

# Effect of Silodosin and Deflazacort Combination in Reducing Symptoms Related to Indwelling Ureteric Stent: A Randomised, Double-Blind Trial

DEBABRATA KUMAR SABAT<sup>1</sup>, DAISY KARAN<sup>2</sup>

## ABSTRACT

**Introduction:** Endoscopic stent placement is an eminent procedure in urological practice and it substantially helps in reducing severe symptoms of ureteral obstruction. However, there may be few adverse events which may significantly affect the Quality of Life (QoL) of patients. These include stent related pain, sexual dysfunction, and Lower Urinary Tract Symptoms (LUTS). Appropriate therapy will reduce LUTS and improve QoL.

**Aim:** To assess the effect of silodosin and deflazacort combination, when compared to silodosin alone, in improving symptoms and QoL in patients with indwelling Double J (DJ) ureteral stents.

**Materials and Methods:** A randomised, controlled trial was conducted at the Department of Urology of a Tertiary Care Hospital, in Eastern India between August 2018 and December 2018; in patients with insertion of DJ stent after ureteroscopy and percutaneous stone removal. Patients were randomised into; Group A, silodosin (8 mg) once daily for two weeks and Group B, silodosin (8 mg) and deflazacort (30 mg) once daily

for two weeks. Outcomes including pain, voiding flank pain, storage symptoms (frequency, urgency, nocturia), QoL were determined. Student's t-test was used for comparison of Visual Analogue Scale (VAS) and International Prostate Symptom Scale (IPSS) scores.

**Results:** Total 144 patients were analysed in the study and were divided into group A (n=72) and group B (n=72). The mean age was 50.93 and 50.91 years; with 60 and 58 males in Group A and B, respectively. The mean VAS for pain was 1.05 and 2.01 for group B and A ( $p < 0.05$ ), respectively; similarly, voiding flank pain was also significantly lower in group B (1.56) than group A (2.80) ( $p < 0.05$ ). Mean score for frequency and urgency were significantly lower in group B (2.16 and 1.64) than group A (3.08 and 2.85); while, score for nocturia were similar between both the groups ( $p = 0.87$ ). The QoL score was significantly better in group B than in group A (1.44 vs. 2.81;  $p < 0.05$ ).

**Conclusion:** Combination therapy with silodosin and deflazacort, instead of monotherapy with silodosin alone, was safe and effective in alleviating stent related LUTS and improving QoL.

**Keywords:** Alpha blocker, Anti-inflammatory, Double J stent, Lower urinary tract symptoms, Steroid, Ureteroscopy

## INTRODUCTION

Endoscopic stent placement is an eminent procedure in urological practice and it substantially helps in reducing severe symptoms of ureteral obstruction. However, there may be few adverse events which may significantly affect the QoL of patients. These include stent related pain, sexual dysfunction, haematuria, dysuria, etc., [1-3].

A meta-analysis suggested that the use of alpha blockers could be effective in view of the similarity of these symptoms to benign prostatic hyperplasia related LUTS [4]. Various pharmacological adjuncts have been tested, but none of the combinations have proven to be definitive in relieving these symptoms considerably.

Silodosin, a highly selective  $\alpha_1$ -adrenoreceptor antagonist, is generally used for the symptomatic treatment of LUTS through relaxation of smooth muscle cells of the lower urinary tract [5-7]. Deflazacort, a glucocorticoid, is used as an anti-inflammatory and immuno-suppressant. In urology practices, it has been used in medical expulsive therapy for distal ureteric stones due to its anti-edema role [8-11].

In spite of several available studies on use of combination of alpha blockers and deflazacort for relief of stent related symptoms, this study will add evidence to the literature. The primary objective of this study was to evaluate the effect of silodosin and deflazacort combination in improving LUTS. The secondary objective was to evaluate QoL in patients with indwelling DJ ureteral stents.

## MATERIALS AND METHODS

This was a randomised, double-blind, parallel group single center study, conducted at the Department of Urology of a Tertiary Care Hospital in Eastern India, between August 2018 and December 2018. This study protocol was approved by the Institutional Ethics Committee (IEC/DMR/IMS-SOA/2018/017). The study was conducted in accordance with the approved protocol, and ethical principles that have their origin in the Declaration of Helsinki and latest amendment (2013). Each study participants provided written informed consent for participation in the study.

**Inclusion criteria:** Patients of either sex, aged between 18 and 50 years who were undergoing unilateral Percutaneous Nephrolithotomy (PCNL) or Ureteroscopic Lithotripsy (URSL) with DJ stenting were eligible to participate.

**Exclusion criteria:** Patients with history of diabetes, hypertension, renal failure or osteoporosis, patients who were receiving nitrate drugs, patients with postoperative residual stone fragments, pregnant or feeding women, patients with bilateral stents, long-term stenting and bladder/prostate pathology were excluded from the study. Patients with history of LUTS, history of chronic use of selective alpha-1 blockers, or history of hypersensitivity to diclofenac, cephalosporins or fluoroquinolones were also excluded from study.

After screening, patients who were eligible and agreed to participate, were randomised (1:1) to one of the treatment groups to receive

silodosin 8 mg once daily (Group A) or silodosin 8 mg plus deflazacort 30 mg once daily (Group B) for two weeks. The randomisation codes were generated using online randomisation tool by a resident who was not involved in the study. Once the patient was screened and found eligible, the resident was contacted for randomisation code to enroll the patient. To maintain the blinding, sugar-coated tablets with similar shape and size were used along with silodosin 8 mg for Group A. Analgesics (diclofenac) was allowed on as required basis. Analgesic requirement and adverse events during study period were noted.

The outcome measures included pain and voiding flank pain which were evaluated using 10-cm linear VAS and the irritability with DJ stent was evaluated using the irritative domain of IPSS before DJ stent removal (two weeks after procedure). Scores for frequency, urgency and nocturia were assessed. QoL due to urinary symptoms was assessed on a 6-point scoring system where 0 indicates delightful and 6 indicates terrible [12].

For URSL, 6.5/8.5 Fr Ureteroscope (Wolf) and pneumatic Lithotripter were used; however, for PCNL, 26 Fr Nephroscope (Wolf) and pneumatic Lithotripter were used. The decision to place DJ stents was taken by the operating urologist based on clinical judgement considering stone burden, mucosal trauma and need for ureteral dilation to access tight ureters, and was not specified by the protocol. Postoperative X-ray (KUB) was done in all patients to rule out residual stone fragment. On the day of surgery, as prophylaxis, each patient received ceftazidime 1 gm (intravenously). In all the patients Foley's catheter was removed on postoperative Day 1. As per institutional protocol, each patient received oral levofloxacin 500 mg once daily for seven days. Patients were informed about DJ stent related symptoms and were given IPSS and VAS at discharge. Patients were instructed to follow-up after one and two weeks or on as required basis.

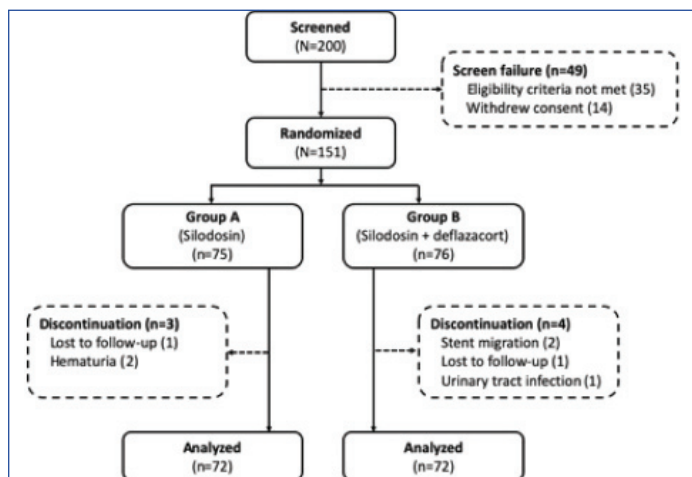
Based on our clinical experience and limited duration of study (academic project), a sample size of 150 was considered sufficient to evaluate stent related symptoms.

## STATISTICAL ANALYSIS

Data was collected and tabulated in an excel sheet and was analysed using IBM SPSS version 20.0 licensed to the institute for generation of inferential statistics. Student's t-test was used for comparison of VAS and IPSS scores. A p-value of <0.05 was considered significant.

## RESULTS

A total of 151 patients were enrolled (Group A, n=75; Group B, n=76). Two patients were lost to follow-up. One patient had urinary tract infection and two patients had haematuria leading to early removal of stent. Two patients had stent migration [Table/Fig-1]. In



[Table/Fig-1]: CONSORT flow diagram.

total, 144 patients were analysed for the study.

The patient demographics, duration of surgery were comparable between the groups [Table/Fig-2]. The mean age was 50.93 and 50.91 years in Group A and B, respectively ( $p < 0.988$ ); 60 (83.33%) and 58 (80.56%) patients were males respectively. The mean duration of surgery was 28.56 and 29.1 minutes in Group A and B, respectively; however, the mean stone size was 9.45 and 9.24 mm, respectively. A total of 59.72% (n=43) patients from Group A underwent PCNL and 40.28% (n=29) underwent URSL;

Variables	Group A (n=72)	Group B (n=72)	p-value
Age (years)	50.93 (10.72)	50.91 (9.65)	<0.988
Weight (kg)	66.4 (4.54)	68.7 (3.11)	0.640
<b>Sex, n (%)</b>			
Males	60 (83.33)	58 (80.56)	0.640
Females	12 (16.67)	14 (19.44)	
Duration of surgery (min)	28.56 (4.68)	29.1 (4.64)	0.618
Stone size (mm)	9.45 (1.62)	9.24 (1.52)	0.150
<b>Procedures</b>			
PCNL	43 (59.72)	44 (61.11)	-
URSL	29 (40.28)	28 (38.89)	

[Table/Fig-2]: Demographic data.

Data is presented as mean (SD), unless otherwise specified; PCNL: Percutaneous nephrolithotomy; SD: Standard deviation; URSL: Ureteroscopic lithotripsy

similarly, 61.11% (n=44) patients from Group B underwent PCNL and 38.89% (n=28) underwent URSL.

As shown in [Table/Fig-3], overall, there was a significant ( $p < 0.05$ ) reduction in Group B as compared to group A in both pain and voiding flank pain. The mean score of frequency on the IPSS and urgency were more in Group A than Group B. The mean score of nocturia on the IPSS was 1.06 in Group A and 1.01 in Group B ( $p = 0.87$ ). The mean score of QoL on the IPSS was significantly

Parameters	Group A (n=72)	Group B (n=72)	p-value
Pain (VAS)	2.01 (0.84)	1.05 (0.35)	<0.05
Voiding flank pain (VAS)	2.80 (0.73)	1.56 (0.67)	<0.05
Frequency	3.08 (0.81)	2.16 (0.87)	<0.05
Urgency	2.85 (0.99)	1.64 (0.45)	<0.05
Nocturia	1.06 (0.54)	1.01 (0.23)	0.87
Quality of life	2.81 (0.77)	1.44 (0.54)	<0.05
Diclofenac use in 1 week, median (range)	3 (1-6)	3 (1-5)	1.12

[Table/Fig-3]: Comparison of ureteral symptom scores and VAS scores.

Data is presented as mean (SD); SD: Standard deviation; VAS: Visual analogue scale

reduced in group B (1.44) compared to Group A (2.81) ( $p < 0.05$ ). There was no significant difference in the use of diclofenac for pain relief. There were no reported adverse events in any of the groups.

## DISCUSSION

The present study assessed the effect of deflazacort in combination with silodosin, on stent related symptoms following ureteroscopy. Most common side effect associated with ureteral stent placement is pain and multiple factors have been linked to this stent pain pathophysiology. High pressure transmitted to the renal pelvis during micturition, trigonal irritation caused by the intra-vesical portion of the stent, or lower ureteral spasm are some of these pain contributing factors in patients with ureteral stent placement [12,13]. Based on above theories, medical treatment with alpha blocker alone or with anti-muscarinics have been used to reduce stent related symptoms. Mechanisms of these drugs in relieving ureteral stent related symptoms are through smooth muscle relaxation of lower

ureter and trigone, reduction in ureter motility, voiding pressure as well urinary reflux [14,15].

Though incidence of ureteral, perineal and loin pain was lower in patients on silodosin than in those on placebo, there are studies where alpha blockers have been combined with Non-Steroidal Anti-inflammatory Drugs (NSAIDs) and anti-cholinergics for better result [16-20]. All these studies could not provide confirmatory complete pain relief and there was a need of proper interventions which will give better relief of symptoms to the patients suffering from pain caused by primary pathology or associated intervention such as ureteroscopy.

At present, there are various treatment options available for relieving stent related symptoms; however, studies demonstrating a definitive treatment or recommendations are lacking. A previous study involving an intravesical instillation of ketorolac, alkalised lidocaine, or oxybutynin in bladder was associated with significant improvement in early pain scores [21]. The role of NSAIDs was probably due to its inhibitory action on ureteral contractility, but its anti-inflammatory role was not much pronounced in this setting. Another study done by Krambeck AE et al., indicated role of ketorolac loaded ureteric stent in reducing pain as compared to controls [22]. A recent study demonstrated combination therapy with tamsulosin and oxybutynin improved irritative symptoms, work performance and sexual matters and recommended combination therapy should be considered for patients who complained of stent related symptoms [23].

The present study hypothesised that steroid being an anti-inflammatory drug, could have a role in alleviating ureteric colic like symptoms in patients with DJ stent. The use of steroids can reduce the risk of edema through inhibition of the inflammation of mucosa caused due to presence of stent in ureter. Movement of stent during patient position aggravates this edematous reaction. Friction between stent and edematous mucosa leads to activation of nociceptors leading to renal colic type of pain. With respect to urological application, deflazacort has been used along with alpha blocker for medical stone expulsive therapy [9]. Deflazacort is a glucocorticoid and it has faster and potent anti-inflammatory action that can be achieved at a low dose [24].

In the present study, patients receiving deflazacort as an adjunct to silodosin reported a significantly better QoL and pain relief, significant reduction in frequency and urgency scores; while similar nocturia score as compared to patients receiving silodosin only. On comparison of VAS pain and voiding flank pain scores between the two groups, it was evident that silodosin in combination with corticosteroid (deflazacort) had better outcomes in comparison to silodosin only group ( $p < 0.05$ ). These observations suggest pain relief with addition of deflazacort to silodosin. This pain relief can be attributed to the anti-inflammatory action of deflazacort on ureteral mucosa. However, due to side effects of long-term steroid therapy, it was given for two weeks period and patient compliance was assured in all cases.

Although there are no direct studies which assessed efficacy of silodosin plus deflazacort in relieving stent related symptoms, the observations of this study are in concordance with the previous studies. Dellabella M et al., evaluated the efficacy of tamsulosin with deflazacort in patients with distal stones and reported that the patients receiving this combination therapy had a significantly higher stone-expulsion rate, a shorter stone expulsion time, no drug-related side effects and shorter hospital stays [25]. Another study by Dellabella M et al., also demonstrated additional benefit of steroids as an increase in expulsion rate from 90% with tamsulosin alone to 96.7% in patients receiving the alpha blocker plus deflazacort. The patients taking the tamsulosin/deflazacort combination also decreased their time of stone passage to 72 hours compared with 120 hours in those on tamsulosin monotherapy [10].

## Limitation(s)

The current study was limited to a relatively small sample size, although it was powered to assess a moderate effect size, based on similar studies. A non-validated symptom questionnaire and a VAS have been used to measure stent related symptoms, for ease and efficiency of use, as opposed to the 38-item Ureteral Stent Symptom Questionnaire (USSQ).

## CONCLUSION(S)

Overall observations of this study suggest that the combination of silodosin and deflazacort provided safe and effective relief of pain component in stent related LUTS as compared to silodosin alone and can be considered a better option for relief of pain in patients with post ureteroscopy DJ stenting.

## REFERENCES

- Joshi HB, Okeke A, Newns N, Keeley FX Jr, Timoney AG Jr. Characterisation of urinary symptoms in patients with ureteral stents. *Urology*. 2002;59(4):511-16. doi:10.1016/s0090-4295(01)01644-2.
- Thomas R. Indwelling ureteral stents: Impact of material and shape on patient comfort. *J Endourol*. 1993;7(2):137-40. doi:10.1089/end.1993.7.137.
- 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(3):1065-69. doi:10.1097/01.ju.0000048980.33855.90.
- Lamb AD, Vowler SL, Johnston R, Dunn N, Wiseman OJ. Meta-analysis showing the beneficial effect of  $\alpha$ -blockers on ureteric stent discomfort. *BJU Int*. 2011;108(11):1894-902. doi:10.1111/j.1464-410X.2011.10170.x.
- Yoshida M, Kudoh J, Homma Y, Kawabe K. New clinical evidence of silodosin, an  $\alpha(1A)$  selective adrenoceptor antagonist, in the treatment for lower urinary tract symptoms. *Int J Urol*. 2012;19(4):306-16. doi:10.1111/j.1442-2042.2011.02957.x.
- Michel MC. The pharmacological profile of the  $\alpha(1A)$ -adrenoceptor antagonist silodosin. *Eur Urol*. 2010;9(4):486-90. doi.org/10.1016/j.eursup.2010.03.006.
- Roehrborn CG, Schwinn DA. Alpha1-adrenergic receptors and their inhibitors in lower urinary tract symptoms and benign prostatic hyperplasia. *J Urol*. 2004;171(3):1029-35. doi:10.1097/01.ju.0000097026.43866.cc.
- Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. *Mol Cell Endocrinol*. 2011;335(1):02-13. doi:10.1016/j.mce.2010.04.005.
- Porpiglia F, Vaccino D, Billia M, Renard J, Cracco C, Ghignone G, et al. Corticosteroids and tamsulosin in the medical expulsive therapy for symptomatic distal ureter stones: Single drug or association? *Eur Urol*. 2006;50(2):339-44. doi:10.1016/j.eururo.2006.02.
- Dellabella M, Milanese G, Muzzonigro G. Medical-expulsive therapy for distal ureterolithiasis: Randomized prospective study on role of corticosteroids used in combination with tamsulosin-simplified treatment regimen and health-related quality of life. *Urology*. 2005;66(4):712-15. doi:10.1016/j.urology.2005.04.055.
- Porpiglia F, Destefanis P, Fiori C, Fontana D. Effectiveness of nifedipine and deflazacort in the management of distal ureter stones. *Urology*. 2000;56(4):579-82. doi:10.1016/s0090-4295(00)00732-9.
- International Prostate Symptom Score (IPSS) form. Available from: <http://www.urospec.com/uro/Forms/ipss.pdf> [Accessed on: 6<sup>th</sup> July, 2019].
- Deliveliotis C, Chrisofos M, Gougousis E, Papatouris A, Dellis A, Varkarakis IM. Is there a role for alpha1-blockers in treating double-J stent-related symptoms? *Urology*. 2006;67(1):35-39. doi:10.1016/j.urology.2005.07.038.
- Lang RJ, Davidson ME, Exintaris B. Pyeloureteral motility and ureteral peristalsis: Essential role of sensory nerves and endogenous prostaglandins. *Exp Physiol*. 2002;87(2):129-46. doi:10.1113/eph8702290.
- Wang CJ, Huang SW, Chang CH. Effects of tamsulosin on lower urinary tract symptoms due to double-J stent: A prospective study. *Urol Int*. 2009;83(1):66-69. doi:10.1159/000224871.
- Tsai PC, Wang CJ, Chang CH, Chen HW, Hsu CS. Effects of silodosin on lower urinary tract symptoms due to a double-j stent: A prospective randomized study. *Int J Nephrol Kidney Failure*. 2015;1(3):01-04. <http://dx.doi.org/10.16966/2380-5498.118>.
- Koprowski C, Kim C, Modi PK, Elsamra SE. Ureteral stent-associated pain: A review. *J Endourol*. 2016;30(7):744-53. doi:10.1089/end.2016.0129.
- Zhou L, Cai X, Li H, Wang KJ. Effects of  $\alpha$ -blockers, antimuscarinics, or combination therapy in relieving ureteral stent-related symptoms: A meta-analysis. *J Endourol*. 2015;29(6):650-56. doi:10.1089/end.2014.0715.
- Park SC, Jung SW, Lee JW, Rim JS. The effects of tolterodine extended release and alfuzosin for the treatment of double-j stent-related symptoms. *J Endourol*. 2009;23(11):1913-17. doi:10.1089/end.2009.0173.
- Tadros NN, Bland L, Legg E, Olyaei A, Conlin MJ. A single dose of a non-steroidal anti-inflammatory drug (NSAID) prevents severe pain after ureteric stent removal: A prospective, randomised, double-blind, placebo-controlled trial. *BJU Int*. 2013;111(1):101-05. doi:10.1111/j.1464-410X.2012.11214.x.
- Beiko DT, Watterson JD, Knudsen BE, Nott L, Pautler SE, Brock GB, et al. Double-blind randomized controlled trial assessing the safety and efficacy of intravesical agents for ureteral stent symptoms after extracorporeal shockwave

- lithotripsy. J Endourol. 2004;18(8):723-30.
- [22] Krambeck AE, Walsh RS, Denstedt JD, Preminger GM, Li J, Evans JC, et al. Lexington Trial Study Group. A novel drug eluting ureteral stent: A prospective, randomized, multicenter clinical trial to evaluate the safety and effectiveness of a ketorolac loaded ureteral stent. J Urol. 2010;183(3):1037-42. doi: 10.1016/j.juro.2009.11.035.
- [23] Maldonado-Avila M, Garduno-Arteaga L, Jungfermann-Guzman R, Manzanilla-Garcia HA, Rosas-Nava E, Procuna-Hernandez N, 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. doi: 10.1590/S1677-5538.IBJU.2015.0186.
- [24] Lodh B, Singh KA, Sinam RS. Role of steroidal anti-inflammatory agent prior to intracorporeal lithotripsy under local anesthesia for ureterovesical junction calculus: A prospective randomized controlled study. Urol Ann. 2015;7(2):188-92.
- [25] Dellabella M, Milanese G, Muzzonigro G. Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones. J Urol. 2003;170(6 Pt 1):2202-05.

**PARTICULARS OF CONTRIBUTORS:**

1. Consultant, Department of Urology, IMS and SUM Hospital, Bhubaneswar, Odisha, India.
2. Consultant, Department of Urology, IMS and SUM Hospital, Bhubaneswar, Odisha, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**

Dr. Daisy Karan,  
IMS and SUM Hospital, Bhubaneswar, Odisha, India.  
E-mail: daisykaran84@gmail.com

**PLAGIARISM CHECKING METHODS:** [\(Main H et al.\)](#)

- Plagiarism X-checker: Nov 25, 2019
- Manual Googling: Jan 09, 2020
- iThenticate Software: Jan 30, 2020 (15%)

**ETYMOLOGY:** Author Origin**AUTHOR DECLARATION:**

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Nov 24, 2019**Date of Peer Review: **Dec 23, 2019**Date of Acceptance: **Jan 09, 2020**Date of Publishing: **Feb 01, 2020**