

Impact of Reducing Irritative Symptoms in Non-Muscle Invasive Bladder Cancer During BCG Instillation: A Pilot Study

Kas İnvaziv Olmayan Mesane Kanserinde BCG Verilmesi Sırasında İrritatif Semptomların Azaltılmasının Önemi: Bir Pilot Çalışma

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ABSTRACT

Objective: We evaluated use of anticholinergics, mirabegron, and combination of anticholinergics with mirabegron during Bacillus Calmette-Guérin (BCG) instillation for reducing irritative symptoms in patients with non-muscle invasive bladder cancer (NMIBC).

Method: Prospectively recorded data of NMIBC patients receiving BCG were retrospectively evaluated between August 2015 and April 2019. Patients with low-grade T1 solitary papillary lesions <4 cm were included in the study. Validated questionnaires (OAB-V8) for irritative symptoms adapted to Turkish language, and QoL index forms were filled out by the study participants. OAB-V8 scores of ≥ 8 were considered as an indication to start medical treatment for irritative symptoms. Groups were formed according to daily used anticholinergic drugs and combinations as follows: Group 1, tolterodine; Group 2, solifenacin 5mg; Group 3, mirabegron, and Group 4, mirabegron with solifenacin 5 mg.

Results: Mean follow-up period was 20.4 \pm 6.8 months. There were 132 patients [110 men (83%) and 22 (17%) women] with irritative symptoms and NMIBC. Mean age of the study population was 59.7 \pm 12.4 years. The OAB-V8 scores and QoL indexes significantly improved with all drugs. However, in subgroup analyses, Group 4 provided the most dramatic improvement in OAB-V8 and QoL index scores (P=0.02 for both). The longest in time to micturition was recorded in Group 4 (P=0.04). Tumour recurrence was similar for groups 12 months after BCG instillation (P=0.9), however the least recurrence was observed in Group 4.

Conclusions: Combination of solifenacin and mirabegron can reduce irritative symptoms, improve QoL, and prolong time to micturition, during BCG instillation in selected NMIBC patients. This combination may also decrease recurrence rates in this patient population.

Keywords: Anticholinergic, Bacillus Calmette-Guérin, bladder cancer, irritative symptoms, quality of life

Öz

Amaç: Kas invaziv olmayan mesane kanseri (KİOMK) hastalarında Bacillus Calmette-Guerin (BCG) uygulaması sırasında irritatif semptomları azaltmak için kullanılan antikolinerjik, mirabegron ve antikolinerjik ile mirabegron kombinasyonunun değerlendirilmesi amaçlandı.

Yöntem: Ağustos 2015 ile Nisan 2019 arasında BCG alan KİOMK hastalarının prospektif olarak kaydedilen verileri retrospektif olarak değerlendirildi. Sadece 4 cm'den küçük soliter papiller lezyonu olan düşük dereceli T1 dahil etme kriterleriydi. Dilimize uyarlanmış aşırı aktif mesane versiyon-8 (OAB-V8) formu ve hayat kalite (QoL) indeksi formları irritatif semptomlar için dolduruldu. OAB-V8 skoru ≥ 8 olması halinde, irritatif semptomlar için tedaviye başlama endikasyonu olarak kabul edildi. Gruplar günlük pratikte kullandıkları antikolinerjik ilaçlara ve kombinasyona göre Grup 1 tolterodin, Grup 2 solifenasin 5 mg, Grup 3 mirabegron ve Grup 4 solifenasin 5 mg mirabegron kullanacak şekilde oluşturuldu.

Bulgular: Ortalama takip süresi 20,4 \pm 6,8 aydı. İrritatif semptomlar ve KİOMK olan 132 hasta [110 erkek (%83) ve 22 (%17) kadın] vardı. Ortalama yaş 59,7 \pm 12,4 yıldı. OAB-V8 skorları ve QoL indeksleri tüm ilaçlarla önemli ölçüde iyileşti. Bununla birlikte, alt grup analizlerinde, Grup 4, OAB-V8 ve QoL indeks puanlarında en fazla iyileşmeyi sağladı (her ikisi için P=0,02). İşeme zamanı en uzun Grup 4'te kaydedildi (P=0,04). Tümör rekürrensi BCG uygulamasından 12 ay sonra gruplar için benzerdi (P=0,9), ancak en az nüks Grup 4'teydi.

Sonuç: Solifenacin ve mirabegron'un kombinasyonu, seçilmiş KİOMK hastalarında BCG aşılama sırasında tahriş edici semptomları azaltabilir, QoL geliştirebilir ve işlemeye kadar olan süreyi uzatabilir. Bu aynı zamanda bu hasta popülasyonunda nüksü azaltabilir.

Anahtar kelimeler: Antikolinerjik, Bacillus Calmette-Guerin, mesane kanseri, tahriş edici semptomlar, yaşam kalitesi

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INTRODUCTION

Intravesical Bacillus Calmette-Guérin (BCG) administration following transurethral resection of moderate and/or high-risk non-muscle invasive bladder cancer (NMIBC) is considered as the most effective treatment to reduce recurrence and progression.^{1,2} Despite its efficacy, side effects of BCG and/or irritative symptoms often limit the patient's ability to tolerate the treatment process.³

Local and systemic side effects may cause discontinuation of intravesical BCG therapy in approximately 20% of the patients.⁴ Storage and irritative symptoms including urgency and pollakiuria were defined as lower urinary tract symptoms (LUTS). Besides, these symptoms usually simulate cystitis-like symptoms and are the most common local side effects of BCG administration.⁵⁻⁷ The accepted duration of effective treatment for BCG instillation is 2 hours.⁷ However, NMIBC patients might micturate before completing 2 hours due to storage symptoms as a part of irritative symptoms.⁸

In addition, transurethral resection can indirectly lead to the development of irritative symptoms with/without urge incontinence. By the way, patients could experience more severe local side effects of BCG.⁹ Moreover, low estrogen levels in postmenopausal women and benign prostatic hyperplasia in men can pose risks for the development of irritative symptoms.^{10,11} In this manner, the co-incidence of bladder cancer (BCa) and symptoms of irritative symptoms can increase with advancing age.¹²

Nevertheless, it is supposed that prevention of irritative symptoms during treatment of NMIBC can improve the quality of life (QoL). Other than this, to prevent irritative symptoms might increase oncological efficacy. Anticholinergic drugs, mirabegron and combination of mirabegron with anticholinergics may be used for these aims. According to our best knowledge, there is no study comparing efficiency of different drugs for irritative symptoms in NMIBC patients, in the published literature.

For this purpose, we aimed to compare the efficacy and oncologic outcomes of using anticholinergics, mirabegron, and solifenacin-mirabegron combination in NMIBC patients with irritative symptoms receiving intravesical BCG. Our hypothesis is that solifenacin and mirabegron combination therapy may prevent symptoms better than other medications.

MATERIAL and METHODS

Prospectively recorded data were retrospectively evaluated regarding irritative symptoms of NMIBC patients between August 2015 and April 2019. This is a non-randomized, multi-centre, and open-labelled study. All patients were informed for the study and signed consent forms were collected. Institutional review board approved the study. Exclusion criteria were presence of multiple tumours in bladder, carcinoma in-situ, high grade T1 BCa, \geq T2 Bca, active urinary infection, previous overactive bladder (OAB) syndrome, other cancer and/or previous pelvic radiotherapy due to cancer, previous endoscopic/open/laparoscopic prostate surgery, and irregular follow-up. Since high grade NMIC patients might need multiple and excessive endoscopic resections, irritative symptoms of them might be more frequent and homogeneous distribution of patients in these groups might be disrupted.

All patients with low-grade T1 NMIBC are asked to complete OAB-V8 forms¹³ under the supervision of a doctor in urology outpatient clinic 1 month after transurethral resection of bladder tumour (TUR-BT). When the OAB-V8 scores were higher than 8, the patient was considered to have significantly severe irritative symptoms. Then, medical treatment was given and again OAB-V8 form was completed in the first week of treatment. Additionally, we asked patients to complete quality of life index (QoL) forms.

All patients were divided into 4 groups according to the use of anticholinergic and combination of solifenacin with mirabegron as follows: Group 1, tolterodine 4 mg; Group 2, solifenacin 5 mg; Group 3, mirabegron; Group 4, mirabegron with solifenacin 5 mg. All drugs were used daily once

according to the prescription information.

All patients with low-grade T1 NMIBC had undergone BCG 80 mg (TICE® strain) therapy. We used 10 Fr urethral catheter and patients were advised not to micturate up to 2 hours. All patients recorded time to micturition after BCG instillation. Because we would like to create homogeneous groups, patients who were receiving standard treatment were enrolled in the study. Patients, who received BCG maintenance therapy were excluded.

All completed forms and patient's data were recorded on Microsoft® Excel Sheets. The Statistical package for social sciences (SPSS) for MacOs V.21 was used. Paired t-tests and chi-square tests were used to compare categorical variables. One-way ANOVA was used to determine differences among groups. The level of statistical significance was accepted as $P < 0.05$.

RESULTS

The mean follow-up was 20.4 ± 6.8 months. Mean age of the patients was 59.7 ± 12.4 years. There were 132 patients [110 men (83%) and 22 (17%) women] with irritative symptoms and low-grade T1 NMIBCs in total. Group 1 included 38, Group 2, 27, Group 3, 32, and Group 4, 35 patients. The demographic data were summarised in Table 1 according to age and gender. There was no statistical difference among all groups. The OAB-V8

Table 1. Demographic data of the groups.

Groups	Female n (%)	Male n (%)	P value
Group 1 (n=38)	6 (15.8%)	32 (84.2%)	0.9
Group 2 (n=27)	5 (18.5%)	22 (81.5%)	
Group 3 (n=32)	6 (18.8%)	26 (81.3 %)	
Group 4 (n=35)	5 (14.3%)	30 (85.7%)	

Table 2. Pre-and post-treatment scores of the groups.

Parameters	Pre-treatment Group 1	Post-treatment Group 1	Pre-treatment Group 2	Post-treatment Group 2	Pre-treatment Group 3	Post-treatment Group 3
OAB-V8 scores	17.5 ± 5.5	15.5 ± 5.2	17.4 ± 4.9	13.7 ± 4.8	16.7 ± 4.9	14 ± 4.1
QoL	2.2 ± 0.8	2.9 ± 1.2	2.2 ± 0.8	3.4 ± 1.3	2 ± 0.9	3.1 ± 1.4
Time to micturition (min.)	65.1 ± 16.3	69.6 ± 15.9	70.6 ± 16.7	77.4 ± 15.9	67.3 ± 12.8	73 ± 12.1

Abbreviations: OAB-V8: Overactive bladder-version 8, QoL: Quality of life

*Statistically significant P value.

scores, time to micturition, and QoL indexes were comparable among the groups before treatment of symptoms (Table 2).

The OAB-V8 scores and QoL indexes significantly increased in all groups. However, in subgroup analyses, most statistically significant improvement was found in Group 4 for OAB-V8 and QoL index scores ($P = 0.02$ for both parameters). Additionally, the longest time to micturition was recorded in Group 4 ($P = 0.04$). All these data are shown in Table 2.

According to follow-up after instillation of BCG for 12 months, disease recurrences were seen in patients in Groups 1 (n=8), 2 (n=5), and 3 (n=6), which were comparable among groups ($P = 0.98$), (Table 3). We offered early radical cystectomy or BCG maintenance therapy for all patients with disease recurrence. All of them wanted to continue BCG. Follow-up period has been continuing.

The most recognized side effect of combination treatment was constipation however; all side effects were well tolerated.

DISCUSSION

In this study we evaluated the effectiveness of the treatment modalities for irritative symptoms in low grade T1 NMIBC. It is supposed that NMIBC patients can have irritative voiding and storage symptoms as a part of BCa symptom complex.¹⁴

Table 3. Recurrence rates in groups.

Parameters	Recurrence	P value
Group 1 (n=38)	8 (21.1%)	0.9
Group 2 (n=27)	5 (18.5%)	
Group 3 (n=32)	6 (18.8%)	
Group 4 (n=35)	6 (17.1%)	

Nevertheless, clinicians usually presume those symptoms as natural manifestations in NMIBC patients after TUR-BT. In addition, BCG instillation can aggravate these symptoms. Thus, discomfort of the patients increases. On the other hand, randomized controlled studies showed a 6-week instillation of BCG could prevent the rate of disease recurrence and progression.^{15,16} Thus, firstly we prefer BCG in patients with NMIBC. It is very well known that the BCG instillation itself and catheterization performed in the course of BCG therapy can increase irritative symptoms. Clinicians usually advise these patients to continue the BCG instillation even they have irritative symptoms and discomfort.¹⁷ Another problem is to provide optimal treatment with BCG. The direct and indirect causes of irritative symptoms in NMIBC patients is their inability to urinate 2 hours after BCG instillation. In the view of all these, to inquire irritative symptoms, to complete OAB-V8 forms, and to initiate treatment of irritative symptoms before BCG treatment seem logical approaches to achieve optimal NMIBC treatment and to avoid recurrences. We could provide these in all groups after treatment of irritative symptoms, however the significant improvement was provided in Group 4. Because we used two different pathways to prevent irritative symptoms with combination of solifenacin and mirabegron. Chung et al.¹⁸ reported effective decrease in catheter related symptoms using solifenacin before BCG instillation after TUR-BT. We did more and one step further as comparing 4 different groups for preventing irritative symptoms during BCG instillation. Combination treatment provided us better results without any additional side effects. Drake et al.¹⁹ reported efficacy of mirabegron-solifenacin combination in a multicentre large cohort study. Sideway et al.²⁰ commented efficacy of this treatment in the course of developing irritative symptoms. Our results are parallel to these reports. On the other hand, Allison and Gibson reported increased QoL with mirabegron and disappointing results of mirabegron-solifenacin combination.²¹ However, our results were completely different from results of Allison et al.²¹ The combination had better results than mirabegron and solifenacin per se in our study. The possible cause of these discrepancy is that

our patients did not have clinical OAB before TUR-BT. We used the similar medical treatment for OAB. However, we just use all anticholinergics, beta3 mimetic, and their combination for irritative symptoms. Nevertheless, we strongly offer clinicians to query irritative symptoms in NMIBC patients. Then, medical treatment of irritative symptoms can reduce symptoms in these patient populations.

Moreover, Group 4 patients could have significantly improved QoL and prolonged time to micturition after treatments. These are clear outcomes of clinical effectiveness of the combination treatment.²² We mentioned the possible causes of irritative symptoms in our study population.²³

Furthermore, mirabegron has similar clinical results with solifenacin per se.²⁴ Over and above, to get higher effectiveness without increasing side effects mirabegron was combined with solifenacin.²⁵ Improved QoL and prolonged time to micturition were the essential parameters of our study outcomes. Besides, combination was better than other treatment modalities. In this way, when the patients' QoL is increased they can be motivated to continue BCG instillation. Besides, prolonged time to micturition can help clinicians to determine optimum treatment.

However, the recurrence rate was similar among all groups the least recurrence was observed in Group 4. This may be a result of all the above. Either none of the patients gave up medication because of side effects of treatment for irritative symptoms or they continued BCG.

We have some limitations. First of all, we could not create groups using all anticholinergic drugs because of missing data. Second limitation was low number of patients in groups. Thirdly, when the patient could not tolerate BCG some modifications could also be tried as use of low dose BCG or change to mitomycin instillation. In addition, BCG-refractory patients were not included in this study.

In view of all these, we focused on the effectiveness of combination treatment in NMIBC during

BCG instillation. We found clinical and statistically significant improvement in symptoms of irritative symptoms, QoL, and time to micturition. This is also the first study that showed benefits of mirabegron and solifenacin combination in NMIBC, in published literature. Nonetheless, our results should be confirmed with large population studies to be conducted in near future.

CONCLUSIONS

Time to micturition is one of the essential criteria during BCG instillation used for the treatment of NMIBC. Clinicians should consider irritative symptoms and QoL in these patient populations. Solifenacin-mirabegron combination can reduce irritative symptoms, improve QoL, and prolong time to micturition during BCG instillation in selected NMIBC patients. However, treatment of irritative symptoms might also provide good results in oncological control which should be confirmed in studies performed with large cohorts of these patient populations.

Ethics Committee Approval: Institutional Review Board approved the study numbered (2018/188).

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