

# Frequency of Complications Post-Intravesical BCG Instillation in Patients with Superficial Urinary Bladder Carcinoma

ABDULLAH<sup>1</sup>, OMER DILAWAR<sup>2</sup>, MUHAMMAD KAMRAN AFZAL<sup>3</sup>, FOZIA NOREEN<sup>4</sup>, RIFAT YASMIN<sup>5</sup>, AAMIRA ALI<sup>6</sup>

<sup>1</sup>Assistant Professor, <sup>2</sup>Consultant Urologist, <sup>3</sup>Senior Medical Officer, Department of Urology, Wah Medical College, POF Hospital, Wah Cantt

<sup>4</sup>Assistant Professor, Department of Pathology, Wah Medical College, Wah Cantt

<sup>5</sup>Assistant Professor, Department of Medicine, Wah Medical College, Wah Cantt

<sup>6</sup>Consultant Oncologist, POF Hospital, Wah Cantt

Correspondence to: Abdullah, Email: [aabdullah694@gmail.com](mailto:aabdullah694@gmail.com), Cell: 0336-1509889

## ABSTRACT

**Objectives:** To analyze patients who underwent intravesical BCG instillation for non-muscle invasive bladder tumor and to determine the frequency of complications after intravesical BCG instillation.

**Study Design:** Cross-sectional study.

**Place and Duration of Study:** Departments of Urology and General Surgery, Pakistan Ordinance Factories Hospital Wah Cantt from 1<sup>st</sup> January 2019 till 31<sup>st</sup> December 2020.

**Methodology:** Fifty patients;

**Results:** The mean age was 57.06±7.93 years. Forty two patients (84%) were male and 8 patients (16%) were female. Four patients (8%) were Ta stage, 34 patients (68%) were Tis stage and 12 patients (24%) were T1 stage. Mean time interval between TURBT and BCG instillation was 28.68±5.07 days, mean number of BCG instillation cycles was 6.80±2.06 days. Ten (20%) patients had urinary tract infection, 19 (38%) patients had bladder TB, 9 (18%) patients had BCG sepsis, 5 (10%) patients had miliary TB, 2 (4%) patients had epididymo-orchitis, 2 (4%) patients developed ophthalmic complications, 1 (2%) patient had polyarthralgia, 1 (2%) patient had septic arthritis and 1 (2%) patient developed spinal

**Conclusion:** Bacillus Calmette-Guérin is most commonly used drug as chemotherapeutic agent for superficial bladder tumors after TURBT. Repeated cycles of BCG i.e. 6-12 cycles have been administered to patients. Previously most of symptoms i.e. LUTS, dysuria, hematuria were being associated with presence of tumor but now many case reports and few studies have associated these symptoms with BCG administration.

**Keywords:** Superficial bladder carcinoma, Intravesical BCG, Lower urinary tract symptoms

## INTRODUCTION

Bladder cancer is more prevalent urological tumor with rate of 11,000 cases increasing per year.<sup>1</sup> Transurethral resection for superficial bladder tumor is recommended method of treatment but it has been recorded that after resection, 61% bladder tumors recur which has brought a recommendation of adjuvant treatment. FDA in 1990 recommended BCG as adjuvant therapeutic agent for superficial bladder tumor.<sup>2</sup> Intravesical bacillus Camille-Guerin (BCG) therapy use as adjuvant therapy for high grade superficial bladder tumors is being done since then.<sup>3</sup>

Intravesical BCG for superficial G2T1 and G3 Ta/T1 transitional cell carcinoma of urinary bladder and for carcinomas in situ ablation is being used for bladder cancer management. It has been observed that early recurrences are less common with intravesical BCG use than transurethral resection (TUR) alone.<sup>1</sup> Mostly an induction course of intravesical BCG followed by maintenance therapy up to 36 months is the therapeutic regimen recommended for treatment.<sup>3</sup>

Adverse effects observed after intravesical BCG can be minor effects to severe effects. Complications of BCG therapy are most commonly cystitis and low-grade fever with bodyaches.<sup>4</sup> BCG-related epididymo-orchitis has been reported in case studies.<sup>5</sup> Other side effects observed include nausea, hematuria, and dysuria. Severe complications post intravesical BCG administration include pneumonitis, hepatitis, sepsis, and even death which have been observed in upto 5% patients.<sup>6</sup>

Systemic complications develop are blood-derived secondary to dissemination of BCG bacilli. Local side effects include chemical cystitis, infective cystitis, gross haematuria, and granulomatous prostatitis. Systemic complications present as high-grade fever, pneumonitis with or without hepatitis, and sepsis.<sup>7</sup> No study had been conducted on overall complication characters and rate on larger scale.

In this study, we goal was to follow patients suffering for non-muscle invasive bladder tumor undergoing intravesical BCG instillation at POF Hospital during last 2-years. Our aim was to determine the frequency of complications after Intravesical BCG instillation.

## MATERIALS AND METHODS

Cross sectional study was conducted in Urology and General Surgery Department, POF Hospital, Wah Cantt from 1st January 2019 till 31<sup>st</sup> December 2020. Non probability consecutive sampling was done. Patients with age more 35 years, from both genders with stage 1 papillary cell carcinoma unifocal disease were included in the study. Patients with Stage II, III and IV disease, recurrence of tumor, multifocal disease, patients with history of chronic renal failure and diabetes mellitus were excluded. After ethical committee approval, patients were admitted through OPD after complete history, physical examination, investigations (blood CP, urine R/E, urine C/S, BSR, RFTS, LFTS, HBsAg and Anti-HCV serology, USG abdomen and pelvis – post void volume) by consultant radiologist and informed consent for inclusion in the study was taken. Patient was kept NPO for 6 hours, I/V line was maintained through 18-G I/V canula and bladder emptied through 16 FR Nelton catheter. Solution for intravesical instillation of BCG was prepared (40 mg in 50 ml Normal Saline) and administered through Nelton catheter by specialist oncologist. Patient was kept in right lateral or left lateral position initially for 30 minutes depending upon the tumor location in urinary bladder. After this position of patient was changed every 30 minutes to cover all surfaces of urinary bladder through prone, head elevation and foot elevation upto 30°. After 2 hours of BCG instillation, patient was allowed micturate by him. Patient was advised Tab. Levofloxacin 500 mg OD for 3 days and counselled for adverse symptoms and complications.

Six cycles of BCG instillation was done on weekly basis then follow up history, examination, Urine R/E, Urine Cytology. Urine C/S, Ultrasound abdomen and pelvis and check cytourethroscopy was done after 12 weeks interval since start of treatment post TURBT. Patients developing complications post BCG instillation were consulted with medical specialist and antituberculous therapy was started. All the findings were recorded. The data was entered and analyzed using SPSS-22.

## RESULTS

Four (8%) patients had age <45 years, 9 (18%) patients had age 45-54 years, 27 (54%) patients had age 55-64 years and 10 (20%)

patients had age >65 years with mean age was 57.06±7.93 years. Forty two patients (84%) were male and 8 patients (16%) were female. Thirty four patients (68%) patients had history of smoking and 16 patients (32%) did not smoke. Fifteen (30%) patients worked in chemical industry, 20 (40%) patients worked in dye industry, 10 (20%) patients worked in leather industry, 3 (6%) patients worked in rubber industry, and 2 (4%) patients worked in other industries (Table 1).

Four 4 patients (08%) were Ta stage, 34 patients (68%) were Tis stage and 12 patients (24%) were T1 stage (Table 2). Fourteen (28%) patients had dysuria, 21 (42%) patients had hematuria, 7 (14%) patients had fever, 3 (6%) patients had LUTS, 3 (6%) patients had bodyaches and 02 (04%) patients had joint pains (Table 3).

Mean time interval between TURBT and BCG instillation was 28.68±5.07 days, mean number of BCG instillation cycles was 6.80±2.06 days and mean time interval between BCG instillation and onset of symptoms was 48.14±12.48 days (Table 4).

Table 1: Demographic information of the patients (n=50)

Variable	No.	%
Age (years)		
< 45	10	20.0
45-54	9	18.0
55-64	27	54.0
> 65	4	8.0
Gender		
Male	42	84.0
Female	8	16.0
Smoking history		
Yes	34	68.0
No	16	32.0
Occupation		
Chemical factory	15	30.0
Dye industry	20	40.0
Leather factory	10	20.0
Rubber factory	3	6.0
Others	2	4.0

Table 2: Frequency of stage bladder tumours

Stage of bladder tumour	No.	%
Ta	4	8.0
Tis	34	68.0
T1	12	24.0

Table 3: Frequency of presenting symptoms

Symptoms	No.	%
Dysuria	14	28.0
Hematuria	21	42.0
Fever	7	14.0
LUTS	3	6.0
Bodyaches	3	6.0
Joint Pains	2	4.0

Table 4: Frequency of BCG therapy and Cycles

BCG therapy and Cycles	Mean±SD
Interval between TURBT and BCG instillation	28.68±5.07
Number of BCG Instillation	6.80±2.06
Duration between Onset of symptoms and BCG instillation	48.14±12.48

Table 5: Frequency of complications after BCG instillation

Complication	No.	%
UTI	10	20.0
Bladder TB	19	38.0
BCG Sepsis	9	18.0
Milliary TB	5	10.0
Epididmo-orchitis	2	4.0
Ophthalmic Complications	2	4.0
Polyarthralgia	1	2.0
Septic Arthritis-Osteomyelitis	1	2.0
Spinal TB	1	2.0

Ten (20%) patients had urinary tract infection, 19 (38%) patients had bladder TB, 9 (18%) patients had BCG sepsis, 5 (10%) patients had miliary TB, 2 (4%) patients had epididmo-orchitis, 2 (4%) patients developed ophthalmic complications, 1 (2%) patient had polyarthralgia, 1 (2%) patient had septic arthritis and 1 (2%) patient developed spinal TB (Table 5)

## DISCUSSION

Among bladder cancer patients; mechanism of action of BCG is internalization of live BCG by malignant cells resulting in MHC-II up-regulation in tumor affected cells resulting in presenting BCG- and/or tumour-specific antigen to T-cells resulting in T-cell-mediated cytotoxicity.<sup>8</sup> Chronic inflammation of the BCG internalized cells/tissue forms granuloma, resulting in fibrosis/calcification. Repeated cycles of BCG activate lymphocytes resulting from previous sessions causing amplifies immune-mediated response.<sup>9</sup>

Mant theories have been proposed for BCG related complications. One theory says hypersensitivity inflammatory reaction being the cause of complications while another theory mentions active infection for such complications.<sup>10,11</sup> In a study by Pérez-Jacoiste et al<sup>12</sup>, systemic adverse event was defined as the effect post BCG instillation which will regress after antituberculosis treatment and no alternative diagnosis for such symptoms was present. Pommier et al<sup>13</sup> defined BCG infection as presence of pyrexia in the absence of aetiology, for at least 48 h, post BCG therapy or at least one other organ involvement other than bladder.

Severe dysuria/urgency, hematuria, strangury, nausea, body aches and lethargy are most common symptoms after intravesical BCG.<sup>14</sup> Granulomatous prostatitis, epididymo-orchitis, renal abscess and cystitis occurs secondary to exposure of BCG contaminated urine. Epididymo-orchitis is rare complication seen in genital system.<sup>15</sup> In another study, systemic complications were presence of pyrexia, bodyaches, low blood pressure and progressive failure of multiple organs.<sup>16</sup>

Reported frequency of severe complications post BCG immunotherapy is 0.4%.<sup>17</sup> In one study patients manifested with pyrexia (1.9%), miliary TB (0.9%), pneumonitis and hepatitis (0.7%), joint pains (0.5%), itching (0.3%), kidney abscess (0.1%), sepsis (0.4%) and anemia (0.1%). These complications are mostly associated with presence of miliary tuberculosis.<sup>17</sup> In the EORTC study 23.6% patients had increased frequency of micturation post BCG therapy and 22.6% patients complained with gross hematuria.<sup>18</sup> Patients who are diagnosed with bacterial cystitis antibiotics are given; mostly ofloxacin helps in improving the symptoms.

A randomized clinical trial studied local complications post BCG therapy.<sup>19</sup> In the study 858 patients suffering from non-muscle invasive ladder tumor underwent intravesical BCG therapy, 13 patients suffered from bladder ulcerations ranging from 10 to 50 mm.<sup>20</sup> Penile complication after BCG therapy such as granulomatous balanitis have been reported, with complaints of penile swelling, blisters, and ulcers, and sometimes inguinal lymphadenopathy.<sup>21</sup> Other associated symptoms include hydrocele, scrotal skin swelling, intrascrotal calcifications, abscesses, and scrotal sinus formation have been reported as well.

A large meta-analysis including 2602 patients; results showed only 0.1% occurrence of renal abscess post BCG instillation.<sup>22</sup> Pyelonephritis after intravesical BCG administration presents along with systemic manifestations, such as low grade fever, body aches, lethargy, loin pain or weight loss. Rarely osteoarticular complications can occur after BCG therapy.<sup>23</sup>

## CONCLUSION

Bacillus Calmette-Guérin is most commonly used drug as chemotherapeutic agent for superficial bladder tumors after TURBT. Repeated cycles of BCG i.e. 6-12 cycles have been administered to patients. Previously most of symptoms i.e. LUTS,

dysuria, hematuria were being associated with presence of tumor but now many case reports and few studies have associated these symptoms with BCG administration. Rare severe complications like disseminated TB, Septic arthritis and testicular complications have been reported as well.

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