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"Effect Of Beta-3 Agonist (Mirabegron) And Alpha Blocker (Tamsulosin) On Treatment Of Ureteral Stent Related Symptoms: A Randomized Controlled Trial"

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Abstract
Introduction
To compare the effects of Mirabegron versus Tamsulosin on improving symptoms and QoL in patients with indwelling ureteral stents using the validated version of USSQ questionnaire.
Materials and methods
This study was conducted on 200 patients (men and women) who underwent DJ stenting after uneventful endourological surgeries. Total of 150 patients reported DJ SRS, they were randomized into 3 groups (A, B, and C) in a ratio of 1: 1: 1. Group A were put on placebo, Group B on Tab Mirabegron 50mg OD, and Group C on Tab Tamsulosin 0.4mg OD. They were given the USSQ questionnaire and asked to complete it on the first week to see the magnitude of DJ SRS and third week before the DJ stent was removed.
Results
Study included total of 141 patients. All baseline characteristics (age, sex, side, indication, length, and duration of stent) were comparable. Average Urinary scores (USs) were 35.20, 35.8, 35.43 at 1st week and 21.64, 17.68, 36.7 at 3rd week, average pain scores (PSs) were 27.54, 28.34, 28 at 1st week and 14.86, 24.03, 26.7 at 3rd week and average sexual scores (SSs) were 7.34, 7.2, 7.2 at 1st week and 2.31, 2.17, 6.2 at 3rd week for Mirabegron, Tamsulosin, placebo respectively.
Conclusion
Tamsulosin improved USs. Mirabegron decreased the PSs and analgesic requirement. Mirabegron also improved WHSs, GHSs. Patients who are burdened by side effects or less improved on treatment with alpha-blockers or antimuscarinics could be additionally given or alternatively given Mirabegron to attenuate DJ SRS.
Keywords:*Urinary symptoms, Endourology, flank pain, DJ stent*

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I. Introduction

ureteral stents enable dilatation of the ureter, divert urine flow to the bladder, and help recover ureteral injury. Despite its advantages, DJ stent can lead to morbid symptoms such as frequency(50–60%), urgency(57–60%), dysuria(40%), suprapubic pain(30%), hematuria(25%), flank pain(19–32%) and urge incontinence which adversely affect the quality of life in approximately 80% of patients[1–3]. Nearly 80% of patients may experience stent related symptoms(SRSs) affecting daily activities, 58% report reduced work capacity and 32% report sexual dysfunction[3]. Joshi et al. had developed "a validated self-administered Ureteral Stent Symptom Questionnaire (USSQ), for evaluating SRSs in the clinical and research settings[4].

Many studies have indicated that agents such as alpha -1 adrenergic receptor antagonists (alpha-1 blockers) or antimuscarinics may decrease SRSs. However, the success of these medications has mixed results. Since some of the stent-induced symptoms are similar to OAB symptoms, there may be potential benefit of using Mirabegron to alleviate bladder discomfort symptoms or pain caused by ureteral stents, as previously reported [5]. There are few studies in published literature to see the efficacy of Mirabegron for ureteral SRSs [5, 6]. There is no published study in literature to compare Tamsulosin and Mirabegron for ureteral SRSs.

II. Materials and methods

This study was conducted on 200 patients (men and women) who underwent DJ stenting after uneventful endourological surgeries from March 2019 to December 2020. Ethical committee and board of members of our institution approved this prospective placebo-controlled double blind RCT, and all patients who gave written informed consent were enrolled for the study. Patients aged between 18 to 50 years undergoing unilateral percutaneous nephrolithotomy (PCNL), Extracorporeal shock wave lithotripsy (ESWL), Retrograde

intra renal surgery (RIRS) or ureteroscopy (URS) with double J (DJ) stenting were evaluated for enrolment in the study.

All patients completed international prostatic symptom score (IPSS) preoperatively and those patients with elevated IPSS were excluded from the study. On the day of surgery, all patients received injection piperacillin and tazobactam, intravenously, prophylactically 30-60 mins before the operation. All stents used were of 5 Fr external diameter and 26 cm length, composed of polyurethane material, non-string, blue coloured double J stents (P flex ureteral stent, BLUENEEM, INDIA). Operating urologist decided the placement of DJ stent depending upon the stone burden, mucosal injury, and need for ureteral dilation for adequate post-operative drainage. Patients were pre informed regarding removal of DJ stent for the purpose of study. Those patients with significant residual stones and positive urine cultures post operatively were excluded from the study to avoid any confounding factors.

Postoperative X-ray KUB was done in all patients on day one to rule out the residual stone fragment and position of DJ stent. Per urethral catheter (PUC) removed on day 1 in URS patients and day 2 in PCNL patients. At the time of catheter removal, urine cultures were sent Nephrostomy tubes were removed on 3rd post-op day in PCNL patients. All patients were explained about the DJ related symptoms and they were called to fill the USSQ questionnaire at first week. A total of 150 patients reported DJ stent related symptoms at the end of first week, and were recruited for the study. They were randomized by a computer-generated module method into 3 groups (A, B, and C) in a ratio of 1: 1: 1. Group A (50 patients) were put on placebo, Group B (50 patients) were put on Tab Mirabegron 50mg once a day, and Group C (50patients) were put on Tab Tamsulosin 0.4mg once a day at night. Tab Diclofenac (50mg) was used for pain relief and advised as per need basis. To eliminate bias, double blinding was used. The side effects of both Mirabegron and Tamsulosin were explained to all patients. They were given the USSQ questionnaire and asked to complete it on the third week before the DJ stent was removed. Scoring at the first week was done to see the magnitude of DJ-related symptoms. Analgesic requirements and side effects of the drug during each group's study period were also noted. Sample size was calculated with the G*Power programme using a priori analysis with an effect size of 0.3. For 85 percent power, 0.05 error probability, and a 20% dropout rate during follow-up, a sample size of 125 patients was estimated.

The primary endpoints would be the USSQ body pain score (PSs) and the USSQ urinary symptom score (USs). The secondary efficacy outcomes would be scores in the other four domains of the USSQ (general health score(GHs), work health score(WHs), sexual score(SS), additional health score(AHs), global quality of life(QoL), and oral analgesic requirements)

The Chi-square test was used to compare categorical variables between treatment groups. The Kruskal Wallis test was used to compare quantitative variables in the three groups, and the Wilcoxon signed-rank test was used to compare means in the first and third weeks of each group. Post Hoc Tukey HSD test done for pairwise comparison. The results were considered significant at $P<0.05$.

III. Results

Total of 150 patients complained of DJ-SRSs and were recruited to the study. 9 patients were excluded and remaining 141 patients were included for the final analysis as shown in figure 1.

Mean age of patients was 32.9, 32.3 and 33.2 years in Placebo, Mirabegron and Tamsulosin group respectively, male to female ratio, average BMI, and procedures performed were uniform in all 3 groups (Table 1). Most common procedure performed in our study was PCNL followed by URS, ESWL and RIRS in descending order. The average duration of stent placement was 21.7, 16.6 and 17 days in placebo, Mirabegron and Tamsulosin group respectively. There was no statistically significant difference between all three groups at their 1st week USSQ scores. (Table 2).

Average USs, PSs, AHs, SSs, WHs and GHs at 1st week and 3rd week are as mentioned in table 3. Mean difference in scores at 3rd week compared to 1st week are shown in Table 3. The average difference in USs from 1st week to 3rd week in Mirabegron, Tamsulosin group and placebo groups are 13.6, 18.12 and 1.27 respectively. The maximum decrease in USs is seen tamsulosin group. Similarly, the maximum decrease in PSs is seen in Mirabegron group with an average of 12.68 points compared to other groups. The average difference in SSs are 5.03, 5.03 and 0.8 in Mirabegron, Tamsulosin and placebo groups respectively (Table 2).

USs decreased maximally with Tamsulosin. PSs, WHs, GHs and analgesic requirement maximally decreased with mirabegron. AHs and SSs reduction are equal with both tamsulosin and Mirabegron(table 2 & 3).

2 out of 47 patients experienced syncopal attacks and 2 patients presented with postural hypotension in tamsulosin groups whereas one patient in placebo group reported dyspepsia and one patient in Mirabegron reported mild headache, none of the patients in Mirabegron reported side effects such as hypertension, urinary retention and tachycardia(p=0.2).

IV. Discussion

Indwelling ureteric stents cause a variety of complications and decrease patients QOL[7]. Joshi et al. reported that "nearly 78% of patients with indwelling ureteric stents had urinary dysfunction symptoms and 80% patients had stent-related pain"[8]. The USSQ was developed to evaluate the discomfort associated with ureteric stents and it is currently widely used [9]. The exact mechanism causing ureteric stent-related discomfort is unknown; however, ureteric spasms, ureteric reflux caused by the ureteric stent, or trigonal irritation have been suggested by several scholars [10]. In our study 75% of patients (150/200) developed SRSs, which is similar to 72.2% as reported by S P Aggarwal et al, 80% as reported by Liu Q et al.[11, 12].

The mean reduction in USs at 1st week to 3rd week were 13.6, 18.1 and -1.24 in Mirabegron, Tamsulosin and Placebo groups respectively and the mean reduction in body PSs were 12.7, 5.3 and 2.3 respectively which are more superior to the results published by B S Tae et all in which the mean decrease in USs and body PSs was 4.66 and 8.0 respectively in Mirabegron group[13].

Alpha blockers have been shown in several RCTs to reduce SRSs. Wang et al. studied "Tamsulosin 0.4 mg once daily in a RCT of 154 patients. Tamsulosin 0.4 mg decreased the USSQ USs from 31.59 in the placebo group to 20.96 in the Tamsulosin group ($p < 0.0001$) and the USSQ body PS from 13.3 in the placebo group to 9.94 in the Tamsulosin group ($p = 0.04$)"[14]. Similarly in our study Tamsulosin 0.4mg showed more decrease in USSQ USs from 35.8 at first week to 17.68 at 3rd week ($p<0.0001$) and the USSQ body PSs from 28.34 at 1st week to 23.04 at 3rd week which is comparable to wang et al. Dellis et al. observed the "effects of Tamsulosin 0.4 mg and alfuzosin 10 mg in a 3-armed RCT of 150 patients. Both alpha blockers significantly reduced USSQ USs and body PSs"[15]. More recently, Singh et al. showed that "Tamsulosin 0.4 mg had positive effects on urinary index and pain index scores in a small RCT ($n = 60$)"[16].

Mirabegron is an agonist of the beta-3 adrenergic receptor, which is thought to be responsible for detrusor smooth muscle relaxation during storage[17]. Currently, agents can now help relax the detrusor smooth muscle, resulting in improved bladder capacity without affecting micturition pressure, post-void residual urine volume, or voiding contractions. Furthermore, Nitti et al. [18] provided a phase III RCT in which Mirabegron tolerability was comparable to that of placebo, with the exception of dry mouth, which occurred five times less often with Mirabegron than with tolterodine extended release 4mg dose[19, 20].

We thought that Mirabegron would be useful for voiding symptoms caused by stent-related pain because of its role as an OAB therapeutic agent. In our study Mirabegron decreased USSQ USs from 35.20 at 1st week to 21.63 at 3rd week, body PSs from 27.54 at 1st week to 14.86 at 3rd week and there was significant improvement in all QoL scores which is similar to the results of the study by Bum Sik Tae et al. [13] where Mirabegron group had lower USSQ body PSs (21.96 vs 13.96, $P = 0.007$) and overall PSs (5.58 vs 2.83, $P = 0.002$) than the control group. The Mirabegron group had lower USSQ USs (32.58 vs 27.92, $P = 0.582$) and a lower USSQ GHS (17.71 vs 14.00, $P = 0.281$), although the difference was not significant.

Recently Hideo Otsuki et al.[21] published study in 2020 to investigate the efficacy of Mirabegron for lower urinary tract symptoms in patients with an indwelling ureteral stent after 76 ureterorenoscopic lithotripsy. IPSS scores decreased from 16.2 to 14.3 (p0.001), whereas IPSS-QoL scores declined from 5.0 to 4.6 ($p=0.012$). The urinary urgency scores (OABSS-Q3) reduced significantly from 3.24 to 2.68 (p0.001), and the OABSS scores improved significantly from 7.7 to 6.8 ($p=0.006$). Mirabegron considerably improved SRSs and the amount of nocturia episodes. Although their study used IPSS, the improvement of lower urinary tract symptoms and QoL scores with Mirabegron is consistent with improvement of USs, PSs and other QoL score by Mirabegron in our study.

Even though Tamsulosin is an established drug in the market for SRSs for last 2 decades and in our study also we found Tamsulosin is superior at improving USs to Mirabegron. However, Mirabegron showed superior results for body PSs, GHSs and WHSs to Tamsulosin. These results support the use of a beta-3 agonist to relieve ureteric stent-related symptoms and improve the quality of life in patients with DJ SRSs. Furthermore, there were no serious adverse effects reported in the Mirabegron population. Notably, no urinary retention was found in any of the Mirabegron treated patients.

In placebo group symptom score improvement in PSs and SSs could be explained on the basis of better tolerance of stent symptoms, lesser psychological stress and lesser inflammation with time from 1st week to 3rd week after the surgical procedure.

There were some limitations to this analysis. Firstly, small number of patients, despite the fact that the measured sample size was adequate. Second, this was an open label analysis. The same formulations and constellation of placebo effects could not be achieved since this research was performed without the assistance of pharmaceutical companies. Finally, all four interventions (PCNL, URS, RIRS, and ESWL) constitute heterogeneous forms of surgical procedures in this study. Despite our attempts to use limited type of instruments such as in PCNL (smaller size sheath 22-24 Fr), RIRS (9.5 Fr), and 6.5/8.5 Fr ureteroscopes in URS, the degree and form of surgery can have an effect on postoperative pain.

Despite these limitations, the current analysis yielded some substantial results. To our knowledge, this is the first randomized study to compare the effects of beta-3 agonist and alpha blocker (Tamsulosin) therapy on ureteric stent-related pain following endourological surgery. Second, as previously reported, since this study was not funded by pharmaceutical firms, any possible bias that could have emerged during the research and interpretation of the findings was reduced [22].

V. Conclusion

Patients who are burdened by side effects or getting less improvement on treatment with alpha-blockers or antimuscarinic agents could be additionally or alternatively given Mirabegron to attenuate DJ SRSs. If future studies confirm that beta-3 agonists have a therapeutic impact in ureteric dilatation, its use for medical expulsion therapy could be considered.

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