

ORIGINAL PAPER

Does intravesical *Bacillus Calmette-Guérin* for bladder cancer protect from COVID-19?

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Summary

Introduction: The study aimed to correlate the history of intravesical BCG as well as infantile BCG immunization with the incidence and severity of COVID-19 infection.

Methods: Retrospective data collection of patients with high-risk non muscle invasive bladder cancer (NMIBC) from two Canadian centers. Data collection included a history of BCG instillation, infantile immunization, and the development of COVID-19 infection. Admission and/ or mortality because of COVID-19 was reported.

Results: We could include data from 348 patients: including 188 and 160 patients from Ontario and British Columbia respectively. COVID-19 affected 15% of these patients. Intravesical BCG was used in 44% of these patients. Intravesical BCG and/or infantile BCG immunization did not correlate with the incidence of COVID-19 infection.

Conclusions: Previous intravesical BCG and/ or a history of infantile BCG vaccination were not more/ less frequent in patients who had COVID-19 infection.

KEY WORDS: Bladder cancer; BCG; COVID-19.

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INTRODUCTION

The COVID-19 pandemic represented an unprecedented time in modern society, resulting in mortality and morbidity worldwide, as well as significant strain on healthcare resources and professionals. Early in the pandemic, tremendous efforts were put forth to identify a vaccination against the etiologic agent in COVID-19 infection, SARS-CoV-2 virus. This infection is associated with deregulation of innate immune responses, ultimately resulting in systemic inflammation and mass virus replication (1). *Trained immunity* (TI) is a non-specific, protective inflammatory response generated from immunization against an unrelated pathogen (2). As such, TI was proposed as a mechanism to tackle infection and spread by creating an early immune response (1). Prior to the creation of COVID-19 specific immunizations, there was interest in the *Bacillus Calmette-Guérin* (BCG) vaccine for protection against COVID-19. The BCG immunization contains live-attenuated *Mycobacterium bovis* and is used to protect against tuberculosis in countries with high incidence (3). The BCG vaccine has reliably demonstrated TI, protecting against

numerous unrelated pathogens, including several respiratory infections such as influenza A and RSV (4). Interestingly, countries with higher rates of BCG immunization were observed to experience lower mortality rates from COVID-19 infections compared to countries with lower rates of immunization during the height of the pandemic (5). BCG therapy also represents an important role in the field of urology. Intravesical BCG therapy is the gold-standard adjuvant therapy for *non-muscle invasive bladder cancer* (NMIBC) (6). Though its specific mechanism remains elusive, its therapeutic role in NMIBC has been attributed to local and systemic immune responses (7). Consequently, there was growing interest in a possible role for this therapy in protection against COVID-19 infection and symptom burden. Some evidence has suggested NMIBC patients receiving intravesical BCG therapy had lower COVID-19 case-fatality rate than the overall population (8). Further research on the role of BCG immunization and intravesical therapy on COVID-19 infection has been limited. As such, we sought to determine whether intravesical BCG and/or infantile BCG vaccination in patients with NMIBC affected the incidence of COVID-19 infection.

METHODS

Retrospective data collection of patients with high-risk NMIBC diagnosed after January 1, 2015, from two Canadian centers. Data collection included basic demographic (age/sex/race), clinical (smoking history/comorbidities/prior BCG vaccination or tuberculosis infection), pathologic (stage/grade of tumour), treatment (intravesical BCG/chemo) and outcome (recurrence/progression) variables. Details on BCG including the number of instillations and duration of treatment were obtained.

A simple survey was also sent to patients to record possible signs and symptoms of COVID-19, or a documented infection. The severity of COVID-19 infection was measured by hospitalization, admission to ICU and death. The survey was sent at the end of the pandemic.

RESULTS

In this study, 348 patients who had been diagnosed with high-risk NMIBC were included. All patients lived in Canada, however, 188 were from Ontario and 160 were

from British Columbia. The mean age was 74 ± 10 . Of the 348 participants, 44% ($n = 152$) had received intravesical BCG therapy. History of BCG immunization could only be obtained from the Ontario cohort, with 60% ($n = 113$) being immunized. It was observed that 24% ($n = 45$) of the Ontario cohort had received both intravesical BCG therapy and had a history of infantile BCG immunization. Overall, 15% of participants were infected with COVID-19. There was no significant difference in the incidence of COVID-19 infection between those with and without a history of infantile BCG immunization ($p > 0.05$) and between those who had and had not received intravesical BCG therapy ($p > 0.05$). Comparison of those with BCG immunization and/or BCG intravesical therapy and those with neither intervention did not identify a significant difference in COVID-19 ($p > 0.05$). Additionally, there was no significant difference in COVID-19 incidence between those with a combined history of intravesical BCG and BCG immunization with other participants ($p > 0.05$). Table 1 illustrates these findings. The median number of BCG doses administered was the same in patients who had been infected with COVID-19 and those who had not (12 vs. 12 doses; $p > 0.05$).

There was one incidence of mortality attributed to COVID-19 infection in a patient who did not receive intravesical BCG nor had infantile BCG. Three cases required non-ICU hospital admission. This included 2 patients who received both infantile and intravesical BCG and one patient who did not receive either. The 3 cases recovered well.

Table 1.
Correlation between BCG vaccination and the development of COVID-19 infection.

		No COVID-19	COVID-19	P value
Infantile BCG	No	58	17	0.3
	Yes	79	34	
Intravesical BCG	No	161	35	0.1
	Yes	135	17	
Infantile and/ or intravesical BCG	No	31	13	0.7
	Yes	106	38	
Infantile and intravesical BCG	No	105	38	0.8

Discussion

Given the widespread implications of COVID-19 infection, significant efforts have been made to understand the relationships between this infection and well-established medical practices. BCG immunization has reliably demonstrated the ability to confer non-specific protection against various illnesses (4). The ability of intravesical BCG therapy to induce such protection remains unclear, although laboratory investigations have suggested intravesical BCG is capable of TI (9). High-risk NMIBC patients who had received intravesical BCG therapy represent a unique group of patients during the pandemic, as they had been treated with an agent hypothesized to confer protection against the SARS-CoV-2 virus.

Our study did not identify a relationship between intravesical BCG administration and COVID-19 infection. This is

perhaps unsurprising as BCG therapy is administered locally to the bladder to prevent the recurrence of bladder cancer. Studies have suggested the ability of intravesical BCG to confer TI against some respiratory infections, however, these have not been assessed in human studies⁹. While these installations are believed to generate both local and systemic inflammatory responses (5), the systemic response may not be strong or broad enough to directly prevent COVID-19. This may be supported by a study by Gallegos *et al.* (2021), that identified a higher cumulative incidence of COVID-19 infection, but lower overall mortality in patients who completed intravesical BCG therapy for NMIBC compared to the general population. These authors theorized that intravesical BCG immunization may confer protective benefits in terms of COVID-19 severity, rather than the development of infection (8).

Interestingly, Pichler *et al.* (2023) assessed the ability of intravesical BCG to induce adaptive and innate immunity. They found that repetitive BCG instillations were able to elicit an innate immune response and thus TI in a laboratory setting. It was theorized that it would require a minimum of 6 weeks to elicit this response (10). In our study, those who developed COVID-19 infection and those who did not both received a median number of 12 doses of intravesical BCG, thus spanning a course longer than 6 weeks. Despite this, there was no difference in the incidence of COVID-19 infection in those receiving BCG immunotherapy.

Our data also demonstrated no correlation between BCG immunization and COVID-19 infection. Given the many examples of TI protection from BCG immunization, there was strong speculation about its ability to protect against SARS-CoV-2 as well. This was supported by the observation that countries with mandatory BCG immunization experienced a lower number of COVID-19 cases, in addition to reduced mortality (11). Despite this observation, the World Health Organization (WHO) declared that there was no evidence that the BCG vaccine can protect against COVID-19 (12). Before the development of COVID-19-specific immunizations, several randomized control trials had been started to determine the efficacy of BCG immunization to protect against this infection (13).

There were several limitations to our study. While intravesical BCG therapy was assessed at two centers, the history of immunization was only assessed at a single center and thus faced inevitable selection bias. Further, our study did not account for the comorbidities of patients, which may have influenced their susceptibility to COVID-19 infection. In this study, we only assessed incidence of COVID-19 infection. Future work may seek to categorize the severity and mortality of these patients.

CONCLUSIONS

Overall, this study did not identify a relationship between the incidence of COVID-19 infection and a history of intravesical BCG therapy or BCG immunization in NMIBC patients. The number of intravesical BCG doses received by those who were and were not infected did not vary. Based on these results, it can be concluded that neither form of BCG therapy confers protection against this infection.

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Conflict of interest: The authors declare no potential conflict of interest.