

Prospective Observational Study of Adverse Reactions following Intravesical BCG in Bladder Cancer Patients in Tertiary Hospital in Kerala

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ABSTRACT

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Intravesical BCG instillation is standard treatment for NMIBC following TURBT for specific indications. The presence of adverse effects following BCG instillation in bladder cancer patients has been a matter of study by several researchers. Though a common treatment protocol prospective studies in this area based in India are less common. In this prospective observational study this has been studied in detail. The adverse effects were classified based on the Cleveland classification and managed accordingly. The findings were analysed. Several conclusions were reached upon.

Keywords: NMIBC, Intravesical BCG, Adverse Effects

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INTRODUCTION

Urothelial carcinoma accounts for 90% of bladder tumors 70% are confined to layers above the muscularis propria. These tumors include stages Ta, T1, and Tis, occurring in 70%, 20%, and 10% of NMIBC cases, respectively. Standard primary treatment for NMIBC is transurethral resection, recurrence rates for TUR alone can be as high as 70% with up to 30% progressing to muscle invasive disease requiring cystectomy. Bacillus Calmette-Guérin (BCG) is the most well known and studied of these adjunctive treatments. Since its first description in 1976 by Morales et al., intravesical BCG has become the standard therapy for NMIBC: superior to any other single chemotherapeutic agent for reducing recurrence and preventing progression. Complete response rates are 55–65% for papillary tumors and 70–75% for carcinoma in situ, which inversely indicates that 30–45% of patients will be BCG failures.

MATERIALS AND METHODOLOGY

Primary Objective

To study the adverse reactions following intravesical BCG in bladder cancer patients

Study design: Prospective observational study

Study setting: Department of Urology, Government

Medical College Hospital, Thiruvananthapuram.

Study population: Patients who underwent TURBT and HPR came as high grade and low grade urothelial carcinoma

Study period: 2014–2017

Number of patients: 52

Exclusion Criteria:

- Immunocompromised
- Uncontrolled diabetes mellitus
- Gross haematuria
- h/o BCG sepsis
- Total incontinence

Methodology

Patients after receiving induction therapy of 6 cycles of BCG immunotherapy were followed up weekly as maximum symptoms occur during initial weeks and the data was collected, tabulated and analysed.

OBSERVATIONS

- In our study we observed patients who received intravesical BCG following TURBT and HPR came as high grade and low grade urothelial carcinoma during the study period 2014–2017. We collected

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Table 1. Symptoms noted		
Symptoms %	Yes %	No %
fever	53.8	46.2
dysuria	48.1	51.9
urgency	23.1	76.9
frequency	28.8	71.2
Abd pain	19.2	80.8
haematuria	21.1	78.9
myalgia	25	75
rash	1.9	98.1
arthritis	3.8	96.2
conjunctivitis	1.9	98.1
hepatitis	1.9	98.1
Epididymo orchitis	1.9	98.1

around 52 patients who took BCG and observed the following adverse reactions. Out of 52 patients we observed on primary analysis 13 had no symptoms and in the rest of the patients most common symptoms are irritative symptoms like urgency (23.1%, frequency (28.8%) dysuria (48.1%) fever (53.8%), myalgia (25%) and abdominal pain (19.2%) and the rarest complications like arthritis (3.8%), rash (1.9%), conjunctivitis (1.9%), hepatitis (1.9%) epididymo orchitis (1.9%) see **table 1**. The timing of onset of symptoms was also noted see **figure 1**.

- Secondary analysis was done using sex, age category as exposure factors and post BCG symptoms as outcome factors.

CLEVELAND CLASSIFICATION

Grade 1: Moderate symptoms < 48 hr

- Mild/moderate irritative voiding symptoms,
- mild hematuria,
- fever < 38.5° C
- assessment:- urine culture
- Symptom Management
- Anticholinergics, analgesics, antipyretic and anti-inflammatory

Grade 2

- Severe symptoms and/or > 48 hrs.
- Severe irritative voiding symptoms,
- Hematuria or symptoms lasting > 48 hrs.
- Assessment:- urine culture, CXR, LFTs
- All maneuvers for grade1 + chest radiograph, liver function tests

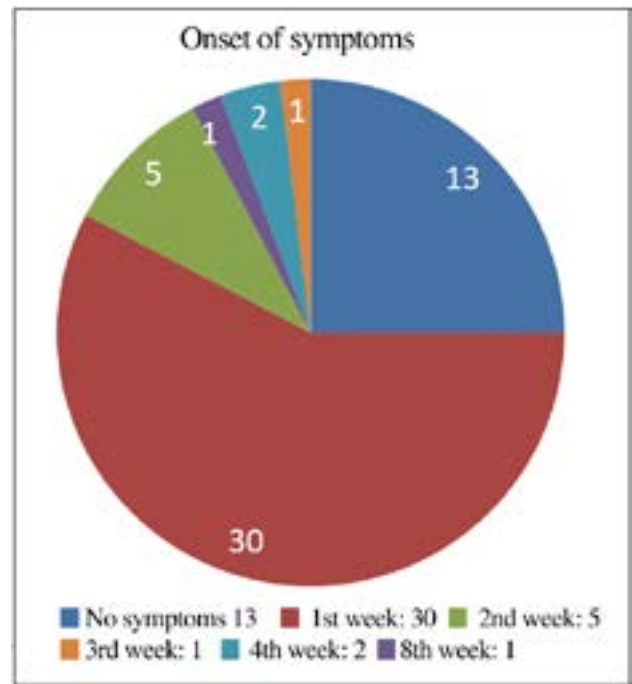


Figure 1. Timing of symptom onset

- Consider dose reduction to one half to one third of dose when instillations resumes.
- Isoniazid and rifampicin, 300 mg/day and 600 mg/day, orally until symptom resolution

Grade 3

- Serious complications hemodynamic changes, persistent high-grade fever, allergic Reactions (joint pain, rash)

Perform all maneuvers described for grades 1 and 2, plus: Isoniazid, 300 mg/day, and rifampin, 600 mg/day, for 3 to 6 months depending on response

Solid Organ Involvement (epididymitis, liver, lung, kidney, osteomyelitis, prostate: Isoniazid, 300 mg/day, rifampin, 600 mg/day, ethambutol, 15 mg/kg/day single daily dose for 3 to 6 months Steroids for septicemia, rash and joint involvement BCG is almost uniformly resistant to pyrazinamide, so this drug has no role.

The symptoms were managed based on these criteria and outcomes tabulated and analyzed see **figure 2**. of symptoms

Onset of Symptoms

- No symptoms 13
- 1st week: 30
- 2nd week: 5
- 3rd week: 1

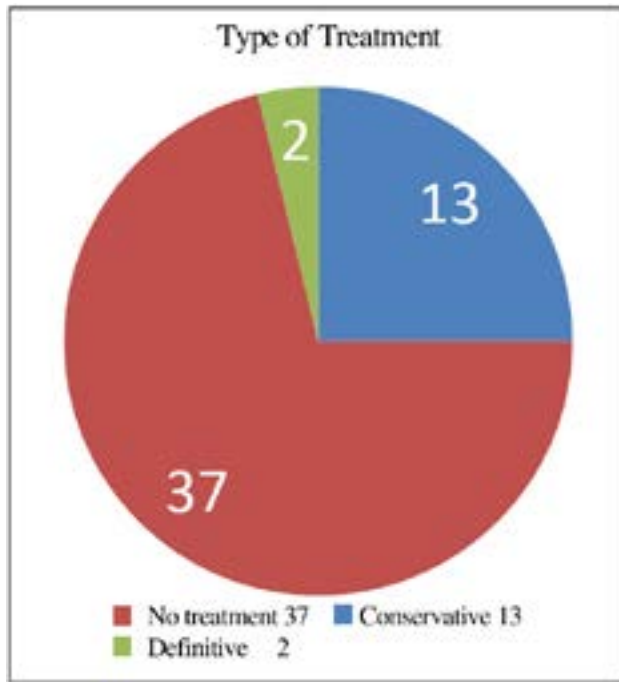


Figure 2. Type of treatment

- 4th week: 2
- 8th week: 1

Type of treatment

- No treatment 37
- Conservative 13
- Definitive 2

Secondary Analysis

Secondary analysis was done using sex, age category as exposure factors and post BCG symptoms as outcome factors.

On analysis the following were found to be statistically significant.

- Age group vs fever (Chi-Square Test) (table 2)
- Age group vs myalgia (Fisher’s Exact Test) (table 3)

DISCUSSION

Intravesical therapy for non-muscle invasive bladder cancer has been a mainstay of treatment since the

		Fever		Total
		Yes	No	
Age 65 or more	Yes	23	12	35
	No	5	12	17
	Total	28	24	52

P value= 0.014
Odds Ratio= 4.600 (1.311-16.139)

		Myalgia		Total
		Yes	No	
Age 65 or more	Yes	12	23	35
	No	1	16	17
	Total	13	39	

P value= 0.026
Odds Ratio= 8.348 (0.985-70.771)

1970s.¹ BCG remains the most effective adjuvant treatment for non-muscle invasive bladder cancer, as demonstrated in multiple clinical trials.² It is also the most effective treatment for carcinoma in situ, in terms of recurrence and progression.³

BCG is a live, attenuated strain of Mycobacterium bovis that was isolated by Calmette in 1921.⁴ The mechanism of tumour destruction due to BCG is not fully understood. One potential mechanism involves internalization of BCG by urothelial cells, which triggers an inflammatory cascade, inducing neutrophil and Th1 chemotaxis.⁵ Th1-induced production of IL-2, TNF, and IFN-γ is thought to mediate tumour destruction.

BCG effectively eradicates existing carcinoma in situ, decreases the likelihood of tumor recurrence, and reduces the odds of disease progression after TUR.

Although its intravesical instillation usually exhibits a favourable safety profile, since it contains viable attenuated mycobacteria the potential for serious adverse events exists.

Most of the data on BCG infection come from single case reports, with only a few observational studies aimed at establishing its incidence. The drawback lies on the lack of diagnostic criteria accurate enough to differentiate true infection from self-limited post-instillation symptoms, and there is no a common disease classification consistently used through the literature.

In an attempt to shed some light on this uncommon complication, we have performed the present institutional observation study

- We have evaluated 52 patients with superficial bladder cancer who underwent BCG only 13 had no symptoms (figure 1) and in the rest of the patients most common symptoms are irritative symptoms like urgency (23.1%), frequency (28.8%) dysuria (48.1%) fever (53.8%) myalgia (25%) and abdominal pain (19.2%) and the rarest complications like arthritis (3.8%), rash (1.9%) conjunctivitis (1.9%), hepatitis (1.9%) epididymo orchitis (1.9%) are also met (table 1)

- Most of the irritative symptoms occurred in the initial weeks of instillation that is first and second week of instillations and treated conservatively and 2 patients developed toxicity treated by definitive treatment
- With aging, the immune system progressively declines in both its innate and adaptive arms. So face an increased risk of complications. In this study we found an apparent association between advanced age and symptoms.

CONCLUSIONS

1. Those who give BCG should be aware of the possible complications and its treatment
2. Side effects occur from the 1st instillation to the last one and the incidence is not increasing over time
3. BCG infection and reaction can occur in any organ or place in the body and this can happen shortly or months to years after BCG treatment making early diagnosis very difficult
4. Most of the common side effects do not need therapy
5. Severe complications are treated with ATT for 6 months

END NOTE

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Editor's Remarks: This original research focuses on the adverse effects of intravesical BCG vaccine instillation for adjuvant treatment in NMIBC patients. There is paucity of dependable Indian studies in this area. This study fills these lacunae. Definitely worth reading.

Conflict of Interest: None declared

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