Clinical case

Intravesical bacillus Calmette-Guérin (BCG) instillation: are we doing things right in Latin America?

Instilación intravesical de bacilo de Calmette-Guérin (BCG): ¿estamos haciendo las cosas bien en América Latina?

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Abstract

Introduction and objectives: seventy five percent of bladder cancer is non muscle invasive (NMIBC) for which intravesical instillation with BCG has been the cornerstone of treatment. BCG has been categorized as dangerous; this is why there are international guidelines that describe its use. The objective of this paper is to investigate the adherence of Latin American health workers with guidelines for the safe intravesical application of BCG for NMIBC.

Materials and methods: we conducted an anonymous and self-administered survey during 2 months of 2023 on a digital platform among health workers. It consisted of 19 questions focusing on compliance with standards set by international organizations and its correct use. Descriptive statistics were carried out; $p<0.05$ was considered statistically significant. Correct and safe use of BCG was evaluated through 4 questions.

Results: a total of 295 completed surveys were recorded from 12 countries. A total of 96.61 % (n= 285) performed BCG instillation incorrectly. Prior training was received by 55 % of which 97.5 % administered it incorrectly against 95.48 % who did so without prior training (p=0.33). Before answering this questionnaire, 90.51 % considered their technique adequate against 83.83 % after answering it, observing a change in the perception of participants (p= 0.0139).

Conclusion: there is almost no adherence of health professionals with protocols, so it is crucial to improve training based on international guidelines to minimize the risk of BCG contamination.

Keywords:
BCG vaccine, instillation, adherence, guidelines

Citation: González C. C., Medel R., García Barrios L., Arbizu M., Gramajo Feijoo M., Sánchez Naranjo B., *et al. Intravesical bacillus Calmette-Guérin (BCG) instillation: are we doing things right in Latin America? Rev Mex Urol. 2024;85*(4) 1-10.

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Accepted: December 9, 2024.
Received: June 30, 2025.

Resumen

Introducción y objetivos: el setenta y cinco por ciento de los casos de cáncer de vejiga son de tipo no músculo invasivo (NMIBC), en cuyo tratamiento la instilación intravesical de BCG ha sido fundamental. La BCG se ha categorizado como peligrosa, por lo que existen guías internacionales que describen su uso. El objetivo de este trabajo es investigar la adherencia del personal sanitario latinoamericano a las guías para la aplicación intravesical segura de BCG para el NMIBC.

Materiales y métodos: se realizó una encuesta anónima y autoadministrada durante dos meses de 2023 en una plataforma digital dirigida al personal sanitario. La encuesta constó de 19 preguntas centradas en el cumplimiento de los estándares establecidos por organizaciones internacionales y su uso correcto. Se realizó estadística descriptiva; un valor de $p < 0,05$ se consideró estadísticamente significativo. El uso correcto y seguro de BCG se evaluó mediante cuatro preguntas.

Resultados: se registraron 295 encuestas completadas en 12 países. El 96,61 % (n= 285) realizó la instilación de BCG de forma incorrecta. El 55 % recibió formación previa, de los cuales el 97,5 % la administró incorrectamente, frente al 95,48 % que lo hizo sin formación previa (p= 0,33). Antes de responder a este cuestionario, el 90,51 % consideró su técnica adecuada, frente al 83,83 % después, observándose un cambio en la percepción de los participantes (p= 0,0139).

Conclusión: la adherencia a los protocolos por parte de los profesionales sanitarios es prácticamente nula, por lo que es crucial mejorar la formación según las directrices internacionales para minimizar el riesgo de contaminación por BCG.

Palabras clave: vacuna BCG, instilación, adherencia, directrices

Introduction

Bladder cancer ranks as the ninth most common cancer globally. Approximately 75 % of these cases are non-muscle invasive bladder cancer (NMIBC), characterized by tumors confined to the mucosa (Ta stage or carcinoma in situ [CIS]) or submucosa (T1).[1,2] For the past four decades, intravesical instillation with a live attenuated strain of *Mycobacterium bovis* (BCG) has served as the cornerstone treatment for intermediate and high-risk NMIBC.[3] A widely adopted protocol for NMIBC involves a six-week induction phase with weekly BCG instillations, followed by a maintenance regimen of three weekly instillations administered every six months for one to three years.[4]

However, several organizations, including NIOSH and USP, have categorized the BCG vaccine as hazardous due to the potential for infection through various routes.[5–7] These infections can range from mild urinary tract infections to severe, life-threatening conditions like disseminated tuberculosis, particularly in

immunosuppressed patients. Consequently, numerous international guidelines, including those validated in Spanish, meticulously detail the preparation, administration, and disposal of the medication, along with essential precautions to prevent cross-contamination.[8,9]

To date, there are no published reports on the adherence to these safety guidelines. This study aims to investigate the adherence of healthcare workers in Latin America to safety protocols for the intravesical application of BCG in the treatment of NMIBC.

Materials and method

Population:

During the months of August and September of 2023, a survey was conducted on a digital platform (QuestionPro) among urologists and urology residents in training who used intravesical BCG for the treatment of bladder cancer.

Questionnaire:

The survey focused on practical aspects of BCG instillation; it was anonymous and self-administered. It consisted of a total of 19 questions focused on compliance with the standards set by international organizations for the preparation, administration and precautions for BCG instillation (Table 1). These questions were based on safety protocols by european guidelines validated in spanish.[8,9]

Table 1. Complete questionnaire

Question
1. You are: a. Urologist b. Urology resident in training
2. Age
3. Country where you work
4. Have you completed training regarding intravesical BCG instillation? a. Yes b. No
5. If the answer is yes, what kind of training?
6. Who taught you how to administer intravesical BCG? a. Another resident b. Urologist c. Nurse d. International guidelines/courses

7. Do you consider that you use an adequate technique for BCG instillations? a. Yes b. No
8. Do you provide verbal/physical informed consent? a. Yes b. No
9. Do you request a urine culture prior to starting BCG therapy? a. Yes b. No c. Sometimes
10. Prior to BCG instillation, do you take into account the medication the patient receives? a. Yes b. No
11. Do you use full PPE for instillation? Full PPE: isolation gown, goggles, N95 mask, double pair of gloves and sterile field a. Yes, complete b. Yes, incomplete c. No
12. Do you use a ventilated office? a. Yes b. No c. Sometimes
13. Do you transport BCG yourself previous to the application? Yes No
14. The BCG vaccine used in your institution comes in: a. A syringe b. A glass vial
15. You use: a. A closed system to apply intravesical BCG b. A syringe with injection of air to improve the aspiration the substance c. An empty syringe to aspirate and the dilute the BCG
16. After the application, do you wash the catheter with a saline solution? a. Yes b. No c. Sometimes
17. You discard the used material in: a. A red bag b. A common bag
18. Mark which of the following post application measures you recommend: a. In a male patient, you indicate that he urinates sitting down to avoid the risk of splashing b. After urination, you recommend flushing twice with the lid down c. After urination, you recommend washing the toilet with bleach d. Wash the urethral meatus with soap and water after urination e. Do not drink liquids 6-8 hours prior to instillation f. Hold urination 1-2 hours after instillation g. Wash your hands with soap and water after urination h. Maintain sexual relations with a barrier method after instillations i. None of the above
19. In a scale from 1 to 10: how well do you think you perform BCG instillations?

Statistical analysis:

Descriptive statistics, including mean, standard deviation and percentages, were carried out based on the collection of responses on the digital platform. A $p<0.05$ was considered statistically significant when comparing the studied groups.

Correct and safe use of BCG was achieved when utilizing complete personal protection elements in a ventilated office with a closed system for dilution and administration of the medication and by discarding used material in a pathological waste bag (questions 11, 12, 15 and 17 of the questionnaire).

IBM SPSS statistics ver. 24 was used (IBM Corp., Armonk, NY) for statistical analysis of the data.

Results

A total of 295 completed surveys were recorded with a completion rate of 75 %. Data was obtained from a total of 12 Latin American countries, the most predominant being Argentina, Mexico and Ecuador (Figure 1). The average age was 52 years with a standard deviation of 10.17. A total of 69.15 % (n= 204) were urologists while the rest were urology residents in training.

Figure 1. Countries represented in the survey with their corresponding responses

Table 2 shows the results of the four questions that determine a correct BCG instillation. A total of 96.61 % (n= 285) of the respondents performed BCG instillation incorrectly and unsafely; the remaining 3.39 % (n= 10) comply with international standards. A total of 54.91 % (n= 162) received prior training for this practice, of which 97.5 % (n= 158) administered the medication incorrectly. Out of the 45 % (n= 133) without prior training, 95.48 % (n= 130) performed the procedure incorrectly. Said training did not demonstrate statistically significant improvement of this medical practice (95 % CI -0.06 - 0.02, p=0.33).

Table 2. Results from questions considered for the correct application of BCG

Question	Number (n)	Percentage (%)
11. Do you use full PPE for instillation? Full PPE: isolation gown, goggles, N95 mask, double pair of gloves and sterile field.		
Yes, complete PPE	33	11.37
Yes, incomplete PPE	136	46.1
No	126	42.53
12. Do you use a ventilated office?		
Yes	139	47
No	104	35.33
Sometimes	52	17.67
15. You use:		
A closed system to apply intravesical BCG	49	16.47
A syringe with injection of air to improve the aspiration of the total BCG	57	19.46
An empty syringe to aspirate and then dilute the BCG	189	64.07
17. You discard the used material in:		
A red bag	290	98.2
A common bag	5	1.8
Global administration of BCG:		
Correct	10	96.61
Incorrect	285	3.39

Question 17 included recommendations given by the professional after administering the medication. The most frequent response among those surveyed was holding urination after instillation for one or two hours (Table 3).

Table 3. Question 17 detailing recommendations given after BCG instillation

Question	Percentage among responses (%)
17. Mark which of the following post application recommendations you tell your patients (multiples options allowed):	
In a male patient, you indicate that he urinates sitting down to avoid the risk of splashing	33.68
After urination, you recommend flushing twice with the lid down	29.47
After urination, you recommend washing the toilet with bleach	37.19
You recommend washing the urethral meatus with soap and water after urination	17.19
You discourage from drinking liquids 6/8 hours prior to instillation	24.21
You recommend holding urination 1/2h after instillation	74.03
You recommend washing your hands with soap and water after urination	55.08
You recommend maintaining sexual relations with a barrier method after instillations	25.26
None of the above	0.03

Questions 5 and 20 were related to the participant's perception in relation to their method for BCG instillation before and after answering the survey. Before answering this questionnaire, 90.51 % considered their technique adequate and 83.83 % continued to consider it after answering the survey, observing a statistically significant change in the perception of the participants (95 % CI 0.12 - 0.01, p= 0.0139).

Discussion

Within the spectrum of bladder cancer, Non-Muscle Invasive Bladder Cancer (NMIBC) predominates as the most common subtype. Approximately 60-80 % of these tumors are treated with Bacillus Calmette-Guérin (BCG), a proven therapy that significantly reduces recurrence rates.[10] While bladder cancer in Latin America accounts for 5.8 % of the worldwide cases, the cancer burden in this area is projected to increase by 67 %, reaching 2.4 million new cases annually by 2040 (for all cancers combined), suggesting a similar rise for bladder cancer specifically within the region.[11]

However, the application of BCG requires specific precautions to prevent cross-contamination of both healthcare personnel and other patients within the same healthcare facility. The risk of *Mycobacterium bovis* infection in healthcare personnel is well-documented. For instance, Vigler *et al.* (2008) reported a case where a professional accidentally inoculated themselves with the bacteria in the hand due to not using a closed circuit during medication dilution, a practice specified in international guidelines.[12]

Furthermore, there is a distinct risk of cross-contamination when handling this type of drug. One of the earliest papers to demonstrate this phenomenon was by Waecker *et al.* (2000),[13] which described three pediatric oncology patients who developed *M. bovis* tuberculosis symptoms without an apparent epidemiological link to justify the infection. Vos *et al.*[14] (2003) later investigated five similar cases across three hospitals in the Netherlands. Their findings indicated that BCG preparation occurred in the same physical space as chemotherapy administration for other patients, establishing this as a probable nexus for cross-contamination.

More recently, Meije *et al.*[15] (2017) studied the epidemiological link for nine patients with central venous catheters who contracted pulmonary tuberculosis in clinics in Barcelona without prior intravesical BCG instillation. Their paper suggests that the primary route of contagion and contamination was aerosolization due to the absence of closed circuits for BCG dilution. This led to contamination of medication subsequently used in other patients' venous catheters. Another route of infection was described by Aqua *et al.* (2021),[16] where a patient underwent surgery in the same operating room where an abdominal procedure had occurred 48 hours prior for peritonitis secondary to intravesical BCG instillation. This patient later developed *Mycobacterium bovis* infection, with the operating room identified as the sole demonstrable epidemiological nexus.

Such documented cases have spurred improvements in BCG preparation and administration processes among healthcare personnel in the United States.[17] To date, no published cases of *M. bovis* cross-contamination in Latin America exist, which could potentially be attributed to the high prevalence of *Mycobacterium tuberculosis* in the region.

Our survey successfully achieved its objective by revealing not only poor adherence to BCG administration protocols but also an erroneous perception of compliance among the studied population. Moreover, prior training did not correlate with improved outcomes in BCG instillation, highlighting a critical need for enhancement in this aspect of urological training. Nonetheless, the survey effectively demonstrated that participants recognize existing deficits and opportunities for improvement regarding intravesical BCG instillation. We believe targeted training should be universally administered to all urologists to refine this technique and minimize infection risks for every patient attending a healthcare center.

Currently, there's a notable lack of studies addressing the safe use of BCG and its impact on both treatment success rates and potential effects on medical personnel who administer the drug. We believe this represents a significant area worthy of epidemiological analysis.

Limitations of our study include the heterogeneous nature of healthcare systems, which may contribute to variations in supply chain difficulties related to BCG acquisition and subsequent application.

Conclusion

Intravesical BCG instillation for NMIBC treatment necessitates strict adherence to safety protocols to protect both healthcare personnel and patients. Our findings highlight a critical gap in compliance among health professionals, underscoring the urgent need for enhanced training programs based on international gui-

delines to minimize the risks of BCG contamination and infection.

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