Effect of Intravesical Immunotherapy on Sperm Parameters in Young Patients With Non–Muscle-Invasive Bladder Carcinoma: Prospective Analysis

Manish Garg, Satya Narayan Sankhwar, Apul Goel, Manoj Kumar, Bhupendra Pal Singh, Vishwajeet Singh, Divakar Dalela, Amit Kumar, Sagorika Paul

Abstract

In this prospective analysis, the effect of intravesical immunotherapy on sperm parameters in 17 young patients (mean age 34.6 years) with non-muscle invasive bladder carcinoma was observed. Total sperm concentration was significantly decreased in 12 patients. Thus intravesical therapy with BCG was found to adversely affect spermatogenesis and sperm preservation should be advised before BCG therapy to avoid fertility issues in future.

INTRODUCTION: To investigate the effects of intravesical immunotherapy on semen parameters in young patients with non-muscle invasive bladder tumour. METHODS: A total of 17 sexually active male patients < 45 years of age underwent transurethral resection of bladder tumour (TURBT) from Jan 2010 to Dec 2012. On HPE analysis, T1 high grade was found in 16 patients and Ta grade high grade in 1 patient. Associated CIS was found in 4 patients. Induction course of 6 weeks of adjuvant BCG therapy was given. Semen analysis was done 1 week prior to BCG therapy and 3 months after BCG therapy. Serum levels of hormones like total testosterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were also measured. RESULTS: Mean age of patients at diagnosis was 34.6 (29-43) years. Total semen volume was found to be decreased in 2 patients. Main parameter which was deteriorated was total sperm concentration which was significantly decreased in 12 patients and 5 patients even had their counts below oligospermia levels. Seven patients had associated decrease in sperm motility. However, no patient showed significant difference in other semen parameters. Also no patient had any change in androgen hormonal status except 2 patients in which serum testosterone was found to be non-significantly decreased. CONCLUSION: Intravesical therapy with BCG was found to adversely affect spermatogenesis and cause oligospermia. It is important that relatively young patients must be informed of these effects and advised to have sperm preservation before instillation of BCG therapy to avoid fertility issues in future.
Intravesical immunotherapy may produce a deleterious impact on the fertility of the patient. Adverse effects of chemotherapeutic and immunological agents on reproductive potential of the patients and semen quality are well-known. Preliminary studies also suggested the adverse effects of BCG therapy on semen quality, and thus intravesical immunotherapy may produce a deleterious impact on the fertility of the patient. There are very few studies that actually studied the effect of intravesical BCG on semen parameters until now.

Our study was designed to investigate whether the deleterious effect of intravesical immunotherapy on semen parameters occurred in young patients with superficial bladder tumor treated with an induction course of 6 cycles of BCG after TURBT.

**Material and Methods**

**Study Population and Protocol**

A total of 17 consecutive male patients < 45 years of age were enrolled in this prospective study from January 2010 to December 2012. Institutional ethical approval was obtained, and it was in accordance with the declaration of Helsinki. All patients had been diagnosed with superficial bladder tumor. Apart from clinical and sexual histories, physical and genital examinations, complete hemograms, renal function tests, liver function tests, coagulation profiles, urine cultures, and sensitivity and renal and bladder ultrasonography were performed in all cases to learn the extent of the tumor. Contrast-enhanced computed tomography (CECT) kidney–ureter–bladder radiography, if needed, was also done in selected patients. Patients underwent TURBT and, if the histopathologic examination (HPE) report was suggestive of T1 or Ta intermediate- to high-grade tumor or CIS, then the patients received an induction course of BCG immunotherapy (10 million colony-forming units) for 6 weeks after 3 to 4 weeks of TURBT. The same strain of BCG (Danish 1336) was used for each treatment. Before the start of BCG therapy, semen analysis was done for each patient, to establish a baseline value of semen parameters according to the World Health Organization criteria. After the completion of 3 months of BCG induction therapy, semen analysis was repeated to evaluate the potential effects of BCG on semen parameters. Strict precautions were taken for semen collection and analysis. Samples were collected from patients after at least 3 days of sexual abstinence; semen analysis was performed in the same laboratory each time. Serum levels of hormones like testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were also measured before the beginning of intravesical BCG and 3 months after the completion of the induction course. All patients were offered sperm banking before the start of the therapy for sperm preservation. Patients whose age was > 45 years, who had a sage pTa low-grade tumor or muscle invasion according to the HPE results, or who did not give consent for the study were excluded from study. Patients with a history of genital surgery, specific medication history that affects spermatogenesis, or history of radiotherapy or chemotherapy were not included in the study. Patients with diabetes mellitus, or recent-onset fever, sepsis, or psychoneurological disease were also excluded. Check cystoscopy tests were repeated at 3-month intervals along with urine testing for malignant cell cytology.

**Statistical Analysis**

The statistical analysis was performed with SPSS version 16.0. The results are presented in means and percentages. The continuous variables were compared by unpaired t test, and changes in variables from preoperative to postoperative test results were compared by paired t test. A P value < .05 was considered significant.

**Results**

A total of 17 male patients with superficial, high-risk bladder tumor managed at our institution were included in this study. The mean age at diagnosis was 34.6 years (range, 29-43 y). These patients were relatively young patients with no comorbidity nor any other condition that might affect their fertility potential. The tumor-node-metastasis (TNM) classification was used to assess the pathologic staging of the urothelial tumor, whereas grading of the tumor followed the World Health Organization grading system. Tumors of grades I and II were categorized as low and intermediate grade and tumors of grade III as high grade. Histopathologic analysis of the biopsy of excised tumor revealed T1 high grade in 16 patients and T1 intermediate grade in 1 patient. Multiple small tumors were present in 1 patient, which on HPE were found to be high grade with lamina propria invasion. Associated CIS was found in 4 patients. All patients underwent complete resection during TURBT and intravesical BCG instillations for 6 weeks, based on their histopathologic reports. No major complications occurred during or after the surgery, and all the patients tolerated the 6 weeks of BCG instillations well. The treatment period was uneventful in all the patients, except for minor complaints of dysuria and high urination frequency (Clavien grade 1) in some patients because of BCG therapy that subsided conservatively.

The total semen volume was found to be decreased in 2 patients, and the rest of the patients had a normal volume of ejaculate.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of Semen Parameters Before and After BCG Instillation</th>
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</thead>
<tbody>
<tr>
<td>Semen Parameter</td>
<td>Pre–BCG Instillation</td>
</tr>
<tr>
<td>Semen volume, mL, mean ± SD</td>
<td>2.78 ± 1.69</td>
</tr>
<tr>
<td>Total sperm concentration, millions/mL, mean ± SD</td>
<td>83.25 ± 23.73</td>
</tr>
<tr>
<td>Total motility, %, mean ± SD</td>
<td>72.57 ± 12.5</td>
</tr>
<tr>
<td>Type A motility, %, mean ± SD</td>
<td>56.47</td>
</tr>
<tr>
<td>Type B motility, %, mean ± SD</td>
<td>33.22</td>
</tr>
<tr>
<td>Type C motility, %, mean ± SD</td>
<td>7.30</td>
</tr>
<tr>
<td>Type D motility, %, mean ± SD</td>
<td>3.01</td>
</tr>
<tr>
<td>Sperm normal morphology, %, mean ± SD</td>
<td>45.34 ± 8.54</td>
</tr>
<tr>
<td>Viable sperm, %, mean ± SD</td>
<td>59.34 ± 11.2</td>
</tr>
</tbody>
</table>

Abbreviation: BCG = Bacillus Calmette–Guérin.
Abbreviations: BCG = Bacillus Calmette-Guérin; FSH = follicle-stimulating hormone; LH = luteinizing hormone.

Table 2 Comparison of Hormonal Levels in the Pre— and Post—BCG Instillation Periods

<table>
<thead>
<tr>
<th>Hormonal Level</th>
<th>Pre—BCG Instillation</th>
<th>Post—BCG Instillation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum testosterone level, ng/mL, mean ± SD</td>
<td>6.7 ± 2.89</td>
<td>5.2 ± 1.99</td>
<td>.06</td>
</tr>
<tr>
<td>Serum FSH level, mIU/mL, mean ± SD</td>
<td>6.9 ± 2.89</td>
<td>8.2 ± 2.75</td>
<td>.13</td>
</tr>
<tr>
<td>Serum LH level, mIU/mL, mean ± SD</td>
<td>4.2 ± 1.12</td>
<td>3.9 ± 1.10</td>
<td>.37</td>
</tr>
</tbody>
</table>

As before. The main parameter that was deteriorated was sperm concentration, which was significantly decreased in 12 patients, and among them, 5 patients had sperm concentrations in range of oligospermia levels (<20 millions/mL). Before intravesical BCG therapy, the mean sperm concentration in these 12 patients was 83.25%, which was decreased to 24.10% after intravesical therapy (P = .0001). Additionally, 7 patients had an associated decrease in sperm motility. The mean percentage of total motile sperms was 72.57% in the preinstillation period, which was reduced to 21.0% after BCG therapy (P = .0001) (Table 1). However, no patient showed a significant difference in morphology or other semen parameter. Also, no patient had any change in the androgen hormonal status, except for 2 patients in which the serum testosterone level was found to be slightly decreased compared with previous values but did not reach a significant value. The serum FSH level was found to be nonsignificantly raised in 1 patient with decreased total sperm count, but this patient had a normal testosterone value (Table 2). The median follow-up period was 11 months. All patients were symptom-free during the follow-up period.

Discussion

Urothelial carcinoma of the urinary bladder is among the most common urological malignancies, with the peak incidence occurs in the sixth decade of life. The condition is less commonly seen in the younger population having incidence of about 0.8%.14,15

The use of intravesical BCG has broadened since its introduction in 1976; for example, and intravesical BCG therapy has been widely used in high-risk superficial bladder tumor. For high-grade non—muscle-invasive bladder cancer and CIS, BCG immunotherapy has become the standard of care in prevention of recurrence and progression.16 Although a 6-week induction cycle is mostly agreed on, various maintenance schedules with different timing and dosing have been implemented without a unifying consensus.17

The exact mechanism of action and cause of the systemic effects of BCG is still under investigation. BCG is a living attenuated organism that is instilled into the bladder and, by a yet undetermined mechanism, a general immunologic response is stimulated, causing the death of tumor cells. Nevertheless, several immunological studies concur that the therapeutic efficacy of BCG relies on a normally intact immune system,18 and its response can be observed by monitoring urine cytokines of the patients.19-21 The cytokine profile after BCG is of a T helper (Th1)—type involving the release of interleukin 12 and interferon-gamma.20,21 Drug-induced cystitis is the most common pathologic response, reported in 30% to 60% of patients, appearing in the immediate postinstillation period and leading to irritative voiding complaints, such as dysuria and high frequency of urination.2 Also, 1% and 34% of patients complain of postinstillation hematuria, and about 17% of patients experience a flulike syndrome with generalized malaise.22,23 Severe adverse effects of intravesical BCG also occur, and dissemination of the inoculum to distant organs can occur. Systemic manifestations such as malaise, influenza-like symptoms, myalgia, pneumonitis, ocular symptoms (including uveitis, conjunctivitis, and iritis), joint symptoms (arthritis or arthralgia), and rash usually occur a result of delayed hypersensitivity.24-26 Genitourinary manifestation of intravesical BCG instillation has been reported in several articles. These manifestations include prostate abscess, epididymo-orchitis,26 symptomatic granulomatous prostatitis,27 and penile edema with meatal ulcer.28 Yates et al. reported a case of granulomatous lesions of the penis and bladder, as well as inguinal adenopathy with histologically identified granulomas.29

Although these adverse effects have been commonly reported in literature, the impact of BCG therapy on the semen quality parameters has been scarcely mentioned. It is well-known that the adverse effects of antineoplastic or immunotherapeutic agents in any form are diverse and include the temporary or permanent influence on fertility. The definite mechanism causing a decrease in semen quality in cancer patients is not well established. Multiple factors are likely involved, including preexisting defects in germ cells and the systemic effects of cancer.30,31 BCG administrations were found to hamper semen quality and thus may influence the reproductive potential of the individuals, as predicted in some of the animal and human studies. In a study, superficial bladder tumors, that is, Ta and T1, were found to be relatively more common in patients in the younger age group (41.6% vs. 39.0% and 35.5% vs. 31.8%, respectively), whereas patients older than 60 years were more likely to have muscle-invasive tumors (29.2% vs. 22.9%; P = .119), although these data were not statistically significant.32 So, these sexually active, younger groups are more likely to receive intravesical therapy and thus more prone to experience the adverse effects of BCG, if any, on fertility. Hence, reproductive and sexual function may be the key issues for such patients.

In an animal study by Naz et al. in dogs and monkeys, azoospermia was induced by a single intratesticular injection of BCG within 3 to 6 weeks, without loss of androgens. Circulating anti-sperm antibodies were not detected in sera of these animals and the return of spermatogenesis was observed after a few days to months. These authors’ results suggested that BCG could affect sperm quality and quantity, and the effects were reversible, both in terms of sperm count and fertility.11 In another study, the intratesticular injection of BCG resulted in severe granulomatous reaction with widespread degeneration and vacuolation of the tubules, resulting in severe azoospermia, which was maintained for 6 to 11 months of the observation period.33

Contrary to these reported results, Singh et al. administered BCG (1 million bacilli) into the lumen of the vas deferens of 12 adult male rats and found no difference in the morphology or motility of the sperms. The histological features of the testis, epididymis, and vas deferens to which BCG was administered were found to have no abnormality, without any inflammatory reaction or granuloma formation.34
Effects of Intravesical Immunotherapy on Sperm Parameters

In a previous study by Raviv et al., of 12 patients who received intravesical chemotherapy or immunotherapy, 6 patients who were treated with mitomycin C showed few insignificant changes in the sperm quality, but in 3 of the BCG-treated patients, severe deterioration was seen in all sperm-quality parameters, with a statistically significant ($P = .0021$) decrease in the sperm count. The authors suggested the potential adverse effects on spermatogenesis in patients treated by intravesical therapy with BCG.12

In the present study, the first analysis of semen samples was done at 3 months, as the known length of the spermatic cycle in humans is approximately 72 days.55 So, the effects of BCG would be evident after completion of at least 1 spermatogenic cycle. The sperm concentration was significantly reduced in 12 patients in the present study, and 5 of these patients had their sperm counts significantly ($P= .001$) reduced, to below 20 millions/mL. 1 patient even had their counts decreased to levels of severe oligospermia (< 5 millions/mL). Sperm motility was significantly affected in 7 patients, but no other parameter was found to be deranged. No correlation was found between systemic symptoms or disease stage and semen abnormalities. No significant ($P=.06$.13 and .37 respectively) change was observed in the serum testosterone, LH, or FSH level.

The study had certain limitations. Although the number of patients in this study was not large enough to generalize the concept, the small sample size could be explained by the low incidence of disease in the younger population. We measured only 2 values of the semen analysis, that is, 1 preoperative and another 3 months after BCG therapy, and only a single semen sample was taken each time. Free testosterone values were not measured, as this may be more important in evaluating the androgen status of patients. The effects of only the induction course (6 doses) of BCG therapy were evaluated; the effects of further doses of BCG administered according to maintenance protocols were not screened in this study. Multi-institutional studies with a longer follow-up period are definitely required to evaluate the long-term effects of BCG therapy in these patients.

Conclusion

Intravesical therapy with BCG was found to adversely affect spermatogenesis and thus may hamper fertility. It is of utmost importance that the relatively young patients who receive such treatment are informed of the possible adverse effects of intravesical immunotherapy on semen parameters and are advised to preserve sperm before the instillation of BCG therapy. Further studies are needed to confirm the long-term impact of BCG on fertility issues in young adults with urothelial bladder cancer.

Disclosure

The authors have stated that they have no conflicts of interest.

References