Running Head: Complications of BCG therapy- kamali et al.

COMPARISONOF THE EFFICACY OF OXYBUTYNIN, PHENAZOPYRIDINE, CELECOXIB, AND PLACEBO IN THE TREATMENT OF URINARY TRACT SYMPTOMS AFTER BCG THERAPY IN PATIENTS WITH BLADDER TUMORS

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Abstract

Purpose: Intravesical BCG (Bacillus Calmette–Guérin) therapy is indicated as an effective treatment for patients with non-muscle-invasive bladder cancer, despite associate with the side effects. In this study, the incidence of BCG therapy adverse effects was compared among three groups of patients who received celecoxib, phenazopyridine, and oxybutynin with placebo.

Materials and Methods: The randomized controlled clinical trial was conducted on four groups using the parallel group method. A checklist is used for weekly assessment of urinary symptoms, systemic symptoms of BCG therapy, and adverse drug reactions.

Results: The study included 120 patients, 10 female and 110 male. The mean age 59.65 ± 6.2 years. The results of multivariate analysis show that there is a significant decrease in urinary frequency for patients who received phenazopyridine (95% CI: 0.09, 0.31, OR = 0.17, *P* <.001) and also celecoxib group (95% CI: 0.10, 0.43, OR = 0.21, *P* <.001) compared to those in placebo group. Patients in celecoxib group (95% CI: 0.02, 0.07 ,OR = 0.04, *P* <.001), phenazopyridine (95% CI : 0.07, 0.37,OR=0.16, *P* <.001) and oxybutynin (95% CI: 0.02, 0.12,OR = 0.05, *P* <.001) were less likely to have urgency than those in placebo. Moreover, significant decrease was found for dysuria in the three treatment groups in comparison with placebo group.

Conclusion: According to the results, celecoxib, phenazopyridine and oxybutynin can effectively decrease the side effects of BCG immunotherapy compared to placebo. Among these three treatments, the most effective and safest treatment option is celecoxib.

Key words: vaccine; complications; intravesical therapy; non-muscle invasive bladder cancer; urinary neoplasms

INTRODUCTION

The treatment of high grade non-muscle-invasive bladder cancer (NMIBC) is a combination of TUR (transurethral resection), adjuvant Intravesical chemotherapy, or BCG (Bacillus Calmette–Guérin) immunotherapy.[1] The European Organization for Research and Treatment of Cancer (EORTC) provides a scoring system for recurrence and progression risk in NMIBCs that includes factors such as age, gender, recurrent tumor, number of tumors, T stage, CIS, and grade.[2]However Intravesical BCG therapy is effective treatment to prevent relapse or delay in progress In NMIBC.[1,3] Despite the recommendations by different guidelines in using BCG therapy as an effective treatment in non-invasive bladder cancers, is associated with adverse effects in the 6-week induction course. BCG therapy adverse effects are reported in 30-80% of cases in different studies. [4] Irritative voiding symptoms and fever are the most common adverse effects of BCG immunotherapy [5,6] while other severe adverse effects like bladder contracture and sepsis are infrequent. [7] If adverse reactions persist over time or become intolerable, symptomatic treatment with spasmolytics, anticholinergics, analgesics, or antiphlogistics are indicated. Administration of NSAIDs (Non-steroidal anti-inflammatory drugs) and corticosteroids is effective for treatment of immunologic reactions like arthralgia. [6] because the completion of the induction course requires management of BCG adverse effects, [8] several studies have proposed different strategies to prevent control the adverse effects including decreasing the therapeutic dose of BCG, increasing the interval of injections, and administering anti TB drugs, ofloxacin, or antimuscarinic drugs such as tolterodine or oxybutynin.

However, according to the latest results, none of these methods is useful in prevention of BCG adverse effects.[4,6,9,10] Among the above drugs, oxybutynin has no positive effect according to a trial[11]and many complications treatment options are not evaluated during placebo-controlled

studies.[6] Although measures like decreasing the BCG dosage are effective, they cannot adequately control the risk of treatment complications. [12]Irritative urinary symptoms are a common side effect of treatment of BCG and that often restrict treatment tolerance. While anticholinergic medications ،antispasmodic agent and NSAID may be used for symptom prophylaxis, they have not been compared with placebo for efficacy in a randomized controlled trial. In this prospective, randomized, double-blind, placebo-controlled trial, we compared the incidence of side effects of BCG therapy (dysuria, urinary frequency, urgency, fever, influenza-like symptoms, arthralgia) and adverse reactions (dry mouth, constipation, and dyspepsia) in three groups of patients receiving celecoxib, phenazopyridine, and oxybutynin versus placebo during six weeks.

MATERIALS AND METHODS

This prospective, randomized, triple-blind, placebo-controlled trial was performed after acquisition of the approval of the Iranian Registry of Clinical Trials (IRCT20171225038070N1). Ethical Principles of this study was approved by the Ethics Committee of the University of Medical Sciences of Iran and are in line with the 1964 Helsinki Declaration.

Study Population

The study population consists of 120 adult patients suffering from non-muscle-invasive bladder cancer attending Hasheminejad Hospital, Tehran, Iran in the semiannual of 2017. In this study all tumors were completely resected with any size and location and all patient became tumor-free. In addition, the tumors pathologically were limited to the mucosa without muscle involvement. The patients were candidates of BCG therapy as a 6-week induction protocol.

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Inclusion and exclusion criteria

The inclusion criteria include patients older than age 18 years, a pathology report confirming NMIBC (cis, Ta, or T1), and being a candidate for intravesical BCG immunotherapy. Patients were excluded from study for an AUA(American Urological Association) symptom score greater than 20, history of peptic ulcer disease, the use of medications for overactive bladder, pelvic surgery within the previous 6 months, a PVR (post-void residual)greater than 50 ml or other medical conditions that would be adversely affected by anticholinergics such as history of urinary retention due to BPH(Benign prostatic hyperplasia), constipation and history of narrow angle glaucoma. After obtaining informed consent, the patients were enrolled.

Procedures

120 eligible patients who met the inclusion and exclusion criteria were randomly assigned to one of the four treatment groups, celecoxib (n=30), phenazopyridine (n= 30), oxybutynin (n=30) and placebo (n=30), using the blocked randomization method with equal block sizes. The object of this study was explained to the participants and their informed consents were obtained. Assignments to treatment groups A to D was done by one of the researchers who was involved in including, excluding, and selecting the patients and opening the envelopes. Thirty patients received celecoxib 100 mg every 12 hours, 30 patients received oxybutynin 5 mg every 12 hours, 30 patients received phenazopyridine 100 mg every 8 hours, and 30 patients received placebo (multivitamin pills) every 12 hours. All drugs were identical in shape and offered in similar capsules. The patients and the physicians were blinded to treatment assignment. Also, the person who was involved in randomization had no role in the data analysis.

Evaluations

The researcher used a checklist for each participant at the beginning (baseline symptoms) and during the study for weekly assessment of urinary symptoms, systemic symptoms of BCG therapy, and possible adverse drug reactions. This checklist included three voiding symptoms as primary outcomes (urinary urgency, urinary frequency, and dysuria), two non-urinary systemic symptoms of BCG therapy (fever and influenza-like symptoms, arthralgia), and adverse drug reactions, including dry mouth, constipation, and dyspepsia as secondary outcomes. Systemic symptoms of BCG and adverse drug reactions were recorded as none (no symptoms), moderate (self-limited, no need for treatment), and severe (treatment required). Urinary frequency was defined as the need to pass urine within 2 hours of the last micturition. Urinary urgency was defined as a recurrent strong desire to void which was difficult to defer due to a fear of leakage or pain, and dysuria was defined as any burning, pain, or discomfort when urination. The urinary symptoms were recorded in an ordinal manner (1= never, 2= less than once in 5 times, 3= less than half of the time, 4= more than half of the time, 5= always). Fever was defined as an oral body temperature above 38˚C, dry mouth(dryness or a feeling of stickiness in mouth), and other symptoms were defined as Constipation(difficulty passing stool and abdominal fullness) , arthralgia(pain in one or more of joints ,that may be described as sharp ,dull ,stabbing ,burning or throbbing), and dyspepsia(an epigastric burning sensation).The study outcomes categorized into dichotomous variables (with or without symptom).

Statistical Analysis

To describe the studied outcomes according to the treatment groups, the Number (percent) was used. The patients were followed for 6 weeks and it is expected that the observations to be

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correlated over time. Since our data was longitudinal with repeated measures, generalized estimating equation (GEE) regression model was used for the data analysis. GEE models were used to estimate the effect of three treatments including celecoxib, phenazopyridine and oxybutynin versus placebo on the urinary symptoms, systemic symptoms and adverse reactions. The studied outcomes were binary data, e.g. with and without urinary symptoms so, the link function in GEE models was logit link. Correlations between the outcomes measures over time was accounted with an unstructured working correlation matrix. The statistical analysis was conducted in two scenarios of univariate and multivariable after adjustment for age and gender. The estimated effects were presented using odds ratio (OR) and 95% confidence interval (CI). *P*-values less than 0.05 were considered significant. The analysis was conducted using stata version 14.

Results:

131 patients were evaluated for eligibility, 11 of these patients were excluded due to exclusion criteria. One patient was excluded for AUA symptom score greater than 20, three patients for history of peptic ulcer disease, two patients for PVR (post-void residual) greater than 50 mL, three patients for history of urinary retention due to BPH (Benign prostatic hyperplasia), and two patients for history of constipation. The treatment continued for a 6-week period in all groups during which adverse effects of BCG were assessed and recorded. All of the patients completed treatment. Details of patients' enrollment flow diagram are outlined in Figure 1.

The study included 120 patients, 10 female and 110 male. The mean age of the participants was 59.65±6.2 years.

Descriptive analysis

Number (%) of patients with and without the urinary symptoms, systemic symptoms, adverse reactions in the treatment groups during follow up are presented in **Table 1**. At first week, the percent of urinary frequency among patient randomized to celecoxib, phenazopyridine, oxybutynin and placebo groups were 13.3%, 40%, 66.7% and 100%, respectively. However, corresponding figures at the end of follow up were 40%, 66.7%, 33.3% and 26.7%, respectively. There was relatively stable trend in percent of urinary urgency among patients in two of celecoxib and oxybutynin groups however there was an increase and decrease trend during follow up for those in phenazopyridine and in placebo group, respectively.

There was a sensible fluctuation in the frequency of dysuria during time among those in placebo, celecoxib and phenazopyridine' however; there was no change in oxybutynin group. In two phenazopyridine and oxybutynin groups, the percent of fever symptom at end of follow up were 43.3% and 33.3%, respectively, while at 1st week corresponding figures were 13.3% and 0%, respectively. In other hands, the celecoxib group had no change in symptom of fever at 1st week compared to the end of the follow up. The observed trend for fever was also found for the symptom of arthralgia in the three treatment groups.

Although no changes occurred in the heartburn symptom in the placebo group, however; the symptom had an increasing trend in other three groups during follow up. A relatively constant trend for constipation was observed in the all 4 treatment groups during time. There was an increasing trend for dry mouth in patients in two groups of celecoxib and oxybutynin; however; the placebo group did not experience dry mouth during follow-up. The percent of dry mouth in the patients who received phenazopyridine decreased from 73.3% at 1st week to 60% at end of follow up.

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Association analysis

The results of univariate analysis are presented in **Table 2**. There was inadequate data in combination of treatment groups and some outcomes including heartburn, constipation and dry mouth, so the OR (95% CI) did not be estimate. The results showed that the odds of urinary frequency decreased among patients in celecoxib and phenazopyridine compared to those in placebo group by 0.70 and 0.77, respectively.

The results showed that the patients in the three treatment groups in comparison with to those in placebo tend, have lower level of the urinary urgency and dysuria e.g. the odds of urgent urination and dysuria in celecoxib were 0.94 and 0.68 lower than in placebo, respectively.

In comparison with placebo, for a patient who received phenazopyridine, her/his odds of having arthralgia is multiplied by 4.10 at the end of follow up (95% CI: 1.37-12.29, OR = 4.10, *P* = .01).moreover, (95% CI: 1.63-10.95, OR = 4.23, *P* = .003) for arthralgia in oxybutynin compared to placebo.

The results of multivariable analysis are shown in **Table 3**. Due to sparse data, OR (95% CI) could not estimate for association between treatment groups and arthralgia. The odds of urinary frequency were lower among patients who received celecoxib compared to those who did receive placebo (95% CI: 0.09- 0.31, OR = 0.17, *P* = .001), after adjusting for age and gender. Additionally, a significant decrease was observed in urinary frequency of patients who received phenazopyridine compared to those in placebo group. According to reciprocal entity of OR, the OR for having urinary frequency for phenazopyridine and oxybutynin in comparison with celecoxib approximately were 1.23 and 3.59, respectively. Patients in celecoxib group (95% CI:

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0.02- 0.07, OR = 0.04), phenazopyridine (95% CI: 0.07- 0.37, OR = 0.16) and oxybutynin (95% CI: 0.02- 0.12, OR = 0.05) were less likely to have urinary urgency than patients in placebo. Moreover, significance decrease was found for dysuria in the three treatment groups in comparison of placebo group. The detail about OR (95% CI) are presented in the **Table 3**.

Discussion:

This study evaluated the effect of treatment with celecoxib, phenazopyridine, and oxybutynin on irritative voiding symptoms (urinary urgency, frequency, and dysuria) and systemic symptoms (fever, arthralgia) associated with BCG immunotherapy compared to placebo. The major adverse reactions of these drugs, including dry mouth, constipation, and dyspepsia were also recorded. The results showed that urinary frequency was the most common adverse effect of BCG therapy (64%) and fever was the second most common side effect. Most symptoms associated with BCG immunotherapy are related to the immune stimulation that is necessary for effective removal of cancer cells. The symptoms contain urinary frequency and burning, mild malaise and low-grade fever. [8]

A meta-analysis that performed by Ari Astram et al. [8] for effective dosage and side effects of BCG treatment shows that the most local complication is drug induced cystitis. This complication is manifested by urinary irritation with negative urine culture and hematuria that stops within 48 hours without suspension of BCG therapy. Therefore, irritative symptoms in BCG therapy is a predictable occurrence, and there is no reason for the interruption of treatment. [8]

In the study of xiaoming Jian, [13] that compared intravesical BCG immunotherapy with radical cystectomy in intermediate or High risk non muscle invasive bladder cancer shows cystitis was the most common complication in the BCG group and rifampin and isoniazid prescribed to complete the course of treatment. However, in the EORTC study, isoniazid administration with the BCG has not been effective in reducing side effects. In our study, celecoxib was more effective than placebo in reducing frequency, dysuria and urgency. Also, in multivariate analysis, celecoxib is more effective in reducing frequency than phenazopyridine and oxybutynin .In this study, the second major complication of BCG therapy was fever (60%). While high fever in only one patient in the phenazopyridine group led to a one-week cessation of treatment, in other patients, fever was controlled by acetaminophen prescribing.

Xioming et al. [8] reported 19% prevalence of fever in BCG treatment. They used oral acetaminophen to control the fever. They also found that fever was associated with decreased recurrence and increased toxicity in BCG immunotherapy. However, it is important to check for concurrent infection during experience of the fever. Concomitant infection occurs locally or systemically in rare cases, and eruption of BCG therapy or antituberculosis drugs is used for treatment. In this paper, celecoxib was more effective in reducing fever. [14]

Micheeh and colleagues [11] in randomized control trial evaluated oxybutynin extended release versus placebo for urinary symptoms during intravesical BCG treatment. They reported increases in urinary frequency and burning on urination, fever, flu-like symptoms, dry mouth and constipation versus placebo. The prevalence of urinary frequency varied from 33.3% to 83.3% in oxybutynin group.

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In this research, multivariate analysis show that oxybutynin does not significantly reduce the odds of urinary frequency compared to placebo. Additionally, significance decrease was observed in urgency, dysuria and fever in patients who received oxybutynin compared with placebo group. Anticholinergic side effects from the use of oxybutynin is commonly observed, however, the severity of them did not lead to stoppage of treatment.

Numerous studies have been performed to achieve the greatest effectiveness of BCG therapy in the treatment of bladder tumors .However, the optimal treatment plan has not been clarified. [14] In our study, despite the limitations of the number of participants and inclusion of only age and sex as covariates, it was tried to compare the proposed treatments for better controlling of the side effects of BCG treatment.

Conclusion

According to the results of the 6-week follow-up, urinary frequency and fever were common side effects of BCG induction therapy. Celecoxib caused a significant reduction in the odds of irritative urinary symptoms (urinary urgency, urinary frequency, and dysuria) and fever compared to placebo group. Phenazopyridine also decreased the odds of fever and irritative urinary symptoms, among which the decrease in fever was not significant compared to placebo group. Moreover, significance decrease was found for irritative urinary symptoms and fever in the oxybutynin treatment group in comparison of placebo group. However, anticholinergic side effects were commonly observed during treatment.

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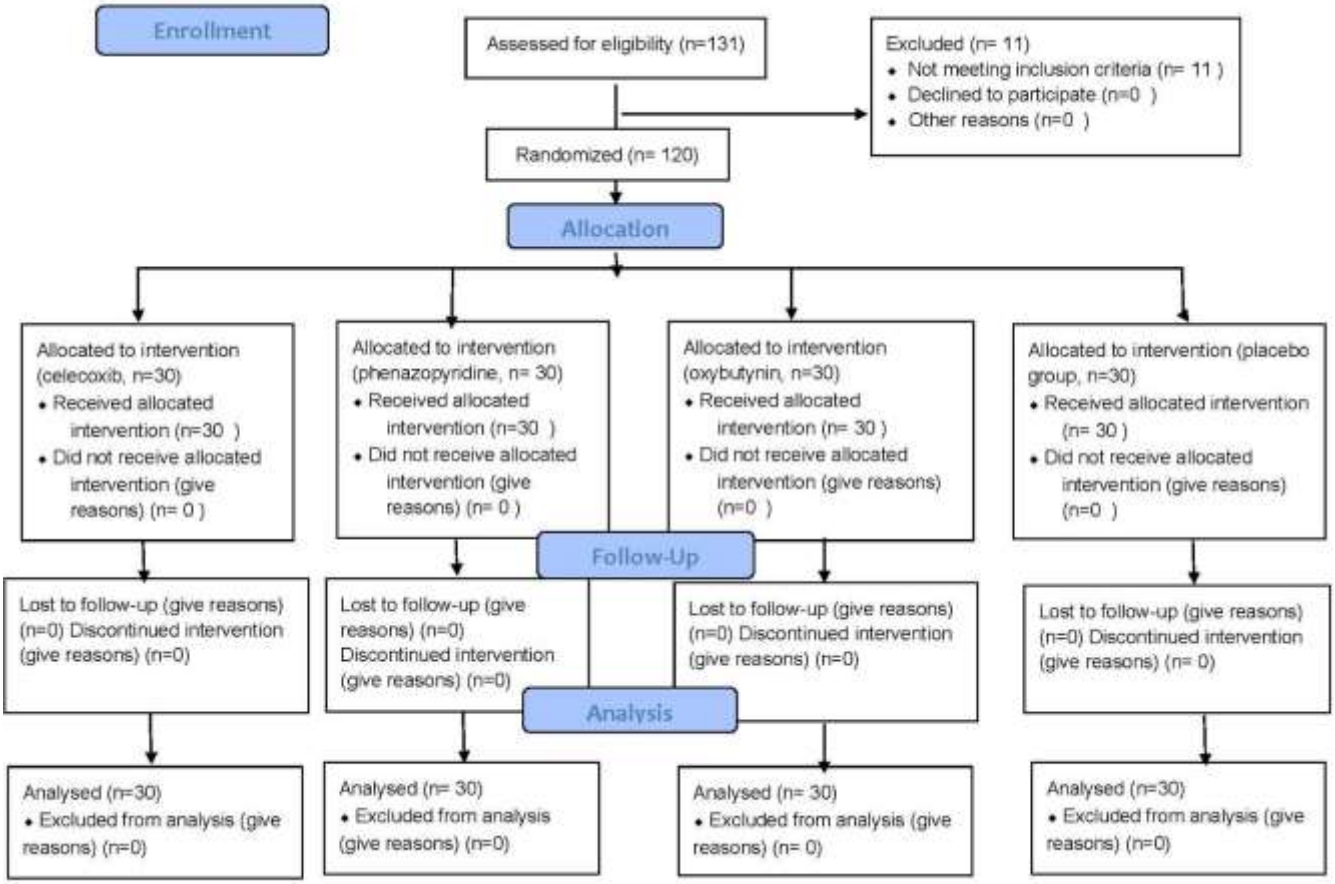
Enrollment
Assessed for eligibility (n=131)
Excluded (n= 11)
• Not meeting inclusion criteria (n= 11)
• Declined to participate (n=0)
• Other reasons (n=0)
Randomized (n= 120)
Allocation
Allocated to intervention (celecoxib, n=30)
• Received allocated intervention (n=30)
• Did not receive allocated intervention (give reasons) (n= 0)
Allocated to intervention (phenazopyridine, n= 30)
• Received allocated intervention (n=30)
• Did not receive allocated intervention (give reasons) (n= 0)
Allocated to intervention (oxybutynin, n=30)
• Received allocated intervention (n= 30)
• Did not receive allocated intervention (give reasons) (n=0)
Allocated to intervention (placebo group, n=30)
• Received allocated intervention (n= 30)
• Did not receive allocated intervention (give reasons) (n=0)
Follow-Up
Lost to follow-up (give reasons) (n=0) Discontinued intervention (give reasons) (n=0)
Lost to follow-up (give reasons) (n=0) Discontinued intervention (give reasons) (n=0)
Lost to follow-up (give reasons) (n=0) Discontinued intervention (give reasons) (n=0)
Lost to follow-up (give reasons) (n=0) Discontinued intervention (give reasons) (n= 0)
Analysis
Analysed (n=30)
• Excluded from analysis (give reasons) (n=0)
Analysed (n= 30)
• Excluded from analysis (give reasons) (n=0)
Analysed (n= 30)
• Excluded from analysis (give reasons) (n= 0)
Analysed (n=30)
• Excluded from analysis (give reasons) (n=0)

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Table 1. Number (%) of urinary symptoms, systemic symptoms, adverse reactions in each treatment groups in 6 weeks follow up

	Urinary frequency											
	Week1		**Week2**		**Week 3**		**Week 4**		**Week 5**		**Week 6**	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Treatment groups												
Placebo	0	30 (100)	0	30 (100)	10 (33.3)	20 (66.7)	10 (33.3)	20 (66.7)	18 (60)	12 (40)	22 (73.3)	8 (26.7)
Celecoxib	26 (86.7)	4 (13.3)	8 (26.7)	22 (73.3)	14 (46.7)	16 (53.3)	14 (46.7)	16 (53.3)	18 (60)	12 (40)	18 (60)	12 (40)
Phenazopyridine	18 (60)	12 (40)	8 (26.7)	22 (73.3)	9 (30)	21 (70)	9 (30)	21 (70)	5 (16.7)	25 (83.3)	10 (33.3)	20 (66.7)
Oxybutynin	10 (33.3)	20 (66.7)	5 (16.7)	25 (83.3)	5 (16.7)	25 (83.3)	5 (16.7)	25 (83.3)	5 (16.7)	25 (83.3)	20 (66.7)	10 (33.3)
	Urgent urination											
	Week1		**Week 2**		**Week 3**		**Week 4**		**Week 5**		**Week 6**	
Treatment groups	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Placebo	5 (16.7)	25 (83.3)	0	30 (100)	5 (16.7)	25 (83.3)	10 (33.3)	20 (66.7)	10 (33.3)	20 (66.7)	20 (66.7)	10 (33.3)
Celecoxib	25 (83.3)	5 (16.7)	25 (83.3)	5 (16.7)	26 (86.7)	4 (13.3)	26 (86.7)	4 (13.3)	22 (73.3)	8 (26.7)	26 (86.7)	4 (13.3)
phenazopyridine	26 (86.7)	4 (13.3)	8 (26.7)	22 (73.3)	22 (73.3)	8 (26.7)	13 (43.3)	17 (56.7)	13 (43.3)	17 (56.7)	13 (43.3)	17 (56.7)
oxybutynin	25 (83.3)	5 (16.7)	25 (83.3)	5 (16.7)	25 (83.3)	5 (16.7)	20 (66.7)	10 (33.3)	25 (83.3)	5 (16.7)	25 (83.3)	5 (16.7)
	Dysuria											
	Week1		**Week 2**		**Week 3**		**Week 4**		**Week 5**		**Week 6**	
Treatment groups	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Placebo	0	30 (100)	5 (16.7)	25 (83.3)	15 (50)	15 (50)	10 (33.3)	20 (66.7)	25 (83.3)	10 (33.3)	25 (83.3)	5 (16.7)

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Celecoxib	26 (86.7)	4 (13.3)	13 (43.3)	17 (56.7)	17 (56.7)	13 (43.3)	18 (60)	12 (40)	18 (60)	12 (40)	18 (60)	12 (40)
phenazopyridine	25 (83.3)	5 (16.7)	17 (56.7)	13 (43.3)	17 (56.7)	13 (43.3)	17 (56.7)	13 (43.3)	17 (56.7)	13 (43.3)	22 (73.3)	8 (26.7)
oxybutynin	20 (66.7)	10 (33.3)	5 (16.7)	25 (83.3)	15 (50)	15 (50)	15 (50)	15 (50)	15 (50)	15 (50)	20 (66.7)	10 (33.3)
	Fever											
	Week1		**Week 2**		**Week 3**		**Week 4**		**Week 5**		**Week6**	
Treatment groups	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Placebo	20 (66.7)	10 (33.3)	15 (50)	15 (50)	10 (33.3)	20 (66.7)	25 (83.3)	5 (16.7)	25 (83.3)	5 (16.7)	30 (100)	0
Celecoxib	30 (100)	0	30 (100)	0	26 (86.7)	4 (13.3)	30 (100)	0	26 (86.7)	4 (13.3)	30 (100)	0
phenazopyridine	26 (86.7)	4 (13.3)	17 (56.7)	13 (43.3)	26 (86.7)	4 (13.3)	17 (56.7)	13 (43.3)	17 (56.7)	13 (43.3)	17 (56.7)	13 (43.3)
oxybutynin	30 (100)	0	15 (50)	15 (50)	20 (66.7)	10 (33.3)	15 (50)	15 (50)	15 (50)	15 (50)	20 (66.7)	10 (33.3)
	Arthralgia											
	Week1		**Week2**		**Week 3**		**Week 4**		**Week 5**		**Week 6**	
Treatment groups	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Placebo	25 (83.3)	5 (16.7)	15 (50)	15 (50)	25 (83.3)	5 (16.7)	25 (83.3)	5 (16.7)	30 (100)	0	30 (100)	0
Celecoxib	26 (86.7)	4 (13.3)	26 (86.7)	4 (13.3)	26 (86.7)	4 (13.3)	26 (86.7)	4 (13.3)	26 (86.7)	4 (13.3)	26 (86.7)	4 (13.3)
phenazopyridine	22 (73.3)	8 (26.7)	22 (73.3)	8 (26.7)	18 (60)	12 (40)	18 (60)	12 (40)	14 (46.7)	16 (53.3)	18 (60)	12 (40)
oxybutynin	30 (100)	0	20 (66.7)	10 (33.3)	15 (50)	15 (50)	15 (50)	15 (50)	15 (50)	15 (50)	10 (33.3)	20 (66.7)
	Heartburn											
	Week1		**Week2**		**Week3**		**Week 4**		**Week 5**		**Week 6**	
Treatment groups	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	

Placebo	30 (100)	0	30 (100)	0	30 (100)	0	30 (100)	0	30 (100)	0	30 (100)	0
Celecoxib	30 (100)	0	30 (100)	0	26 (86.7)	4 (13.3)	26 (86.7)	4 (13.3)	22 (73.8)	8 (26.7)	26 (86.7)	4 (13.3)
phenazopyridine	26 (86.7)	4 (13.3)	22 (73.8)	8 (26.7)	26 (86.7)	4 (13.3)	26 (86.7)	4 (13.3)	22 (73.8)	8 (26.7)	22 (73.8)	8 (26.7)
oxybutynin	30 (100)	0	20 (66.7)	10 (33.3)	20 (66.7)	10 (33.3)	20 (66.7)	10 (33.3)	15 (50)	15 (50)	20 (66.7)	10 (33.3)
	Constipation											
	Week2		**Week 2**		**Week3**		**Week 4**		**Week 5**		**Week 6**	
Treatment groups	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	
Placebo	30 (100)	0	30 (100)	0	30 (100)	0	30 (100)	0	30 (100)	0	30 (100)	0
Celecoxib	17 (56.7)	13 (43.3)	17 (56.7)	13 (43.3)	17 (56.7)	13 (43.3)	17 (56.7)	13 (43.3)	22 (73.8)	8 (26.7)	22 (73.8)	8 (26.7)
phenazopyridine	21 (70)	9 (30)	21 (70)	9 (30)	25 (83.3)	5 (16.7)	25 (83.3)	5 (16.7)	25 (83.3)	5 (16.7)	25 (83.3)	5 (16.7)
oxybutynin	10 (33.3)	20 (66.7)	10 (33.3)	20 (66.7)	15 (50)	15 (50)	25 (83.3)	5 (16.7)	15 (50)	15 (50)	15 (50)	15 (50)
	Dry mouth											
	Week3		**Week2**		**Week 3**		**Week4**		**Week 5**		**Week6**	
Treatment groups	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	
Placebo	30 (100)	0	30 (100)	0	30 (100)	0	30 (100)	0	30 (100)	0	30 (100)	0
Celecoxib	26 (86.7)	4 (13.3)	26 (86.7)	4 (13.3)	22 (73.8)	8 (26.7)	22 (73.8)	8 (26.7)	22 (73.8)	8 (26.7)	22 (73.8)	8 (26.7)
phenazopyridine	8 (26.7)	22 (73.3)	12 (40)	18 (60)	8 (26.7)	22 (73.3)	8 (26.7)	22 (73.3)	8 (26.7)	22 (73.3)	12 (40)	18 (60)
oxybutynin	25 (83.3)	5 (16.7)	5 (16.7)	25 (83.3)	10 (33.3)	20 (66.7)	30 (100)	0	10 (33.3)	20 (66.7)	10 (33.3)	20 (66.7)

Table 2. univariate analysis for effect of treatment groups on urinary symptom

	Urinary frequency		**Urgent urination**		**Dysuria**		**Fever**		**Arthralgia**	
Treatment group	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-va**
Placebo	Reference		Reference		Reference		Reference		Reference	
Celecoxib	0.23 (0.10, 0.51)	<0.001	0.06 (0.2, 0.13)	<0.001	0.32 (0.15, 0.70)	0.004	0.05 (0.02, 0.12)	<0.001	1.79 (0.47, 6.83)	0.39
Phenazopyridine	0.30 (0.14, 0.67)	0.003	0.30 (0.15, 0.60)	0.001	0.24 (0.11, 0.51)	<0.001	1.11 (0.61, 2.00)	0.73	4.10 (1.37, 12.29)	0.01
Oxybutynin	0.99 (0.46, 2.12)	0.98	0.06 (0.02, 0.18)	<0.001	0.53 (0.26, 1.06)	0.07	1.03 (0.57, 1.87)	0.91	4.23 (1.63, 10.95)	0.00

Abbreviations: OR; odds ratio, CI; confidence interval

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Table 3. multivariable analysis for effect of treatment groups on urinary symptom

	Urinary frequency		**Urgent urination**		**Dysuria**		**Fever**	
Treatment group	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Placebo	Reference		Reference		Reference			
Celecoxib	0.17 (0.09, 0.31)	<0.001	0.04 (0.02, 0.07)	<0.001	0.25 (0.14, 0.46)	<0.001	0.02 (0.006, 0.10)	<0.001
Phenazopyridine	0.21 (0.10, 0.43)	<0.001	0.16 (0.07, 0.37)	<0.001	0.18 (0.09, 0.36)	<0.001	0.64 (0.36, 1.14)	0.13
Oxybutynin	0.61 (0.28, 1.32)	0.21	0.05 (0.02, 0.12)	<0.001	0.33 (0.17, 0.63)	0.001	0.48 (0.27, 0.88)	0.02
Age	0.97 (0.94, 1.01	0.20	1.10 (1.05, 1.15)	<0.001	0.97 (0.93, 1.008)	0.13	0.94 (0.91, 0.98)	0.005
Gender								
Male	Reference		Reference		Reference			
Female	0.17 (0.09, 0.33)	<0.001	0.12 (0.05, 0.25)	<0.001	0.15 (0.07, 0.32)	<0.001	Not estimated	

Abbreviations: OR; odds ratio, CI; confidence interval

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