

Antiplatelet İlaç Kullanımının Mesane Kanseri Tanısı Üzerindeki Etkileri: Kolaylaştırıcı mı, Zorlaştırıcı mı?

Effects of Antiplatelet Therapy Use on the Diagnosis of Bladder Cancer: Is it a Facilitator or Complicator?

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Özet

Amaç: Mesane kanserinde en sık görülen semptom olan hematurî bazı ilaçların etkisiyle ortaya çıkabilir. Bu çalışmanın amacı antiplatelet (AP) ilaçların mesane kanseri tanısındaki rolünü değerlendirmektir.

Gereç ve Yöntemler: Üroloji kliniğimize Ocak 2013 - Aralık 2018 tarihleri arasında başvuran ve primer mesane kanseri tanısı ile transüretral rezeksiyon (TUR) uygulanan hastalar retrospektif olarak incelendi. Hastalar AP ilaç kullanımına göre 2 gruba ayrıldı (grup 1: AP tedavisi almayan, grup 2: AP tedavisi alan). Gruplar demografik veriler, başvuru şikayeti, sigara içme durumu, tümör büyüklüğü, multifokalite, patolojik evre ve derece ile mesane kanseri risk grubu açısından karşılaştırıldı.

Bulgular: Çalışmaya; grup 1'de 233, grup 2'de 57 olmak üzere toplam 290 hasta alındı. Hastaların yaş ortalaması $68,69 \pm 9,48$ yıldır ve 246'sı (% 84,8) erkekti. Gruplar arasında yaş, cinsiyet, başvuru semptomu, sigara içme durumu, tümör büyüklüğü, multifokalite, patolojik evre, derece ve mesane kanseri risk grubu açısından istatistiksel olarak anlamlı fark yoktu.

Sonuç: Sonuçlarımıza göre, mesane kanserindeki AP ilaç kullanımının ilk tanıda patolojik sonuçlar, tümör boyutu, multifokalite ve başvuru semptomu üzerinde hiçbir etkisinin olmadığı ve mesane kanserinde erken veya gecikmiş tanıya neden olduğu sonucuna varılamayacağı tespit edildi.

Anahtar Kelimeler: Antiplatelet, erken tanı, hematurî, mesane kanseri, transüretral rezeksiyon

Abstract

Objective: Haematuria, which is the most common presenting symptom in bladder cancer (BCa), may also occur with the effect of some medications. The aim of this study was to evaluate the role of antiplatelet (AP) drugs in the diagnosis of BCa.

Material and Methods: Patients who applied to our urology clinic between January 2013 and December 2018 and underwent transurethral resections (TURs) for primary BCa were reviewed retrospectively. Patients were divided into 2 groups according to AP drug use (group 1: no AP therapy, group 2: receiving AP therapy). The groups were compared in terms of demographic data, complaint of admission, smoking status, tumor size, multifocality, pathologic stage and grade, and BCa risk group.

Results: A total of 290 patients, 233 in Group 1 and 57 in Group 2, were included in the study. The mean age of the patients was 68.69 ± 9.48 years and 246 of (84.8%) patients were male. There was no statistically significant difference between groups in terms of age, sex, presenting symptom, smoking status, tumor size, multifocality, pathological stage and grade and BCa risk groups.

Conclusion: According to our results, AP drug use in BCa was found to have no effect on pathologic results, tumor size, multifocality and presenting symptom at the first diagnosis and cannot be concluded that cause early or delayed diagnosis in BCa.

Keywords: Antiplatelet; bladder cancer; early diagnosis; haematuria; transurethral resection

INTRODUCTION

Bladder cancer (BCa) is the eighth most frequently diagnosed cancer in men worldwide [1], and it is associated with high morbidity and mortality rates if not treated properly [2]. The incidence of this disease varies between the genders, and men are three to four times more likely than women to develop the disease, with lifetime risks of 1 in 26 for men and 1 in 88 for women [3]. Painless haematuria is the most common symptom of BCa [4,5]. Approximately 1.3% of the patients with asymptomatic microscopic haematuria (range: 0.4% to 6.5%) have BCa [6], and gross haematuria is associated with a higher rate (~20%) of malignancy [7]. Although the most commonly presenting symptom is haematuria in BCa cases, the underlying cause in most patients presenting with haematuria is not a malignancy [8]. With the exception of malignancies, the conditions that cause haematuria include urinary tract infections, urinary stones, exercise, trauma, recent urological procedures (e.g. catheterization), renal parenchymal diseases and medications (e.g. antiplatelet and anticoagulant drugs) [9].

Oral AP agents are the cornerstone of the secondary prevention strategies for vascular disease [10]. Despite their proven benefits, the number of AP agent side effects has been increasing, and they are among the drugs most commonly associated with adverse events [11]. The observational studies and randomized clinical trials of AP agents have focused mainly on intracranial haemorrhaging, gastrointestinal bleeding and all-cause bleeding as adverse events [12,13]. To our knowledge, studies in which haematuria is a side effect in patients treated with AP agents are limited, and the relationship with BCa is largely unknown.

Based on the abovementioned information, the aim of this study was to investigate the relationship between haematuria and AP use in patients with BCa. More importantly, we determined whether AP drug use could influence the early diagnosis of this disease.

MATERIAL AND METHODS

Study Population and Clinical and Pathological Evaluations

We conducted a population-based retrospective

study of patients diagnosed with BCa in our clinic between January 2013 and December 2018. Local ethics committee approval was obtained for this study (approval No:71522473/050.01.04/33). The patients were divided into two groups according to the use of AP drugs. Group 1 consisted of those patients who were not receiving AP therapy, and group 2 was made up of those patients receiving AP therapy for any reason. Based on departmental consultations, it was determined that the medications of the patients receiving AP therapy should be stopped for five to seven days before their surgeries. All of the patients underwent transurethral resections (TURs) after confirming the initial diagnosis of BCa. The TUR specimens were examined by pathologists according to the 2016 World Health Organization classifications. All of the patients underwent urinary ultrasonographic evaluations and urine culture analyses before their surgeries. The patient demographics, including the age, gender, smoking status, admission complaints, tumour size, multifocality status, pathological stage, grade and risk group, were noted and compared between the groups. The BCa risk group was determined according to the European Association of Urology (EAU) guidelines. For the tumour size, the largest tumour diameter was accepted based on the ultrasonography results or operation notes.

Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics for Windows, (Version 21.0; IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to evaluate the appropriateness of the data to a normal distribution. The continuous variables with normal distributions were shown by the mean and standard deviation (mean \pm SD), whereas the non-normally distributed variables were shown by the median and minimum-maximum (min-max). The categorical variables were shown as the number of cases (n) and percentage (%). We compared the continuous data of the 2 groups using the independent samples t test or Mann-Whitney U test, and we compared the categorical data using the chi-squared test or Fisher's exact test, as appropriate. A p value of < 0.05 was considered to be statistically significant.

RESULTS

A total of 290 patients (233 in group 1 and 57 in group 2) were included in this study. The mean age of the patients was 68.69 ± 9.48 years old, and 246 (84.8%) of them were males. Haematuria was the first symptom in 236 (81.4%) of the patients, and a bladder mass was detected incidentally in 54 (18.6%) of the patients. During the preoperative imaging, the mean tumour size was 29.88 ± 18.69 mm, and multiple tumours was detected in 107 (36.9%) of the patients. Conversely, no masses were detected in 21 patients during the preoperative screening. During the pathological evaluation, the tumour

stage was Ta in 143 (49.3%) of the patients, T1 in 90 (31%) and T2 in 57 (19.7%). Additionally, 169 (58.3%) of the patients had high grade tumours. Moreover, 76 (26.2%) of the patients were at low risk, 35 (12.1%) were at moderate risk and 179 (61.1%) were at high risk according to the EAU risk groups. There were no statistically significant differences between the groups in terms of the age, sex, presenting complaints, smoking status, tumour size, multifocality status, pathological stage, pathological grade or risk group (Table 1). In addition, the patients who presented with haematuria were evaluated separately, and there was no difference between the groups.

Table 1. Patient characteristics

		Group 1 (AP+) (n = 233)	Group 2 (AP-) (n = 57)	Total (n = 290)	P value
Age (years) (mean \pm SD)		68.26 \pm 9.72	70.47 \pm 8.27	68.69 \pm 9.48	0.114*
Sex (n) (%)	Female	37 (15.9)	7 (12.3)	44 (15.2)	0.497**
	Male	196 (84.1)	50 (87.7)	246 (84.8)	
Symptoms (n) (%)	Incidental	43 (18.5)	11 (19.3)	54 (18.6)	0.883**
	Haematuria	190 (81.5)	46 (80.7)	236 (81.4)	
Smoking (n) (%)		183 (78.5)	43 (75.4)	226 (77.9)	0.613**
Tumour size (mm) [median (min-max)]		29.50 (5-82)	24.50 (8-90)	28.50 (5-90)	0.186***
Multifocality (n) (%)		81 (34.8)	26 (45.6)	107 (36.9)	0.128**
Pathological stage (n) (%)	pTa-pT1	184 (79)	49 (86)	233 (80.3)	0.234**
	pT2	49 (21)	8 (14)	57 (19.7)	
Pathological grade (n) (%)	Low	96 (41.2)	25 (43.9)	121 (41.7)	0.715**
	High	137 (58.8)	32 (56.1)	169 (58.3)	
Risk group (n) (%)	Low	60 (25.8)	16 (28.1)	76 (26.2)	0.930**
	Intermediate	28 (12.0)	7 (12.3)	35 (12.1)	
	High	143 (62.2)	34 (59.6)	179 (61.7)	

AP: antiplatelet therapy, SD: standard deviation

*Independent samples *t* test

**Chi-squared test

***Mann-Whitney *U* test

DISCUSSION

In the surgical treatment of BCa, it is important to determine whether or not the tumour is muscle invasive. In this respect, an early diagnosis and treatment should be the aim in order to prevent BCa from reaching a higher stage and grade. Some previous studies have identified haematological and molecular biomarkers that may have benefits for the early diagnosis and

prognosis of BCa [14-18]. The positive effects of early treatment on the surveillance and survival of patients with early BCa diagnoses are irrefutable [19]. In the diagnosis of BCa, the most common symptom seen at the first presentation is haematuria; therefore, it is very important to carefully assess the symptoms. If haematuria is present, an aetiological investigation should be conducted. Haematuria is seen in approximately 85%

of all BCa cases when they are first diagnosed [20]. In our study, we found that 81.4% of the patients with BCa exhibited haematuria when they were first diagnosed.

Antiplatelet drugs have an important place among the medications that may cause haematuria, in addition to increasing bleeding in other body systems [21]. This increased haematuria incidence leads to an increase in the number of emergency department admissions. In their population-based study, Wallis et al. found that AP drugs were significantly associated with haematuria-related complications (including emergency department visits, hospitalizations and urological procedures) [22]. With regard to the difficulty coping with haematuria and its complications in patients receiving AP therapy, another important point is to determine the aetiology of the haematuria. Establishing whether the haematuria is due to the drug use or whether the drugs have aggravated another underlying pathology is very important so that potential malignancies are not missed. In one systematic review with a high number of patients, the overall risk of visible haematuria was 0.5% in the patients receiving AP therapy. Additionally, upper urinary tract imaging and cystoscopy revealed underlying urological pathologies in 44% of the patients, with a 17% risk of underlying malignant pathologies [23].

Today, increased cardiovascular and cerebrovascular diseases are the most important causes of increased AP drug use, and AP therapy is the cornerstone for the secondary prevention of these diseases [24]. Older male patients and smokers have increased risks of developing vascular diseases, and they often receive AP therapy [25-27]. These risks are shared with BCa, but studies regarding the relationship between AP drugs and BCa are limited.

Picozzi et al. reported that the perioperative results, including the surgery time, haemoglobin reduction and postoperative complications (such as blood transfusions and cardiac events), were similar in BCa patients who were receiving AP therapy and those who were not; however, the pathological results were not mentioned [28]. In a recently reported retrospective analysis of 325 patients with BCa who underwent TURs, it was found that the group receiving AP drugs

was older with more comorbid diseases, but there were no significant differences in the tumour localizations and pathological results [29]. However, although it was not statistically significant, smaller tumour sizes and lower T2 rates were detected in the group receiving AP therapy, which raised the question of whether AP therapy might lead to an earlier diagnosis of BCa. Moschini et al. found that those patients being treated with antiaggregant and anticoagulant drugs were older, had smaller tumour sizes and had lower stage and grade tumours in the pathological evaluations. Therefore, they concluded that the patients with BCa who received antiaggregant and anticoagulant therapy presented with haematuria earlier, and they were diagnosed earlier [30]. However, in our study, we found that there were similar tumour stage and grade rates in the two groups, contrary to the previous study, and that AP therapy was not associated with the pathological results. Therefore, we did not interpret the results as signifying that BCa patients receiving AP therapy would be diagnosed earlier. Based on our results, although there were no significant differences between the two groups, the larger tumour size, higher T2 rate and higher tumour grade rate in the AP drug group were contrary to the results of a few studies in the literature. This suggests that early haematuria caused by AP drugs may lead to a delay in the diagnosis of BCa based on the assumption that haematuria is a drug-related condition, rather than resulting in the early diagnosis of BCa.

Our study did have some limitations. First, it was limited by its retrospective nature. Second, the same surgeon did not operate on all of the patients, and the specimens were not evaluated by the same pathologist, which may have affected the results. Lastly, the data regarding the time between the first signs of haematuria in the patients and their surgeries were inadequate, and there was no standardization.

CONCLUSION

The results of our study were similar to those of some of the studies in the literature, but they contradicted the results of others. We were unable to conclude that AP drug use caused an early or delayed diagnosis in BCa cases. Therefore, we believe that a careful evaluation of patients with haematuria receiving AP drugs

is important so that possible urological malignancies are not missed. Additionally, we believe that in the management of these patients, more studies are needed in order to determine the answers to certain questions, such as when cystoscopy should be performed, in order to avoid unnecessary invasive interventions.

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