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Role of oral pentosan polysulfate in Bacillus Calmette–Guérin therapy in patients with non-muscle-invasive bladder cancer

Ho Yeon Lee, Seung Il Jung, Do Gyeong Lim, Ho Seok Chung, Eu Chang Hwang, Dong Deuk Kwon

Department of Urology, Chonnam National University Medical School, Gwangju, Korea

Purpose: Intravesical Bacillus Calmette–Guérin (BCG) instillation, although an important treatment for non-muscle-invasive bladder cancer, exerts local and systemic adverse effects. Pentosan polysulfate (PPS) is a bladder mucosal protective drug that acts by replacing mucus in the glycosaminoglycan layer of the damaged urothelium. We hypothesized that co-administration of oral PPS with BCG instillation would relieve BCG-related adverse effects without affecting its efficacy.

Materials and Methods: A total of 217 patients receiving BCG instillation were enrolled. They were placed in two groups and analyzed retrospectively: group A (n=122) received BCG instillation only and group B (n=95) received 100 mg of PPS thrice daily during the BCG treatment.

Results: After BCG instillation, the rate of BCG-treatment discontinuation owing to adverse effects was 15.6% in group A and 6.3% in group B (p=0.034). The proportion of patients with bacteriuria after BCG was higher in group B; however, no statistical difference was observed (28.7% vs. 41.1%; p=0.057). The proportion of patients with pyuria was significantly higher in group B (81.1% vs. 91.6%; p=0.029). The proportion of patients using antibiotics was significantly higher in group A (73.8% vs. 43.2%; p=0.001). The recurrence rate within 1 year was 29 (23.8%) in group A vs. 19 (20.0%) in group B (p=0.507). Univariate and multivariate analyses showed that antibiotic use had a statistically significant effect on BCG discontinuation.

Conclusions: Oral PPS effectively decreased the discontinuation rate and antibiotic use without affecting the BCG efficacy.

Keywords: Bladder cancer; Intravesical instillation; Pentosan polysulfate; Recurrence; Urinary tract infection

INTRODUCTION

Bladder cancer is among the most common cancer types. It is of two types: muscle-invasive bladder cancer (MIBC) and non-muscle-invasive bladder cancer (NMIBC). Approximately 75% of patients with bladder cancer have NMIBC [1]. If a patient is diagnosed with NMIBC, intravesical Bacillus Calmette–Guérin (BCG) treatment is administered to prevent tumor progression and recurrence after surgical treatment. Although patients generally tolerate BCG treatment, various BCG-related local and systemic adverse effects occur after treatment, such as dysuria, hematuria, frequency, urgency, urinary tract infection (UTI), and pyuria [2]. These adverse effects also affect patient treatment compliance and can lead to BCG-treatment discontinuation. Because of BCG-treatment-related adverse effects, 55% to 83% of treated pa-

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Corresponding Author: Seung Il Jung https://orcid.org/0000-0003-4864-8175
Department of Urology, Chonnam National University Hwasun Hospital, 322 Seoyang-ro, Hwasun-eup, Hwasun 58128, Korea
TEL: +82-61-379-7749, FAX: +82-61-379-7750, E-mail: drjsi@yahoo.co.kr

tients reduce the dose of BCG or delay the treatment, while up to 30% discontinue the treatment altogether [3].

Pentosan polysulfate (PPS) is used in patients with bladder pain syndrome and interstitial cystitis (IC). PPS effectively improves urinary tract symptoms such as dysuria, urgency, and frequency. It is a bladder mucosal protective drug that acts by replacing mucus in the glycosaminoglycan (GAG) layer of the damaged urothelium [4]. Damage to the GAG layer increases the risk of bacterial invasion of the urothelium, which adversely affects UTI occurrence. It has also been reported that PPS administration reduces the incidence of recurrent UTI in women [5].

We hypothesized that, if the administration of oral PPS could help reduce the adverse effects of BCG, including various urinary tract symptoms and UTI, patient compliance could be improved and the BCG-discontinuation rate may be reduced. The reduction in the discontinuation rate should in turn reduce the tumor recurrence rate. Therefore, this study aims to investigate whether the discontinuation rate of BCG treatment can be reduced by reducing the local adverse effects and whether these results affect BCG treatment outcomes.

MATERIALS AND METHODS

This retrospective cohort study was conducted at the Urologic Department of Chonnam National University Hwasun Hospital, South Korea, between January 2017 and December 2020. Patients diagnosed with NMIBC after transurethral resection of bladder tumors (TUR-BT) were enrolled. After TUR-BT surgery, the patients received weekly intravesical BCG instillation for up to 6 weeks. We mixed 125 mg of BCG (Oncotice, Merck, Jersey City, NJ, USA) with 50 mL of saline and instilled it into the bladder using a urethral catheter. Patients diagnosed with NMIBC who did not receive BCG treatment were excluded from the study. A total of 217 patients receiving BCG instillation were selected and placed into two groups, group A (n=122) and group B (n=95), for retrospective analysis. Group A received BCG instillation only, while group B received 100 mg of PPS thrice daily during BCG treatment.

The clinical and oncological characteristics of the two groups were compared. The study outcomes were pyuria, bacteriuria, UTI, BCG-discontinuation rate, antibiotic use rate, non-steroidal anti-inflammatory drug (NSAID) use rate, and tumor recurrence rate after BCG instillation. Further, we evaluated the factors contributing to the discontinuation of BCG treatment.

1. Statistical analysis

Statistical analyses were performed using SPSS software ver. 23.0 (IBM Corp., Armonk, NY, USA). All p-values were two-sided. Statistical significance was set at $p<0.05$. Continuous variables were reported as mean and standard deviations, while categorical variables were reported as frequency (%). Intergroup comparisons were performed using an independent sample t-test for continuous variables and the chi-squared test for categorical variables. Multivariate logistic regression (stepwise backward procedure) was performed to determine the factors influencing the discontinuation of BCG treatment.

2. Ethical approval

The study protocol was reviewed and approved by the Institutional Review Board of Chonnam National University Hwasun Hospital (IRB approval no. CNUHH-2019-223). The study was conducted in accordance with the Declaration of Helsinki and common ethical guidelines for clinical studies. As this is a retrospective study, the need for informed consent of the patients was waived off. All patient data were anonymized and de-identified prior to the analysis.

RESULTS

The baseline clinical and oncological characteristics of both groups prior to the initiation of BCG treatment are presented in Table 1. The two groups had similar mean patient age: 69.1±10.9 years for group A and 70.6±10.3 years for group B. In addition, the two groups had similar clinical characteristics for sex, hypertension, and diabetes mellitus; however, the mean body mass index was significantly higher in group A (25.1 vs. 24.1 kg/m^2; p=0.016), while the proportion of smokers was significantly higher in group B (41.8% vs. 56.8%; p=0.041). The oncological characteristics related to the size, grade, and stage of the tumor did not significantly differ between the two groups; however, patients in group A had a higher number of tumors (81.1% vs. 61.1%; p=0.001). Postoperative urinalyses and urine cultures were performed at 1 to 2 weeks after TUR-BT. No significant differences in the ratios of postoperative pyuria and bacteriuria were observed between the two groups.

After intravesical BCG instillation, the rates of BCG-treatment discontinuation, pyuria, bacteriuria, UTI, and the use of antibiotics and NSAIDs were compared between the two groups (Table 2). The rate of BCG-treatment discontinuation owing to adverse effects was 15.6% in group A and 6.3% in group B, showing a statistically significant difference (p=0.034). The reasons for BCG-treatment discontinuation

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were local or systemic symptoms, such as dysuria, fever, UTI, and hematuria. The proportion of patients with bacteriuria after BCG instillation was higher in group B; however, no statistical difference was observed (28.7% vs. 41.1%; p=0.057). In contrast, the proportion of patients with pyuria after BCG instillation was significantly higher in group B (group A vs. group B, 81.1% vs. 91.6%; p=0.029). The proportion of patients using antibiotics was significantly higher in group A (group A vs. group B, 73.8% vs. 43.2%; p=0.001).

The follow-up period after BCG treatment was significantly shorter in group B than that in group A (group A vs. group B, 32.0±11.1 months vs. 18.6±10.1 months). However, no significant intergroup difference for tumor recurrence rate was observed within 1 year (group A vs. group B, 23.8% vs. 20.0%; p=0.507; Table 3). Univariate and multivariate analyses were conducted to investigate the factors affecting the BCG-treatment discontinuation rate (Table 4). Oncological characteristics, PPS use, and NSAID use did not affect the BCG-discontinuation rate; however, antibiotic use was a significant factor affecting the BCG-treatment discontinuation rate (p=0.011).

Table 1. Comparison of clinical and oncological characteristics between groups before BCG instillation

Variable	Group A (n=122)	Group B (n=95)	p-value
Age (y)	69.1±10.9	70.6±10.3	0.293[a]
Sex, male	104 (85.2)	84 (88.4)	0.496[b]
Body mass index (kg/m^2)	25.1±2.9	24.1±3.1	0.016[a]*
Hypertension	59 (48.4)	55 (57.9)	0.163[b]
Diabetes mellitus	33 (27.0)	28 (29.5)	0.694[b]
Smoker			0.041[b]*
Non-	71 (58.2)	41 (43.2)	
Ex-	34 (27.9)	36 (37.9)	
Current	17 (13.9)	18 (18.9)	
Multiplicity			0.001[b]*
<3	23 (18.9)	37 (38.9)	
≥3	99 (81.1)	58 (61.1)	
Size (cm)			0.128[b]
<3	112 (91.8)	81 (85.3)	
≥3	10 (8.2)	14 (14.7)	
Grade			0.182[b]
PUNLMP	2 (1.6)	0	
Low	35 (28.7)	20 (21.1)	
High	85 (69.7)	75 (78.9)	
Stage			0.421[b]
Tis	11 (9.0)	14 (14.7)	
Ta	73 (59.8)	54 (56.8)	
T1	38 (31.1)	27 (28.4)	
Postoperative pyuria	88 (72.1)	72 (75.8)	0.544[b]
Postoperative bacteriuria	5 (4.1)	8 (8.4)	0.184[b]

Values are presented as mean±standard deviation or number (%).
BCG, Bacillus Calmette–Guérin; Group A, BCG alone; Group B, BCG+oral pentosan polysulfate; PUNLMP, papillary urothelial neoplasm of low malignant potential.
[a]:t-test; [b]:chi-squared test.
*Statistically significant p<0.05.

DISCUSSION

Bladder cancer is classified into NMIBC and MIBC, with the former accounting for approximately 75% of bladder cancers. If a patient is diagnosed with NMIBC after surgery,

Table 3. Comparison of recurrence rate and follow-up durations between two groups after BCG instillation

Variable	Group A (n=122)	Group B (n=95)	p-value
Recurrence	41 (33.6)	27 (28.4)	0.415
Within 1 y	29 (23.8)	19 (20.0)	0.507
Follow-up period (mo)	32.0±11.1	18.6±10.1	0.001*
Period to first recurrence (mo)	10.0±8.0	8.5±5.8	0.17

Values are presented as number (%) or mean±standard deviation.
BCG, Bacillus Calmette–Guérin; Group A, BCG alone; Group B, BCG+oral pentosan polysulfate.
*Statistically significant p<0.05.

Table 2. Comparison of BCG discontinuation rate, prophylactic antibiotics use rate and NSAID use rate between two groups after BCG instillation

Variable	Group A (n=122)	Group B (n=95)	p-value[a]
BCG discontinuation due to local or systemic symptoms	19 (15.6)	6 (6.3)	0.034*
Pyuria	99 (81.1)	87 (91.6)	0.029*
Bacteriuria	35 (28.7)	39 (41.1)	0.057
Prophylactic antibiotic use during BCG treatment	90 (73.8)	41 (43.2)	0.001*
With bacteriuria	58 (47.5)	8 (8.4)	
Without bacteriuria	32 (26.2)	33 (34.7)	
NSAID use during BCG treatment	96 (78.7)	67 (70.5)	0.168

Values are presented as number (%).
BCG, Bacillus Calmette–Guérin; NSAID, non-steroidal anti-inflammatory drug; Group A, BCG alone; Group B, BCG+oral pentosan polysulfate.
[a]:Chi-squared test.
*Statistically significant p<0.05.

Table 4. Univariate and multivariate analyses of factors contributing to discontinuation of BCG treatment

Variable	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Tumor multiplicity (≥3)	1.60 (0.58–4.49)	0.366	1.01 (0.33–3.04)	0.989
Tumor size (≥3 cm)	0.30 (0.04–2.37)	0.257	0.40 (0.05–3.26)	0.394
Antibiotic use	8.94 (2.05–39.0)	0.004*	7.23 (1.58–32.9)	0.011*
Pentosan polysulfate use	0.44 (0.16–1.18)	0.106	0.61 (0.21–1.69)	0.341
NSAID use	1.84 (0.61–5.64)	0.281	1.23 (0.38–4.00)	0.722

BCG, Bacillus Calmette–Guérin; OR, odds ratio; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug.
*Statistically significant p<0.05.

the BCG treatment is administered to prevent tumor recurrence and progression [1]. Over the past 20 years, several studies have investigated the efficacy of intravesical BCG therapy for reducing the risk of recurrence and progression of moderate/high-risk bladder cancer, demonstrating that intravesical BCG therapy after TUR is more effective than TUR alone or a combination of TUR and conventional chemotherapy. In two meta-analyses, intravesical BCG therapy was reported to prevent or at least delay the risk of tumor progression [6,7].

Despite its high efficacy, BCG therapy has several potential local and systemic side effects such as hematuria, pyuria, bacteriuria, dysuria, urgency, and UTI. Consequently, up to 30% of patients discontinue the treatment and 55% to 83% of patients delay the treatment or reduce the number of instillations [3]. Even though treatment may be continued using medications such as anticholinergics for lower urinary tract symptoms, NSAIDs for pain, and antibiotics for BCG-related local or systemic infections [8,9], the discontinuation of BCG treatment due to adverse effects persists.

Several solutions have been proposed to reduce the rate of BCG-treatment discontinuation and the associated discomfort during BCG treatment while also reducing the incidence of side effects. BCG should not be administered in cases of TUR within the previous 2 weeks, traumatic catheterization, macroscopic hematuria, urethral stenosis, active tuberculosis, prior BCG sepsis, immunosuppression, and UTI [10]. The use of ofloxacin as a prophylactic antibiotic has also been investigated. Oral ofloxacin administration after BCG injection reduces the incidence of side effects. However, the long-term efficacy of ofloxacin is unknown and its long-term use carries the risk of bacterial resistance [11,12].

Prophylactic administration of ofloxacin has been proposed to reduce the incidence of side effects of intravesical BCG therapy; a decrease in side effects was reported when two doses of ofloxacin were administered immediately after nine BCG instillations [11,12]. Thus, the prophylactic administration of ofloxacin prior to each BCG instillation may yield good results at a lower cost to the healthcare system. However, it must be discussed that bacterial resistance may increase if ofloxacin is used prophylactically for several weeks.

Whether the use of antibiotics affects the effectiveness of intravesical BCG is also controversial. Several studies have shown that the use of antibiotics disrupts the balance of the gut microbiota, thereby reducing the effectiveness of immune checkpoint inhibitors [13,14]. The bladder microbiome may influence the effectiveness of BCG treatment through various mechanisms, including interference with BCG adhesion to fibronectin [15]. Owing to the potential relationship between the microbiome in the bladder and the mechanism of action of BCG, antibiotic therapy may influence the efficacy of BCG treatment. A recent study reported that long-term antibiotic use in high-risk NMIBC patients receiving intravesical BCG treatment negatively affected disease recurrence and progression [16]. In our study, although the types of antibiotics differed, their use could have affected the BCG-treatment discontinuation.

The prophylactic administration of isoniazid and the reduction of the BCG dose have also been attempted. One study reported that the co-administration of BCG and isoniazid did not effectively reduce the side effects of BCG [17]. Patients treated with a reduced BCG dose had similar recurrence and progression rates and significantly fewer side effects than those in whom the BCG dose was not reduced [18,19]. However, in a randomized EORTC-GU study comparing one-third and full-dose and 1- and 3-year maintenance BCG treatments, no significant differences were detected in BCG toxicity by dose or duration [20].

GAG replacement therapy is a new treatment for bladder pain syndrome/IC by intravesical GAG administration such as hyaluronic acid (HA), PPS, heparin, chondroitin sulfate (CS), and dimethyl sulfoxide, with a response rate of 30% to 80% [21,22]. Several studies demonstrated that fewer urinary tract symptoms showed significant improvement after the intravesical administration of HA and that GAG can be used to treat local side effects of BCG [23,24]. In addition,

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HA reportedly significantly reduced the visual analog scale score for bladder pain [24]. Other studies reported benefits of intravesical HA/CS in patients with BCG-induced chemical cystitis [25]. Although the GAG supplementation therapy can prevent bladder cancer cells from adhering to the urothelium by strengthening the protective barrier, the effect of intravesical HA/CS instillation on bladder cancer recurrence and progression remains unclear [26].

We used oral PPS, a less invasive and more compliant route of drug administration than intravesical administration, as in the previous study on HA [25,26]. To the best of our knowledge, only one study to date determined the efficacy and dose of oral PPS for decreasing BCG-treatment-related local side effects [2]. PPS, an oral medication used in patients with IC or bladder pain syndrome, is chemically and structurally similar to heparin and GAG and is known to effectively reinforce the damaged urothelium in the GAG layer as a bladder mucosal protective drug [27]. Damage to the GAG layer can increase the risk of bacterial invasion of the urothelium, which affects UTI occurrence. In one study, PPS had a low binding affinity to both Gram-negative and Gram-positive bacteria commonly found in the bladder, helping prevent bacterial cystitis [2]. Other studies have shown that PPS administration reduces the incidence of recurrent UTI in women and improves dysuria in patients during intravesical BCG treatment [5]. The question remains as to whether PPS administration interferes with the mucosal attachment of BCG. However, since PPS has a relatively strong binding force to mycobacteria, it enhances the BCG-induced immune response by allowing BCG to attach to the urinary tract epithelium [2].

A correlation between BCG side effects and treatment efficacy was reported by several authors, indicating that patients with many local side effects have a significantly longer time to first tumor recurrence. However, patients with better outcomes would have had more local side effects because of the longer duration and higher amount of BCG instillation. Local or systemic side effects of BCG prior to 6 months have not been identified as prognostic factors for subsequent tumor recurrence. Therefore, it is impossible to ascertain whether the side effects of BCG actually lead to improved results [28].

Physicians have used discretion in the management of symptoms during BCG therapy and the prophylactic use of antibiotics. Because urine culture usually takes 1 to 2 days, patients are treated presumptively based on pyuria and lower urinary tract symptoms. Although symptomatic UTIs remain an absolute contraindication for BCG therapy, bacteriuria cannot be assessed on the day of the BCG treatment. Therefore, prophylactic use of antibiotics is higher in group A, which implies more symptoms in group A under clinical situations.

The present study showed that oral PPS administration significantly decreased the intravesical BCG-treatment discontinuation rate. Although the ratio of pyuria and bacteriuria were higher among patients who received oral PPS, PPS administration reduced the use of prophylactic antibiotics. In addition, a comparison of the two groups did not show any difference in the tumor recurrence rate. Therefore, it was confirmed that the administration of PPS did not affect the efficacy of BCG. It is well known that the discontinuation of BCG therapy has negative effects on the incidence of tumor recurrence [29]. Therefore, using PPS without antibiotics might be preferable to mitigate side effects and maintain BCG therapy schedules.

This study has several limitations. First, since over 85% patients were male, lower urinary tract symptoms such as frequency, urgency, and nocturia may appear after BCG instillation and/or due to benign prostatic hyperplasia. Second, due to the characteristics of the retrospective study, the enrollment periods, follow-up periods, and the types of antibiotics differed between two groups. In addition, the smoking status, a risk factor for bladder cancer, and oncological characteristics were inconsistent between the two groups. Furthermore, it was conducted at a single tertiary care center in a specific region of Asia. Nevertheless, our study is significant in that it is the largest study to date in such a patient population. Further accurate results can be obtained if a higher number of patients are investigated over a longer follow-up period.

CONCLUSIONS

Oral PPS effectively decreased the discontinuation rate and antibiotic use without affecting the BCG efficacy. Antibiotic use affected the discontinuation of BCG treatment. The study findings suggest a role of PPS in reducing the local side effects of BCG and could be used to design larger randomized controlled trials that assess the safety and efficacy of PPS administration during BCG treatment.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Seung Il Jung. Data acquisition: Ho Yeon Lee and Seung Il Jung. Statistical analysis: Seung Il Jung and Eu Chang Hwang. Data analysis and interpretation: Ho Yeon Lee, Seung Il Jung, and Eu Chang Hwang. Drafting of the manuscript: Ho Yeon Lee, Seung Il Jung, and Do Gyeong Lim. Critical revision of the manuscript: all authors. Obtaining funding: Seung Il Jung. Administrative, technical, or material support: Seung Il Jung, Ho Seok Chung, and Dong Deuk Kwon. Supervision: Seung Il Jung. Approval of the final manuscript: all authors.

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