Effects of Mirabegron on JJ Stent-Related Symptoms: A Multicentric Study

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Abstract

Purpose: To investigate the effect of mirabegron 50 mg/daily for JJ stent-related symptoms after ureteroscopic stone surgery. Methods: Medical records of 145 patients who were given a single daily oral dose of 50 mg of mirabegron for relieving stent-related symptoms were retrospectively analyzed. Demographic and clinical data and stone parameters were recorded. All participants completed the Turkish version of the Ureter Symptom Score Questionnaire (USSQ-T) on the postoperative seventh day, and again after at least three weeks, before JJ stent removal. The severity of stent-related symptoms was statistically compared before and after the mirabegron treatment. Results: The mean urinary symptoms score decreased significantly from 30.87 ± 9.43 to 22.61 ± 6.78 ($p < 0.0001$), mean body pain score decreased significantly from 21.82 ± 11.22 to 14.03 ± 7.52 ($p < 0.0001$), mean work performance score decreased from 10.50 ± 8.61 to 7.02 ± 6.51 ($p < 0.0001$), and mean general health score decreased significantly from 15.43 ± 6.50 to 11.12 ± 3.70 ($p < 0.0001$). The mean sexual matters score significantly decreased from 3.88 ± 3.40 to 2.48 ± 2.03 ($p < 0.0001$), the additional problem score decreased from 9.31 ± 4.61 to 6.51 ± 2.83 ($p < 0.0001$), and the overall quality of life (QoL) score decreased from 5.18 ± 1.94 to 4.23 ± 1.71 after mirabegron use ($p < 0.0001$). Conclusion: Daily use of 50g of mirabegron significantly improved stent-related symptoms, sexual matters, and quality of life.

Introduction

Ureteral JJ stenting is an integral part of endoscopic ureteral stone surgery which provides urine passage against either internal or external obstructive causes [1]. The incidence of stent-related symptoms (SRS), including frequency, urgency, dysuria, hematuria, pain, and sexual problems, varies from 19–76% [2–5]. The International Prostate Symptom Score, Visual Analog Pain Scale, and Overactive Bladder Symptom Score were used to evaluate SRS in clinical studies until Joshi et al. developed the Ureteral Stent Symptom Questionnaire (USSQ), which included six main domains [6]. The USSQ has been translated into different languages, including Turkish (USSQ-T), and has been widely used in clinical trials to investigate patients' discomfort [7].

The storage and voiding function of the bladder is regulated by the brain, spinal cord, and otonomous nervous

system. The urine storage and relaxation of the bladder occurs via activation of noradrenaline-mediated beta-3-adrenoreceptors, and bladder contraction/urination occurs via activation of acetylcholine-mediated receptors [8, 9]. M1, M2, and M3 subtypes of muscarinic receptors have been shown in the human bladder. Activation of the M3 receptors by acetylcholine causes detrusor contraction, and subsequently micturition starts. Antimuscarinic agents, alpha-blockers, and combination therapies have been reported to improve SRS [10, 11]. Mirabegron is the first selective beta-3-adrenoreceptor agonist that has been reported to be an effective treatment for overactive bladder syndrome, reducing bladder contractions, urgency, and frequency of urination [12, 13].

In the present study, we aimed to investigate the impact of mirabegron use in the treatment of JJ stent-related symptoms after ureterorenoscopic stone surgery using the USSQ-T.

Patients and Method

This multicentric, retrospective study was carried out after approval was given by the Ethics Committee of Zonguldak Bulent Ecevit University (approval no: 2019/14). The number of patients was determined by power analysis. Demographic and clinical data of patients who underwent unilateral JJ stent placement after ureteroscopic stone surgery (USS) were evaluated. Because patients with JJ stents show a marked increase in SRS score from the seventh postoperative day [14, 15], all participants were assessed for the presence of SRS at least one week after the surgery, called the "first control visit." Patients were given the validated Turkish version of the USSQ, which consists of six main domains: urinary symptoms, body pain, general health, work performance, sexual matters, and additional problems. The scores of each domain were summed, and the higher the total score, the higher the severity of SRS-related discomfort. Patients were given 50 mg of mirabegron once a day to relieve SRS from the first control visit and continued for at least three weeks until stent removal. Each patient was examined by a urologist to rule out urinary tract infection (UTI) and SRS before the JJ stent removal. The JJ stent was removed endoscopically after kidney-ureter-bladder (KUB) X-ray films were performed. The patient completed the USSQ-T form before stent removal. The design of the study is summarized in Figure 1.

Inclusion Criteria

- Patients above the age of 18 years.
- Patients who had undergone unilateral ureteroscopy stone surgery.
- Patients with stone-free status.
- Patients who had been catheterized with six French (Fr) JJ stents.
- Patients with SRS and without UTI at the first control visit.

Exclusion Criteria

- Concomitant use of alpha-adrenergic receptor antagonists or antimuscarinics.
- Pre-existing neurogenic bladder, interstitial cystitis, overactive bladder syndrome, chronic prostatitis, or chronic pelvic pain syndrome.
- Concomitant UTI.
- JJ stent displacement.
- Presence of significant residual stone fragment in the ureter.
- History of urinary tract surgery or any drug allergy.
- History of neurologic or psychiatric disease, or dementia.
- Pregnancy.
- Uncontrolled hypertension.

Statistical Analysis

All statistical results were analyzed using the Statistical Package for the Social Sciences version 21.0 (SPSS Inc, Chicago, IL, USA) for Microsoft Windows. The data of the patients were given as mean $\pm$ standard deviation (SD) and numbers (%). Results were analyzed using the paired samples t -test. A p value < 0.05 was considered statistically significant.

Results

After the patients with incomplete data were excluded, 145 patients (100 men and 45 women) were evaluated. The mean age of the patients was 47.0 ± 15.0 years, and the mean body mass index (BMI) was 26.93 ± 6.18 kg/m^2. The stone localization was grouped as proximal (n = 71), middle (n = 31), and distal ureter (n = 43) and the mean stone width and length was 9.2 ± 4.0 mm and 11.6 ± 5.9 mm, respectively. Demographic data and other characteristics of the patients are summarized in Table 1.

The mean urinary symptoms scores were 30.87 ± 9.43 and 22.61 ± 6.78 at first visit and before stent removal (after mirabegron therapy), respectively ($p < 0.0001$). The mean body pain scores were 21.82 ± 11.22 and 14.03 ± 7.52 ($p < 0.0001$); the mean work performance scores were 10.50 ± 8.61 days and 7.02 ± 6.51 days ($p < 0.0001$); the mean general health scores were 15.43 ± 6.50 and 11.12 ± 3.70 ($p < 0.0001$); the mean sexual matters scores were 3.88 ± 3.40 and 2.48 ± 2.03 ($p < 0.0001$); the mean additional problems scores were 9.31 ± 4.61 and 6.51 ± 2.83 ($p < 0.0001$); and the global quality of life (QoL) scores were 5.18 ± 1.94 and 4.23 ± 1.71 at the first control visit and after mirabegron monotherapy ($p < 0.0001$), respectively (Table 2).

Discussion

In the present study, we showed that mirabegron significantly improved JJ stent-related symptoms. For a long time, ureteral JJ stents have been used in urology practice used to prevent ureteral obstruction. However, stent-related pain and urinary symptoms negatively affect the quality of life in patients with JJ stents after ureteroscopic surgery [6, 16]. Several treatment options have been attributed to overcome these problems, including antimuscarinic agents, alpha-adrenergic receptor antagonists, or combination therapies [10, 11]. Alpha-adrenergic receptor antagonists alleviate the symptoms related to the JJ stent and reduce the use of analgesics [11, 17]. Similarly, mirabegron, a beta-3 receptor agonist, is being used in the treatment of overactive bladder disease, and has also been shown to improve urinary symptoms due to JJ stent insertion [18, 19].

Until recently, non-specific questionnaires such as the International Prostate Symptom Score or Overactive Bladder Symptom Score [18, 20] were used to evaluate the effect of mirabegron use for JJ stent-related symptoms. However, the non-specific nature of these questionnaires undermined the value of these studies. Therefore, in the present study, we used the Turkish-validated USSQ-T questionnaire [7]. In addition, the USSQ was used in only two studies to evaluate the effect of mirabegron for JJ stent-related symptoms. Tae et al. showed that mirabegron slightly lowered the mean urinary symptoms score from 32.58 ± 6.67 to 27.92 ± 7.72 ($p = 0.582$) [19]. Considering that mirabegron shows its maximum antimuscarinic effect after three weeks, a clinically insignificant decrease in mean urinary symptoms score can be explained by the fact that mirabegron was only used for two weeks in that study [19]. Yavuz et al. reported the results of 180 patients regarding the changes on the ureteral stent symptom questionnaire four weeks after ureterolithotripsy plus ureteral stenting. They randomized the patients into three groups receiving placebo, tamsulosin, and mirabegron (50 mg) once a day and found similar rates of urinary symptoms scores between the mirabegron and control patients (27.8 vs 24.5, $p = 0.423$) [21]. In contrast to that study, we compared the impact of mirabegron on changes of urinary symptoms scores in patients between postoperative first visit and at least four weeks after surgery. For the first time in the literature, we showed that mirabegron monotherapy significantly decreased the SRS compared to pretreatment levels.

In addition to an increased rate of SRS, patients with a JJ stent may also suffer from stent-related pain [22]. Although the mechanism of urinary symptoms and pain has not been exactly defined yet, ureteric spasm, trigonal irritation, and urinary reflux to the renal pelvis may play a role [23]. Trigonal irritation provokes detrusor contractions mediated by muscarinic receptors. Antimuscarinics alone or in combination with an alpha-receptor antagonist have been reported to be effective for SRS reduction [10, 11]. Recent meta-analyses have demonstrated that antimuscarinic monotherapy reduces the SRS and body pain scores [11, 24, 25]. Several reports showed that all subtypes of beta-adrenergic receptors were expressed in the human ureteral smooth muscle [26, 27], and use of beta-1 and beta-3 agonists might help to reduce symptoms

secondary to ureteral smooth muscle spasm [18]. In a recent study, mirabegron monotherapy was shown to reduce the USSQ body pain score and the overall pain score compared to the control group [19]. In accordance with the literature, this present study showed that JJ stent placement increased patients' pain score, and mirabegron monotherapy significantly reduced the stent-related pain score.

Ureteral stenting causes stent-related sexual dysfunction in both genders [3, 28]. Joshi et al. also reported that sexual dysfunction was observed in 38% and work performance was negatively affected in 58% of ureteral stent patients [22]. Deliveliotis et al. showed that alfuzosin, an alpha-adrenergic receptor blocker, improved SRS and sexual function [29]. Another study showed that a tamsulosin and oxybutynin combination restored the work performance, additional problems, and general health scores [30]. In accordance with these studies, our results showed that mirabegron use significantly reversed JJ stent-related decreased work performance and sexual dysfunction, and increased quality of life.

This present study has some limitations:

1. Retrospective design of the study.

2. Lack of a control group.

Conclusion

In conclusion, mirabegron monotherapy improved the JJ stent-related urinary symptoms, body pain, work performance, sexual matters, additional problems, and general health scores. Further studies are needed to clarify the role and mechanisms of mirabegron in the management of SRS.

Competing interests: The authors declare that they have no competing interests.

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References

1. Beysens M, Tailly TO. Ureteral stents in urolithiasis. Asian J Urol. 2018;5(4):274–86.
2. Joshi HB, Okeke A, Newns N, Keeley FX Jr, Timoney AG. Characterization of urinary symptoms in patients with ureteral stents. Urology. 2002;59:511–16.
3. Bolat MS, Akdeniz E, Asci R, Erdemir F, Cinar O, Tomak L. Ureterorenoscopy with stenting and its effect on male sexual function: a controlled randomised prospective study. Andrologia. 2017;49(9):10.1111/and.12746.
4. Miyaoka R, Monga M. Ureteral stent discomfort: etiology and management. Indian J Urol. 2009;25:455–460
5. Vega Vega A, Garcia Alonso D, Garcia Alonso CJ. Characterization of urinary tract symptoms and quality of life in patients with double-pig-tailed ureteral stents. Actas Urol Esp. 2007;31:738–42.
6. Joshi HB, Newns N, Stainthorpe A, Mac-Donagh RP, Keeley FX Jr, Timoney AG. Ureteral stent symptom questionnaire: development and validation of a multidimensional quality of life measure. J Urol. 2003;169:1060.
7. Tanidir Y, Mangir N, Sahan A, Sulukaya M. Turkish version of the ureteral stent symptoms questionnaire: linguistic and psychometric validation. World J Urol. 2017;35:1149–54.
8. Palmer CJ, Choi JM. Pathophysiology of overactive bladder: current understanding. Curr Bladder Dysfunct Rep. 2017;12:74–9.
9. Thiagamoorthy G, Cardozo L, Robinson D. Current and future pharmacotherapy for treating overactive bladder. Expert Opin Pharmacother. 2016;17(10):1317–25.
10. Yakoubi R, Lemdani M, Monga M, Villers A, Koenig P. Is there a role for α-blockers in ureteral stent related symptoms? A systematic review and meta-analysis. J Urol. 2011;186:928–34.

11. Zhou L, Cai X, Li H, Wang KJ. Effects of α-blockers, antimuscarinics, or combination therapy in relieving ureteral stent-related symptoms: a meta-analysis. J Endourol. 2015;29:650–6.
12. Cui Y, ZongH, YangC, YanH, Zhang Y. The efficacy and safety of mirabegron in treating OAB: a systematic review and meta-analysis of phase III trials. Int Urol Nephrol. 2014;46:275–84.
13. Warren K, Burden H, Abrams P. Mirabegron in overactive bladder patients: efficacy review and update on drug safety. Ther Adv Drug Saf. 2016;7:204–16.
14. Giannarini G, Keeley Jr FX, Valent F, et al. Predictors of morbidity in patients with indwelling ureteric stents: results of a prospective study using the validated ureteric stent symptoms questionnaire. BJU Int. 2011;107:648–54.
15. Calvert RC, Wong KY, Chitale SV, et al. Multi-length or 24 cm ureteric stent? A multicentre randomised comparison of stent-related symptoms using a validated questionnaire. BJU Int. 2013;111:1099–104.
16. Nestler S, Witte B, Schilchegger L, Jones J. Size does matter: ureteral stents with a smaller diameter show advantages regarding urinary symptoms, pain levels and general health. World J Urol. 2020;38(4):1059-1063.
17. Deliveliotis K, Papatsoris AG, Skolarikos A, Mitsogiannis I, Tzannis K, Dellis AE. Management of stent-related symptoms with the use of α-blockers: a meta-analysis. Arab J Urol. 2019;18(1):14–21.
18. Otsuki H, Yamasaki T, Hori S, et al. The efficacy of mirabegron for the relief of ureteral stent-related symptoms. Acta Med Okayama. 2020;74(2):145–50.
19. Tae BS, Cho S, Jeon BJ, et al. Does mirabegron relieve ureteric stent-related discomfort? A prospective, randomized, multicentre study. BJU Int. 2018;122(5):866–72.
20. Sahin A, Yildirim C, Yuksel OH, Urkmez A. Treatment of ureteral catheter related symptoms; mirabegron versus tamsulosin/solifenacin combination: a randomized controlled trial. Tratamiento de los sintomas relacionados con los catéteres: mirabegon vs tamsulosina-solifenacina en combinación: un estudio prospectivo randomizado. Arch Esp Urol. 2020;73(1):54–9.
21. Yavuz A, Kilinc MF, Aydin M, Ofluoglu Y, Bayar G. Does tamsulosin or mirabegron improve ureteral stent-related symptoms? A prospective placebo-controlled study [published online ahead of print, 2020 May 14]. Low Urin Tract Symptoms. 2020;10.1111/luts.12320.
22. Joshi HB, Stainthorpe A, MacDonagh RP, Keeley FX Jr, Timoney AG, Barry MJ. Indwelling ureteral stents: evaluation of symptoms, quality of life and utility. J Urol. 2003;169:1065–9.
23. Lang RJ, Davidson ME, Exintaris B. Pyeloureteral motility and ureteral peristalsis: essential role of sensory nerves and endogenous prostaglandins. Exp Physiol. 2002;87:129–46.
24. Wang J, Zhang X, Zhang T, Mu J, Bai B, Lei Y. The role of solifenacin, as monotherapy or combination with tamsulosin in ureteral stent-related symptoms: a systematic review and meta-analysis. World J Urol. 2017;35(11):166980.
25. Yan H, Wang Y, Sun R, Cui Y. The efficacy of antimuscarinics alone or in combination with alpha-blockers for the treatment of ureteral stent-related symptoms: a systematic review and meta-analysis. Urol Int. 2017;99(1):6–13.
26. Matsumoto R, Otsuka A, Suzuki T, et al. Expression and functional role of β3-adrenoceptors in the human ureter. Int J Urol. 2013;20(10):1007–14.
27. Shen H, Chen Z, Mokhtar AD et al. Expression of beta-adrenergic receptor subtypes in human normal and dilated ureter. Int Urol Nephrol. 2017;49:1771–8.
28. Akdeniz E, Bolat MS. Ureterorenoscopy with stenting and its effect on female sexual function. Urol J. 2017;14:3059e63.
29. Deliveliotis C, Chrisofos M, Gougousis E, Papatsoris A, Dellis A, Varkarakis IM. Is there a role for alpha1-blockers in treating double-J stent-related symptoms? Urology. 2006;67:35–9.
30. Maldonado-Avila M, Garduno-Arteaga L, Jungfermann-Guzman R, et al. Efficacy of tamsulosin, oxybutynin, and their combination in the control of double-j stent-related lower urinary tract symptoms. Int Braz J Urol. 2016;42(3):487–93.

Figure Legends:Figure 1. The study design.**Table 1.** Demographic features.**Table 2.** USSQ scores.

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