiro-Wilk test. Statistical relationships between the groups were analyzed using the chi-square test. P<0.05 was considered statistically significant.

Results: There were 34 individuals who had a history of COVID-19 infection and 665 who did not, and 273 individuals who received BCG treatment and 426 who did not. A history of COVID-19 infection was encountered in 18 (6.6%) of the 273 patients who received BCG treatment and in 16 (3.8%) of the 426 patients who did not receive BCG treatment. The 2x2 statistical association between the groups was analyzed using the chi-square test and a statistically significant relationship was not determined (p=0.065).

Conclusion: As we initiated the study, we expected lower rates of COVID-19 infection in patients who received intravesical BCG; however, the results of this study showed us that this was not the case. The disease was encountered at higher rates in those who received intravesical BCG in contrast with our expectations; however, this difference was not statistically significant.

Keywords: COVID-19, BCG, intracavitary immunotherapy

Öz

Amaç: Kas invaziv olmayan mesane kanseri (KİOMK) hastalarına uygulanan intravezikal Bacillus Calmette-Guérin'in (BCG) Koronavirüs hastalığı-2019'a (COVID-19) karşı koruyucu etkisinin olup olmadığını araştırmaktır.

Yöntem: KİOMK'li 699 hasta çalışmaya alındı. Hastalar BCG tedavisi alma ve COVID-19 enfeksiyonu geçirme durumlarına göre 2x2 gruba ayrıldı. Dağılımın normalliği Shapiro-Wilk testi kullanılarak analiz edildi. Gruplar arasındaki istatistiksel ilişkiler ki-kare testi kullanılarak analiz edildi. P<0,05 istatistiksel olarak anlamlı kabul edildi.

Address for Correspondence/Yazışma Adresi: Mert Hamza Özbilen MD, University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Clinic of Urology, İzmir, Turkey
Phone: +90 507 993 06 06 **E-mail:** merthozbilen@hotmail.com
ORCID ID: orcid.org/0000-0002-5733-6790

Received/Geliş tarihi: 31.01.2022
Accepted/Kabul tarihi: 14.02.2022

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Öz

Bulgular: COVID-19 enfeksiyonu öyküsü olan 34, olmayan 665 kişi ve BCG tedavisi alan 273, almayan 426 kişi vardı. BCG tedavisi alan 273 hastanın 18'inde (%6,6), BCG tedavisi almayan 426 hastanın 16'sında (%3,8) COVID-19 enfeksiyonu öyküsüne rastlandı. Gruplar arasındaki 2x2 istatistiksel ilişki ki-kare testi kullanılarak analiz edildi ve istatistiksel olarak anlamlı bir ilişki saptanmadı (p=0,065).

Sonuç: Çalışmayı başlatırken intravezikal BCG alan hastalarda daha düşük COVID-19 enfeksiyon oranları bekliyorduk; ancak bu çalışmanın sonuçları bize durumun böyle olmadığını gösterdi. Beklentilerimizin aksine intravezikal BCG uygulananlarda hastalığa daha yüksek oranda rastlandı; ancak bu fark istatistiksel olarak anlamlı değildi.

Anahtar Kelimeler: COVID-19, BCG, intrakaviter immünoterapi

Introduction

Coronavirus disease-2019 (COVID-19), which has become global since December 2019, occurs due to becoming infected with the Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) virus, a member of the coronavirus family culminating in severe acute respiratory syndrome[1,2]. The fact that the disease causes mortality around the world has entailed a search for medications and vaccination research. To this day, antimalarial medication such as hydroxychloroquine, antiviral medication such as favipiravir and antibiotics such as azithromycin have been used in the hope of reducing mortality[3]. At times, neutralizing antibodies were given to the patients as a last resort in advanced cases by obtaining convalescent plasma; however, unfortunately, the desired effect could not be achieved[4,5].

Particularly in the beginning of the outbreak, higher levels of mortality were expected in developing countries due to the shortcomings of the health infrastructure as opposed to expectations of lower mortality in developed countries. However, as the days progressed, a different reality was encountered, where the disease demonstrated the highest number of deaths in countries such as the United States of America and Italy and surprised many scientists by showing a milder progression in African countries[6]. Certain hypotheses have been proposed to explain these surprising findings, including the hypothesis that "it is caused by the protective effects of the Bacillus Calmette-Guérin (BCG) vaccine[7]. When the situation is considered in this regard; the BCG vaccine was never included in the national immunization policy in countries such as Italy and the United States, where the virus caused the highest mortality[8]. Meanwhile, the BCG vaccine is included in the national immunization policy in countries such as China and Russia and the mortality associated with the virus has been lower in these countries. However, countries such as Germany have abandoned routine BCG vaccination in children and only vaccinate certain risk groups[8]. It has been determined that the BCG vaccine reduces neonatal mortality and that conditions such as sepsis, respiratory tract infection and fever are encountered less frequently in BCG-vaccinated neonates[9].

As a result, studies have reported that the BCG vaccine has a protective effect against COVID-19 infections[10]. Certain articles have even proposed interesting ideas such as; "Does the intravesical BCG administration performed for immunotherapy in bladder cancer also have a protective effect against COVID-19?"[7]

In this study; we investigated whether the intravesical BCG administered to patients with non-muscle invasive bladder cancer (NMIBC) has a protective effect against COVID-19.

Materials and Methods

Patients who presented to the urology polyclinic between March 2020-March 2021 were retrospectively reviewed and 699 patients with NMIBC were enrolled to the study. The patients were divided into 2x2 groups based on the conditions of having received BCG treatment and having had a COVID-19 infection. The normality of the distribution was analyzed using the Shapiro-Wilk test. Statistical relationships between the groups were analyzed using the chi-square test. Statistical associations were investigated using IBM Statistical Package for Social Sciences version 25.0. P<0.05 was considered statistically significant.

Results

The mean age of the 699 patients included in the study was 67.41±11.46 (19-97) years. There were 34 individuals who had a history of COVID-19 infection and 665 who did not, and 273 individuals who received BCG treatment and 426 who did not. A history of COVID-19 infection was encountered in 18 (6.6%) of the 273 patients who received BCG treatment and in 16 (3.8%) of the 426 patients who did not receive BCG treatment. The 2x2 statistical association between the groups was analyzed using the chi-square test and a

statistically significant relationship was not determined (p=0.065) (Tables 1, 2).

Discussion

When the pathophysiology of the clinical picture caused by the COVID-19 virus, which has spread over the entire world, is considered; it is thought that the pathogen recognition receptor (PRR) fails to recognize the virus or that the virus can somehow evade the receptor, resulting in viral infiltration extending to the alveoli of the host, particularly in COVID-19 cases with severe and fatal progressions[11,12]. The escape of the virus from the receptor and the subsequent release of cytokines such as tumor necrosis factor, interleukin (IL)-6, IL-1 β, which is termed as a cytokine storm, cause an unregulated increase in vascular permeability, leading to multiple organ failure and a rapid loss of patients[12]. Because the clinical picture is sometimes severe to such extents, an urgent need for vaccination research emerged[13]. However, protective factors that could alleviate the destructive effects of the disease or prevent its transmission were investigated until the development of an effective vaccine, and at this particular stage, studies that have reported favorable results about the protective effects of the BCG vaccine were published[14]. When the literature is reviewed concerning the mechanism underlying this protective effect of the BCG vaccine, a protective effect encompassing herpes and influenza viruses is described. Some studies have shown that the BCG vaccine decreases the risk of viral pneumonia in elderly patients and the protective effect was reported to originate from the IL1-β-based immunomodulatory effect of the BCG vaccine[15-18]. Another study reported that that the BCG vaccine reduces the cytokine storm caused by the COVID-19 virus, thus causing the COVID-19 infection to have a milder progression[19]. In countries such as Italy and the United States of America, where the virus caused the highest levels of mortality, the BCG vaccine was never included in the national immunization policy. However, the BCG vaccine is included in the national immunization policy in countries such as China and Russia and the mortality associated with the virus was lower in these countries[8]. This situation serves to support the protective effect of the BCG vaccine.

As is known, the BCG vaccine is not only used in the prevention of the infection caused by the tuberculosis bacilli, it is also administered intravesically for treating NMIBC in the urology practice[20]. Although the literature holds questions as to the protective effect of intravesical BCG administration against the COVID-19 infection[7], no studies have been conducted on this matter.

Study Limitations

The retrospective design of our study and the small number of cases who had a history of COVID-19 infection constitutes the primary aspects of this work that are open to criticism and the limitations of our study. Prospective clinical studies including larger patient populations are needed for confirmation.

Table 1. Data of the 2x2 groups

	BCG (-) n (%)	BCG (+) n (%)	Total
COVID-19 (-)	410 (96.2%)	255 (93.4%)	665 (95.1%)
COVID-19 (+)	16 (3.8%)	18 (6.6%)	34 (4.9%)
Total	426 (100%)	273 (100%)	699 (100%)

COVID-19: Coronavirus disease-2019, BCG: Bacillus Calmette-Guérin

Table 2. Statistical analysis results

Chi-square tests

	Value	df	Asymptotic significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson chi-square	2,895[a]	1	0.089		
Continuity correction[b]	2,314	1	0.128		
Likelihood ratio	2,818	1	0.093		
Fisher's exact test				0.105	0.065*
Linear-by-linear association	2,891	1	0.089		
N of valid cases	699				

[a]0 cells (0%) have expected count less than 5. The minimum expected count is 13.28.

[b]Computed only for a 2x2 table.

*p<0.05

Conclusion

Our study is the first study in the literature in this regard. As we initiated the study, we expected lower rates of COVID-19 infection in patients who received intravesical BCG; however, the results of this study showed us that this was not the case. In our study, rates of COVID-19 were 6% and 3% in bladder patients who received intravesical BCG and in those who did not, respectively. Therefore, the disease was encountered at higher rates in those who received intravesical BCG in contrast with our expectations; however, this difference was not statistically significant.

Ethics

Ethics Committee Approval: Ethics committee approval was not obtained due to the retrospective nature of the study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.Z.K., M.H.Ö., K.T., Design: M.Z.K., M.H.Ö., K.T., Data Collection or Processing: M.Z.K., M.H.Ö., K.T., Analysis or Interpretation: M.Z.K., M.H.Ö., K.T., Literature Search: M.Z.K., M.H.Ö., K.T., Writing: M.Z.K., M.H.Ö., K.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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