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To Evaluate The Effects Of Tamsulosin, Solifenacin And Combination Therapy For The Treatment Of Urethral Stent Related Discomforts.

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Abstract:
INTRODUCTION: *Despite the usefulness of stents in the modern urological practice,the patients experience various stent-related symptoms, such as pain, frequency, and urgency causing significant decrease in patient quality of life in both genders.Thus the pharmacologic management with selective alpha-1-blockers and antimuscarinic agents believed to be simpler and less invasive than other ways.*
AIMS & OBJECTIVES: *To evaluate the effect of tamsulosin, solifenacin and combination therapy of the two agents in improving the lower urinary tract symptoms of patients with indwelling double-J ureteral stents.*
MATERIALS & METHODS:*A total of 70 patients with ureteral stenting were randomly divided into 4 groups,group I no treatment(control group),group II received tamsulosin 0.4 mg daily, group III received solifenacin 10 mg daily, and group IV combination*
On preoperative day, postoperative day 1 and postoperative day 14, all patients completed the IPSS, quality of life and VAPS questionnaire.
OBSERVATIONS & RESULTS: *scores at pre-insertion and POD-1 in groups I to IV were nonsignificant.At 2 wks after insertion there was significant difference in scores with minimum score in combination therapy.The p value of IPSS scores including Storage symptom, Voiding symptom and Total scores at 2 wks post stenting in group II and III were nonsignificant.The storage symptom score was less in Group III compared to Group II (6.64 v/s 7.66)& the voiding symptom score was less in Group II compared to Group III(4.84 v/s 5.12).*
CONCLUSIONS:*. The combination therapy appeared to improve the VAS score, IPSS score and QOL at 2 wks after insertion as the values were significantly different from the control group and the individual groups. Thus combination therapy should be strongly considered for patients who complain of stent-related symptoms.*
Key Words:*dj stents, tamsulosin, solifenacin, stent-related discomforts*

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I. Introduction

Ureteral stents, which were introduced by Zimskind et al[1] in 1967, are widely used for urinary tract disease .Ureteral stents have been used in urology for over 50 years. Ureteral stents are soft, pliable, and, most often made of plastic, tubes designed to allow urine to flow through or around them to bypass an obstruction in the urinary system. Ureteral stents are commonly called "double-J" or "pig-tailed" catheters[2], referring to the soft coils at either end of the tube that prevent the stent from migrating in the urinary system. Common indications[3,4,5,6], or reasons for placing a ureteral stent include:

- Intrinsic (or internal) ureteral obstruction – as from kidney stone
- Extrinsic (or external) ureteral obstruction – as from a compressing malignancy
- Post-operatively following ureteroscopic surgery
- Manipulation of a kidney stone
- Biopsy of renal pelvis or ureteral malignancy
- Dilation of a ureteral stricture

The double-J stent[5,6], which is the most common form of ureteral stent, is used in obstructive pyelonephritis, intolerable acute renal colic, ureteral edema, ureter perforation following endoscopic procedures, and diseases such as steinstrasse .

Despite the usefulness of stents, however, patients experience various stent-related symptoms[6,7], such as pain, frequency, and urgency, which cause a significant decrease in patient health-related quality of life .These symptoms represent a prevalent problem with considerable effects on the quality of life, substantial general health, work performance, and sexual matters in both genders .

The etiology of these symptoms is unknown. Thomas et al[8] reported that an important factor of stent-related symptoms is the pressure transmitted to the renal pelvis during urination and trigonal irritation by the intravesicular part of the stent.

Most symptoms[9,10] associated stents are attributed to mechanical stimuli and irritation from the coil that rests in the bladder. The ureteral orifices (where the ureter enters the bladder) defines the lateral edge of the trigone (or central portion of bladder defined by the ureteral orifices and the urethra) so that the stent rests on this, very sensitive, area of the bladder. Most irritative symptoms are worse during the day, indicating that awareness plays a role in stent symptoms[11]. Alternatively, studies also demonstrate that stents can move as much as 2.5cm in movement of the stent based solely on patient position – indicating that daytime activity also likely plays a role in symptoms.[10] Interestingly, a randomized clinical trial demonstrated that longer stents were associated with more symptoms and worse quality-of-life.[12]

Flank pain at the end of voiding is often mild to moderate and not related to stent length or positioning.Expectation of flank pain can often alleviate many patient concerns with this phenomenon. Suprapubic pain[13,14,15] is most often related to stent position and mechanical irritation of the trigone.

Tamsulosin[16,17]acts as a selective inhibitor of α-1a/1d-mediated contraction of the smooth muscles in distal ureter, bladder trigone, and bladder neck . It is thought that relaxing these smooth muscles decreases bladder outlet resistance and voiding pressure, with beneficial effect on stent related LUTS. Solifenacin [18,19,20]acts as a muscarinic receptor antagonist used for treatment of patients with overactive bladder (OAB) and might be effective as well for stent-related symptoms .

The pharmacologic management is believed to be simpler and less invasive than other ways. There are few studies investigating the efficacy of pharmacological management of dj stent related symptoms.The purpose of this study is therefore to analyze and assess the effectiveness of a selective alpha-1-blocker (tamsulosin) and antimuscarinic (solifenacin)[18,19,20] in improving the lower urinary tract symptoms of patients with indwelling double-J ureteral stents.

Aims And Objectives

To evaluate the effect of tamsulosin, solifenacin and combination therapy of the two agents in improving the lower urinary tract symptoms of patients with indwelling double-J ureteral stents.

II. Review Of Literature

Ureteral stents have become an integral part of contemporary urologic practice.[3] They are typically placed to prevent or relieve ureteral obstruction due to a variety of intrinsic or extrinsic etiologies. These include obstructing ureteral calculi[5,6,7], ureteral strictures, congenital anomalies such as ureteropelvic junction obstruction, retroperitoneal tumor or fibrosis, trauma, and iatrogenic injury. Stents are also placed to provide urinary diversion or postoperative drainage or to help identify and prevent inadvertent injury to the ureters before surgical procedures.

In 1967, the era of the modern long-term indwelling ureteral stent began when Zimskind[1] and colleagues reported the use of open-ended silicone tubing inserted endoscopically to bypass malignant ureteral obstruction or ureterovaginal fistulas.

In 1974, the Gibbons stent became the first commercially available "modern" internal ureteral stent. The important problem of stent migration was solved in 1978 when double-J (DJ) stents were described by Finny.[2] The tips of these stents are J-shaped on either side to prevent upward and downward migration and urologists place them endoscopically.

According to Beiko DT et al[17] 2003 Biomaterials such as urethral catheters, urethral stents, and ureteral stents are commonly used in patients with urologic disorders.

According to Saltzman B. et al[6]no stent is ideal, and as such it is incumbent on the surgeon to be familiar with the various indications for usage, selection, modes of insertion, and potential for complications. Thus the surgeon will optimize the efficacy and safety of this device in the care ofpatients.

Turner et al[21] Ureteric injury is a recognized complication of hysterectomy and may present with obstruction or fistula. Between 1987 and 1989 in Oxford nine patients with 10 injured ureters underwent attempted retrograde placement of double J stents.Theyadvocated the initial use of double J stents in gynaecological ureteric injury. This approach is simple and may cure the fistula. If it is unsuccessful, subsequent reimplantation is not hindered.

Chew et al[19] in 2004 emphasised that Ureteral stents are a mainstay of today's urological armamentarium. This review critically evaluates the recent literature and provides a concise summary of the use of stents in urology today. According to Levinthal et al[5]distal ureteral calculi are a common urological problem often requiring surgical and anesthetic intervention. Ureteral stents are often used to stabilize symptomatic patients preoperatively.

According to M.Shehab et al[23] 2013 in study ofOne-hundred and thirty-eight patients with obstructive uropathy Fifty-seven patients treated by ureteral stenting (group I) and 81 patients were treated by other treatment

modalities (group II). Renal glomerular filtration rate (GFR) was used as an indicator for improvement of renal function after fixation of ureteric stent. In group I, 56 (71.8%) kidneys showed significant recovery compared to 61 kidneys (66.3%) in group II.

Haleblian G et al[7] in 2008 summarised that Stenting is not mandatory after uncomplicated simple ureteroscopy and shock wave lithotripsy. Patients with stents seem to have significantly more bladder and lower urinary tract symptoms than those in whom stents are not placed.

Pollard et al[10] in 1988 investigated whether use of the Double-J ureteral stent causes untoward symptoms and complications. Of 20 patients evaluated by questionnaire 18 suffered 1 or more symptoms in the upper (for example loin pain) or lower (for example dysuria and frequency) urinary tract in the absence of infection. Despite the undoubted benefit in many patients, troublesome symptoms are common.They recommend early removal of the stents but cannot implicate any correctable technical factors.

Vallejo et al[24] in 1998 the double-J ureteral stent has become an integral part of the urological armamentarium. It allows good urinary drainage from the kidney to the bladder and is generally safe and well-tolerated. However, different complications may occur with short- or long-term use of indwelling stents. These complications vary from minor side effects such as hematuria, dysuria, frequency, flank and suprapubic pain, to major complications such as vesico-ureteric reflux, stent migration, encrustation, urinary infection, stent fracture, necrosis and ureteral fistula. Most of these complications require removal of the catheter.

Hao P. et al[25] 2008 studied 2685 stent placements to review the indications, procedures, complications, and related treatments of double pigtail stent (DPS) placement as an adjunct for some types of endoscopic and open urologic surgery.Their conclusion was that DPS is a safe and useful adjunct for both endoscopic and open procedures to treat upper urinary tract diseases. Most of the complications of DPS placement can be well managed.

Richter S. et al[23] 2009reviewed the morbidity and complications of ureteric stent insertion and to evaluate specifically the effect of an indwelling ureteric stent on the changes in hydronephrosis after stenting.They concluded that although ureteric stenting is undoubtedly an important procedure to relieve ureteric obstruction, the indications for stent insertion should be considered carefully in every patient. The close follow-up of stented patients is valuable for the early detection of morbidity or complications and in such cases the stent should be removed or exchanged as soon as possible.

Lim J S et al[27] 2010 reported that Frequency and urgency on the storage symptom score, residual urine sensations, and intermittency on the voiding symptom score were significantly aggravated at the initial stenting ($p<0.05$), but the sum of the storage symptom score and urgency improved with time ($p<0.05$).

Thomas et al[8] reported that an important factor of stent-related symptoms is the pressure transmitted to the renal pelvis during urination and trigonal irritation by the intravesicular part of the stent. For this reason, several attempts to minimize stent-related symptoms have recently been reported.

Joshi et al[4,11] reported that,Ureteral stents cause various side effects Urinary symptoms, pain, work performance, and general health were the most important. Most patients (80%) experienced bothersome urinary symptoms and stent-related pain. Storage symptoms and incontinence were significant urinary symptoms affecting quality of life. As many as 40% of patients experienced sexual dysfunction .

Gupta et al[28] 2010 found that there was a significant decrease in the reported postoperative pain score between the botulinum toxin type A and control group at 3.4 vs 6.0 ($p = 0.02$). Periureteralbotulinum toxin type A[28] injection improves ureteral stent tolerability by significantly decreasing postoperative pain and narcotic requirements. Improvement in irritative symptoms was not observed.

Ahmad R E Nahas et al[29] 2006concluded that proper positioning of the coils of the stent, eradication of infection, and shorter stenting duration are advised to decrease patient discomfort during the period of ureteral stenting.

Molecular pharmacology of the bladder

Cholinergic Receptors of the Urinary Bladder

Five *muscarinic receptor subtypes* (M1 to M5)[31] have been identified so far. The bladder has mainly M1, M2 (80%) and M3 (20%) cholinergic receptor types, but only M3 cholinergic receptors are responsible for the parasympathetic detrusor contraction. M3 receptors of the bladder are found mainly in smooth muscles and glands. Stimulation of M3 receptors with acetylcholine causes the release of IP_3 and calcium, which leads to smooth muscle contraction.

Adrenergic Receptors of the Urinary Bladder

Adrenergic receptors[30] of the sympathetic nervous system are classified into α1, α2, β1, β2 and β3-receptors.

β-Receptors:

The stimulation of β-receptors leads to the activation of adenylyl cyclase, to the release of cyclic AMP (cAMP) and to the inhibition of the detrusor muscle. Unspecific stimulation of β-receptors are not an option for inhibition of detrusor overactivitity due to cardiovascular side effects. However, β3-receptors are not responsible for cardiovascular effects and are also present in the bladder wall. Newly developed β3-agonists (Mirabegron, Solabegron) have shown efficiency in the treatment of overactive bladder and are well tolerated. There are also efforts to identify a specific phosphodiesterase inhibitor for the bladder.

α-Receptors:

α-Receptors are located in the trigonum and in the urethra. α1-Receptors are common in men, α2-receptors are common in women. α-Receptors are rare in the detrusor muscle.

Alpha;1-Receptors are classified into three subtypes (A, B and D), in the urinary bladder and urethra $\alpha 1_A$-receptors prevail. The adrenergic stimulation of $\alpha 1_A$-receptors leads to an increase of bladder closure. The inhibition of $\alpha 1_A$-receptors leads to a reduction of bladder closure; adrenergic substances increase the bladder neck closure and are used to treat urinary incontinence.

Purinergic Receptors of the Urinary Bladder

The involvement of the neurotransmitter ATP in the control of the bladder is largely unclear. However, ATP plays a role in the unstable bladder and in the bladder afferent innervation.

Nitric Oxide (NO)

NO is one of the main transmitter for urethral smooth muscle relaxation during micturition. Nitric oxide is released from parasympathetic nerves.

Vanilloid Receptors of the Urinary Bladder

Vanilloid receptors are pain receptor fibers. In the bladder, the inactivation of vanilloid receptors by repeated doses of *capsaicin* or *resiniferatoxin* is used for the treatment of unstable bladder.

Afferent Neuropeptides

Many neuropeptides have been detected in the urinary bladder: Substance P, neurokinin A and B, calcitonin gene-related peptide (CGRP). These substances are mainly found in capsaicin-sensitive afferent nerve fibers. After stimulation, these neurotransmitters are also the cause of the neurogenic inflammation that accompanies painful stimuli (plasma extravasation, vasodilation and increased smooth muscle activity).

Prostaglandins

PGF2α, PGE and PGE2 lead to detrusor contraction.

The most important receptors for activation of contraction are muscarinic (M_3) and purinergic receptors ($P2X_1$). The contribution of these receptors to contraction may differ between species. In the normal human detrusor, the muscarinic component predominates; however, this contribution may change in different pathophysiological conditions. The main relaxant pathway is via the adenylyl cyclase/cAMP pathway, which is activated by adrenergic β_3-receptors, although other relaxant pathways also may contribute.

Therefore safe and convenient ways to improve stent-related symptoms were sought and pharmacologic managementwas one of those ways. Stent-related symptoms are similar to the benign prostatic hyperplasia symptoms caused by urethral and bladder resistance and bladder instability. For this reason, some studies have reported that selective alpha-1-blockers improve stent-related symptoms.

Deliveliotis et al[32] in 2006studied 100patients to evaluate the effect of alfuzosin in improving symptoms in, and quality of life of patients with indwelling double-J ureteral stents.

The stent-related pain was reported by 44% of patients in group 1(takingalfuzocin) and 66% of patients in group 2 (control group) ($P = 0.027$). The mean pain index score was 14.6 in group 1 and 17.4 in group 2 ($P = 0.047$). The mean general health index score was statistically greater ($P < 0.001$) in group 1 compared with in group 2 (8 versus 11.4, respectively). Among sexually active patients, the mean sexual score was 2.3 in group 1 and 2.9 in group 2 ($P = 0.017$).Thus they concludedthat stent-related symptoms were present in 66% of the controls (group 2). Alfuzosin improved a subset of stent-related urinary symptoms and pain. Patients receiving alfuzosin had their sexual function and general health better preserved.

Damiano et al[16] in 2008 conducted a randomized study to evaluate the effect of tamsulosin in improving symptoms and quality of life (QoL) in patients with indwelling double-pigtail ureteral stents, using both generic and specific questionnaires.They enrolled 75 patients, who underwent ureteral stent positioning and were assigned to one of two study groups. In group A (n = 38), patients were discharged with a prescription for tamsulosin, 0.4mg once daily. In group B (n = 37), patients received no alpha(1)-blocker (control group).In

the study they found that one week after stent placement (visit week 1 [W1]), analysis of the ureteral stent symptoms questionnaire showed a significant worsening of urinary symptoms and pain in patients not receiving tamsulosin. There was also a significant difference in the mean visual analog score (VAS) of health scale between the two groups ($P < 0.001$) compared with the result obtained at the W4 evaluation (visit). The proportion of patients reporting level 2 or 3 for the pain/discomfort domain in the QoL questionnaire from W4 to W1 varied between the two groups in a highly statistically significant manner ($P = 0.006$).Thus their findings indicate that administration oftamsulosinhasapositiveeffectonstent-relatedurinary symptoms and QoL.

Beddingfield R et al[33] in 2009 studied 55 patients and reported that patients taking alfuzosin 10 mg daily had improved frequency and flank pain.Thus they concluded that alfuzosin improves the patient discomfort associated with ureteral stents by decreasing urinary symptoms and kidney pain but it does not affect the amount of narcotics that patients use while the stent is in place.

Wang et al[17] in 2009 did studyto evaluate the effect of tamsulosin in improving symptoms in patients with indwelling double-J ureteral stents in total of 154 patients, with insertion of a double-J ureteral stent after ureteroscopic stone removal.They concluded in their study that patients receiving tamsulosin had less urinary symptoms and body pain and better general health and quality of life than those on placebo. Remarkably, only 3% of patients in the tamsulosin group required narcotics, compared to 33% in the placebo group. Thus alpha-blockers may alleviate stent discomfort by decreasing ureteral spasm, decreasing trigone sensitivity, decreasing voiding pressures or decreasing resting ureteral pressure and peristalsis

Navanimitkulet al[33] in 2010 did study to evaluatethe efficacy of tamsulosin in improving stent-related symptoms and quality of life in patients with in-dwelling double-J ureteral stents.

Lamb et al[35] in 2011 did a meta-analysis incorporating five randomized controlled trials provides evidence that alpha-adrenoceptor antagonists reduce stent-related pain and storage symptoms as assessed by the Ureteric

Yakoubi R et al[33] 2011 did a study to evaluate the efficacy of α-blockers to improve ureteral stent related morbidity and quality of life.They performed a search of MEDLINE®, Embase™ and The Cochrane Library and controlled trials comparing treatment for ureteral stent symptoms with α-blockers.

Dellis et al[37] in 2014 used the Ureteric Symptom Score Questionnaire (USSQ) to evaluate, in a randomized control study, the effect of 2 different α-blockers in improving symptoms and quality of life in patients with indwellingureteralstents.

Singh I. et al[38] in 2014 did study to evaluate the efficacy of tamsulosin therapy in reducing ureteral double-J stent morbidity by evaluating USSQ, IPSS, QOL and VAS (primary objective) and to evaluate the morbidity and or complication(s) associated with indwelling double-J ureteral stent(s) and to evaluate the safety of tamsulosin therapy for "morbidity associated with double-J stents" by evaluating its tolerability, side effects and adverse events if any.

According to Abrams P. et al[39] 2007 Overactive bladder (OAB) is a syndrome characterized by urinary urgency, with or without urgency urinary incontinence, usually with frequency and nocturia. OAB symptoms are often associated with detrusor overactivity (DO). Acetylcholine[31] is the primary contractile neurotransmitter in the human detrusor, and antimuscarinics exert their effects on OAB/DO by inhibiting the binding of acetylcholine at muscarinic receptors M(2) and M(3) on detrusor smooth muscle cells and other structures within the bladder wall.

According to Hegde S. et al[40] 2006Comparative clinical studies have shown that oxybutynin and solifenacin may be marginally more effective than tolterodine, although the latter seems to be better tolerated.Pharmacokinetic-pharmacodynamic analyses using plasma concentrations of 'total drug' indicate that, at therapeutic doses, the clinical efficacy of darifenacin and solifenacin may be driven primarily by selective M(3) receptor occupation, whereas the pharmacodynamic effects of pan-selective molecules (such as tolterodine, trospium) may potentially involve multiple receptors, including M(2) and M(3). Furthermore, high M(3) receptor occupation is the likely explanation for the greater propensity of darifenacin and oxybutynin to cause dry mouth and/or constipation.

Park SC et al[41] in 2009studied fifty-two patients (33 men and 19 women; mean age 52.0 years) who underwent insertion of a Double-J stent after urological surgery to evaluate the effects of tolterodine extended release (ER) and alfuzosin for the treatment of Double-J stent-related lower urinary tract symptoms and prospectively randomized into three groups. Group 1 included 20 patients who received 10 mg of alfuzosin, once daily for 6 weeks; group 2 included 20 patients who received 4 mg of tolterodine ER, once daily for 6 weeks; group 3 included 12 patients who received a placebo for the same protocol. All patients completed a validated Ureteral Stent Symptom Questionnaire at 6 weeks after the stent placement.

Nazim S.M. et al[42] 2012studied to the effect of alfuzosin on urinary symptoms, quality of life, and pain in patients after Double-J ureteral stent placement in a randomized, placebo-controlled trial.

Norris RD et al[43] in 2008 evaluated the use of extended release oxybutynin versus phenazopyridine versus placebo for the management of ureteral stent discomfort after ureteroscopy.Agarwal A. et al[44]in 2006 did

a study to evaluate the efficacy of oxybutynin and tolterodine in preventing catheter related bladder discomfort.

Van Kerrebroeck Pet al[45] 2013 did study to evaluate the combination of an antimuscarinic (solifenacin) with an α-blocker (tamsulosin) versus tamsulosin alone in the treatment of men with LUTS.Combination therapy was associated with significant improvements in micturition frequency and voided volume versus tamsulosin alone .Lee et al[46] in 2010 did a study to evaluate the clinical factors that impact ureteral stent-related lower urinarytract symptoms (LUTS) after ureteroscopicureterolithotomy, including the stentposition and medication.They studied fifty-three patients who underwent ureteroscopicureterolithotomywith indwelling a stent were distributed into three groups.

Pilcher JM et al[47] in2002derived a formula based on the patient's height for choosing the correct length of ureteric stent and to compare its accuracy with that of direct ureteric length measurement.

Ho CH et al[48] in 2008 did a study to evaluate whetherstent length affects the symptoms after stent insertion and to determine the appropriate stent length according to the stent configurations and the related symptoms simultaneously.

PaickSH. et al[49] in 2005 investigated the reliability of a patient's height as a measure of ureteric length.Theymeasured the actual length of the ureteric trace (ALUT) and the linear distance (LD) from the ureterorenal junction to the ureterovesical junction by intravenous pyelography (IVP), using a 15 min view.

Kawahara et al[50] 2012evaluated the association between the ureteral length and each of the following parameters: body height, body surface area,ureteral trace by intravenous urography, linear distance (liner distance 1) from the ureteropelvic junction to the ureterovesical junction by intravenous urography, linear distance (liner distance 2) from the mid kidney to the ureterovesical junction by intravenous urography, and the distance from the level of the renal vein to the ureterovesical junction by axial computed tomography (axial computed tomography distance).They concluded that Axial computed tomography distanceshowed the best correlation with the actualureteral length.

KuyumcuogluU. et al[51] in 2011 did study to evaluate the frequency of lower urinary tract symptoms (LUTS) increase in patients in whom double-J stents were applied. They also evaluated several medical therapyprotocols to treat symptoms related with ureteral stents

VISUAL ANALOGUE SCALE

Visual Analogue Scale (VAS)[52,53] is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a of continuum of values and cannot easily be directly measured as a psychometric response scale,which can be used inquestionnaires. It is a measurement instrument for subjective characteristics or attitudes that cannot be directly measured. When responding to a VAS item, respondents specify their level of agreement to a statement by indicating a position along a continuous line between two end-points. As such an assessment is clearly highly subjective, these scales are of most value when looking at change within individuals, and are of less value for comparing across a group of individuals at one time point.

According to Franklin E Kuehaaset al[54] in 2012 Pain perception at the time of colic did not vary according to sex (P = .804), age (P = .674), or DJ stent length (P = .389).

III. Material and Methods

During the period from January 2013 to November 2014, patients undergoing DJ Stenting in the Department of Surgery at S.N. Medical College, Agra with required eligibility criteria were considered in this study.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

Patients greater than 18 years undergoing Double-J stenting for urinarytract calculi were included in the study. These underwent thorough clinical, general, systemic examinations and the required investigational procedures to exclude any neurological, organic and systemic cause for their symptoms. Only those patients who had no obvious neurological, organic and systemic causes were included in the study.

EXCLUSION CRITERIA

Patients who met the following criteria were excluded from the study:

1. Patient not willing for inclusion in the study.
2. Age less than 18 years and greater than 60 years.
3. Pregnantwoman.
4. Mental disorders or illnesses
5. History of previous ureteral stenting.
6. Previousurinary bladder pathology.
7. Benign prostatic hyperplasia.
8. Overactivebladder.

9. Urinary tract infections.
10. Previous use of selective alpha-1- blocker and /or antimuscarinic agent or with known history of orthostatic hypotension,allergy,hypersensitivity to one or more alpha blockers.

Methods

The study protocol was approved by the ethics committee of the hospital,and all the patients enrolled in this study provided writtenbilingual informed consent..On the screening visit detailed history,general examination and detailed urological examination was carried out and the enrolled patients were worked up as per protocol and data was recorded in data sheet The surgery was performed under general/spinal anesthesia.

A 5 Fr polyurethane ureteral stents were used in all patients. Only coiled distal end was present in the bladder without any part of distal shaft .The position of the stent was confirmed by plain abdominal X-ray.

A total of 70 patients were chosen after assessing inclusion/exclusion criteria.The patients were randomized into four groups:

- **Group 1**(n= 17)was the control group and did not takeany drugs.
- **Group 2**(n= 18)receivedtamsulosin 0.4 mg once a day every day.
- **Group 3**(n= 16) received solifenacin 10 mg once a day every day.
- **Group4**(n= 19) received tamsulosin 0.4 mg and solifenacin 10 mgincombinationdaily.

Patients Assessment and Outcome Measurements:

The daybefore surgery, on postoperative day 1 and on the on postoperative day 14, each patient completed written International Prostate Symptom Score/quality of life (IPSS/QoL) and visual analogue pain scale (VAPS) questionnaires. The IPSS was divided into the total score, obstructive symptom score, and irritative symptom score, and each was compared. Visual Analogue Pain Scale graded from 1(minimal or no symptoms) to 10 (symptoms of maximal severity).Any need for analgesics were recorded and compared between the groups. Each group's preoperative day, postoperative day 1 and post operative day 14 scores were compared.

OBSERVATIONS

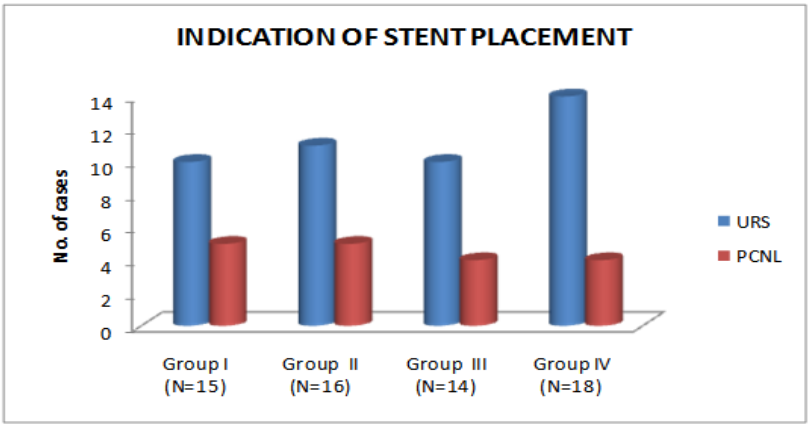
This study was a prospective, randomized and comparative studycarried out between January 2013 and November 2014 to evaluate the effect of tamsulosin, solifenacin and combination therapy of the two agents in improving the lower urinary tract symptoms of patients with indwelling double-J ureteral stents.

A total of70patients were enrolledin the study and 63 patients completed the study (2 patients from groupI,2 patientsfromgroupII,2 patientsfromgroupIII,and1patient fromgroupIVdroppedout).

- **Group 1**(n=15)was the control group and did not take any drugs.
- **Group 2**(n=16)received tamsulosin 0.4 mg once a day every day.
- **Group 3**(n=14) received solifenacin 10 mg once a day every day.
- **Group 4**(n=18) received tamsulosin 0.4 mg and solifenacin 10 mg incombinationdaily.

TABLE NO. 1: AGE GROUP WISE DISTRIBUTION OF THE PATIENTS

Age groups	GroupI (N=15)		GroupII (N=16)		GroupIII (N=14)		Group IV (N=18)	
	No.	%	No.	%	No.	%	No.	%
<20	2	13.33	2	12.50	2	14.28	3	16.67
21-40	6	40.00	8	50.50	5	35.71	8	44.44
41-60	7	46.67	6	37.50	7	50.00	7	38.88
Total	15	100.00	16	100.00	14	100.00	18	100.00

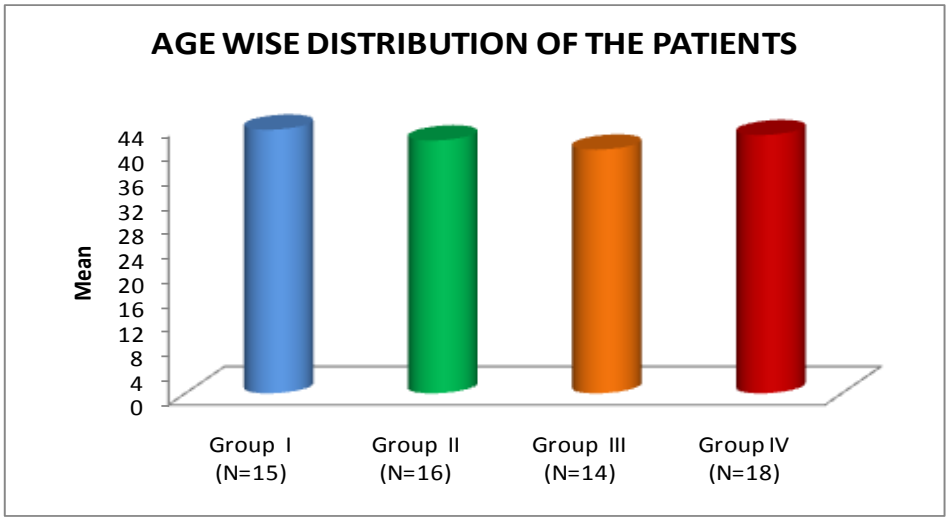


As seen in table no 1 , according to patientsage, in Group I out of total 15 maximum47% were in41-60 age group, in Group II out of total 16 maximum 50% were in 21-40 age group,in Group III out oftotal 14 maximum 50% were in 41-60 age group,in Group IV out of total 18 maximum 44% were in 21-40 age group.

TABLE NO.2: AGE WISE DISTRIBUTION OF THE PATIENTS

	GroupI (N=15)	GroupII (N=16)	GroupIII (N=14)	Group IV (N=18)	F-value*	p-value
Mean age	43.27	41.5	40.00	42.39	0.110288	0.9537 NS
SD	15.12	15.71	14.57	18.05		

*Anova: Single Factor



As seen in Table No 2mean age in, Group I was43.27± 15.12 years,Group II was 41.5 ± 15.71 years, Group III was40.0 ± 14.57 years, and Group IV was42.39 ± 18.05years. p value was 0.9537 which was insignificant.

TABLE NO.3 : SEX WISE DISTRIBUTION OF THE PATIENTS

	GroupI (N=15)	GroupII (N=16)	GroupIII (N=14)	Group IV (N=18)	Ch^2value	p-value
Male	9	11	10	11	0.8876	0.8284^{NS}
Female	6	5	4	7		

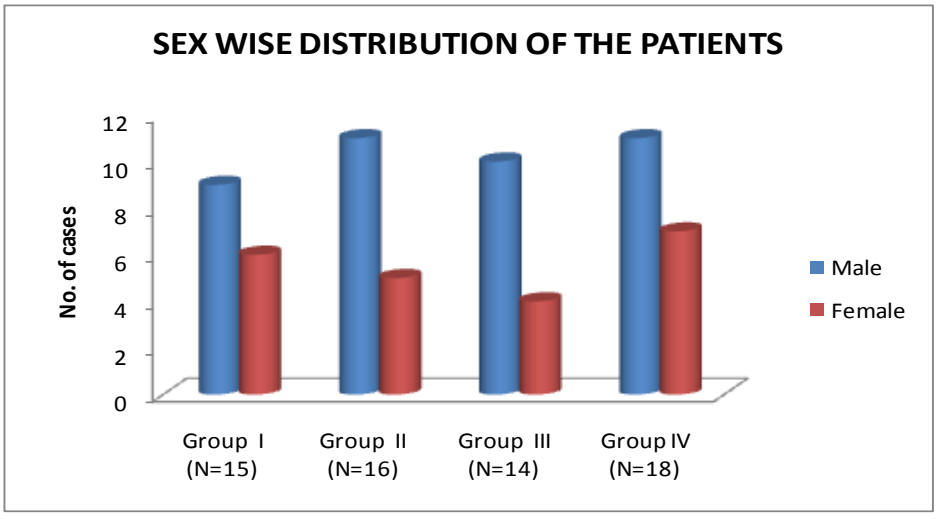
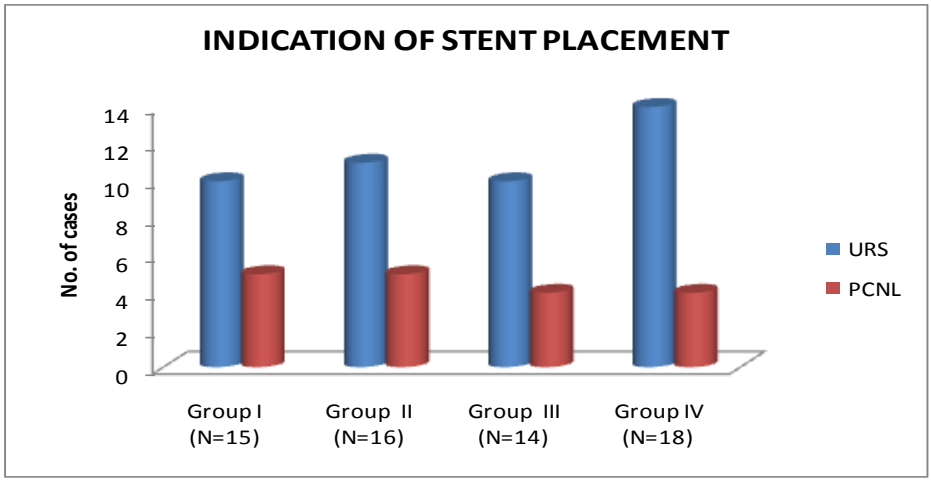


Table No. 3 shows that Group I (15 patients) consisted of 9 men and 6 women,Group II (16 patients) consisted of 11 men and 5 women, Group III (14 patients) consisted of 10 men and 4 women and Group IV (18 patients) consisted of 11 men and 7 women.Thus total males were 65.1% and females were 34.9%.p value was 0.8485 and was insignificant.

.TABLE NO. 4 : INDICATION OF STENT PLACEMENT

	GroupI (N=15)	GroupII (N=16)	GroupIII (N=14)	Group IV (N=18)	Ch^2value	p-value
URS	10	11	10	14	0.90134	0.8251 NS
PCNL	5	5	4	4		

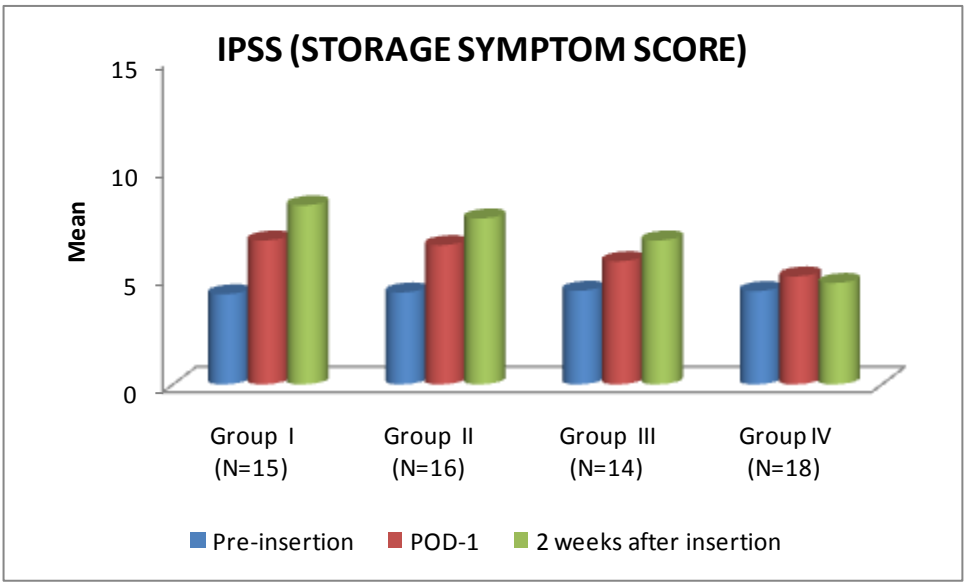


As seen in Table no 4main indication ofureteral double –Jstent placement was URS and PCNL, out of total 63 patientsmaximum no of patients 71.4%(45 out of 63) were URS cases and 28.6% (18 out of 63)were PCNL cases..Between the two groupsp value was 0.8251 which was insignificant.

COMPARISON OF IPSS SCORES IN ALL THE GROUPS

TABLE NO. 5 : IPSS (STORAGE SYMPTOM SCORE)

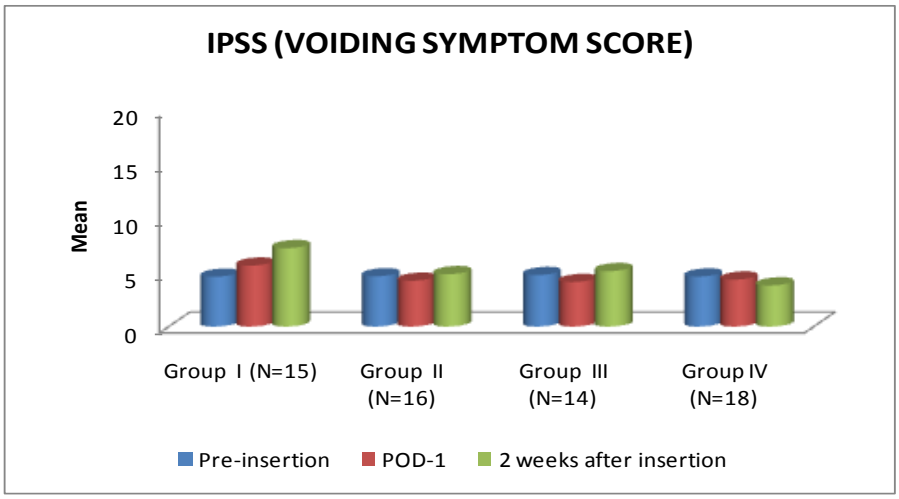
	GroupI (N=15)	GroupII (N=16)	GroupIII (N=14)	Group IV (N=18)	p-value
Pre-insertion	4.16±2.44	4.24±2.52	4.32±2.66	4.30±2.42	0.896 NS
POD-1	6.64±3.25	6.42±2.96	5.68±3.08	4.98±2.88	0.5921 NS
2 weeks after insertion	8.26±3.42	7.66±3.64	6.64±3.90	4.68±3.32	0.00236*



According to Table No. 5 the IPSS Storage symptom scores at pre-insertion and POD-1 in groups I to IV were nonsignificant i.ep value was 0.896 and 0.5921 at pre-insertion and POD-1 respectively. At 2 wks after insertionthere was significant difference in scores(p value was 0.00236) with minimum score in combination therapy and maximum score in control group.

TABLE NO. 6 : IPSS (VOIDING SYMPTOM SCORE)

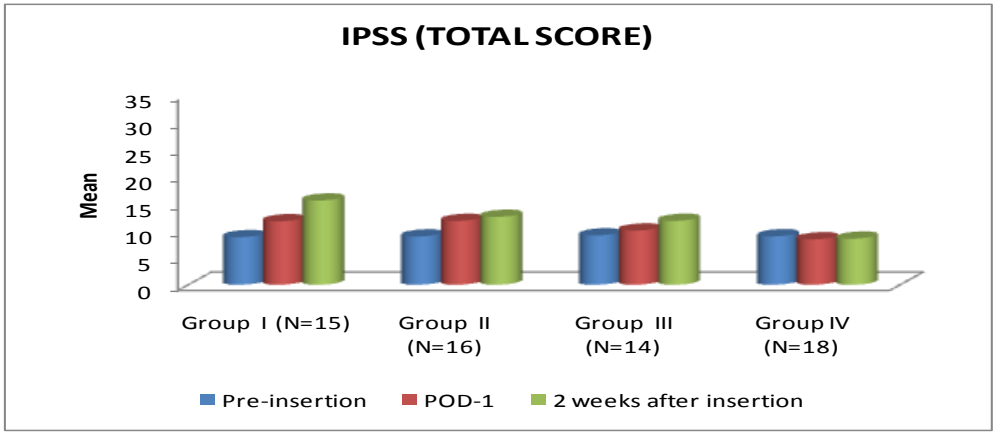
	GroupI (N=15)	GroupII (N=16)	GroupIII (N=14)	Group IV (N=18)	p-value
Pre-insertion	4.60±2.84	4.64±2.66	4.76±2.54	4.62±2.48	0.9864 ^{NS}
POD-1	5.63±2.51	4.23±2.28	4.12±2.34	4.34±2.67	0.8753 ^{NS}
2 weeks after insertion	7.24±2.44	4.84±2.64	5.12±2.80	3.80±2.04	0.000142*



According to Table No. 6 theIPSS Voidingsymptom scores at pre-insertion and POD-1 in groups I to IV were nonsignificant i.ep value was 0.9864 and 0.8753at pre-insertion and POD-1 respectively. At2 wks after insertionthere was significant difference in scores(p value was 0.000142) with minimum score in combination therapy and maximum score in control group.

TABLE NO. 7: IPSS (TOTAL SCORE)

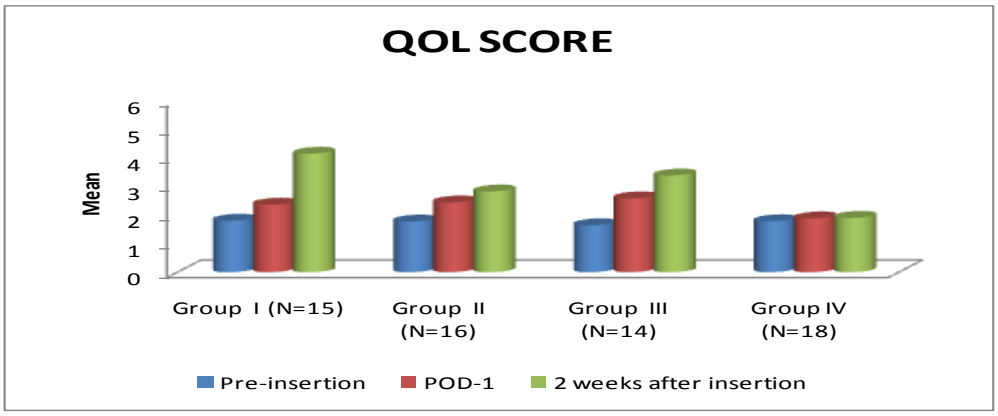
	GroupI (N=15)	GroupII (N=16)	GroupIII (N=14)	Group IV (N=18)	p-value
Pre-insertion	8.76 ±4.44	8.88±4.28	9.08±3.84	8.92±4.14	0.9682 ^{NS}
POD-1	11.68±4.48	11.74±4.26	9.98±3.97	8.36±4.12	0.8642 ^{NS}
2 weeks after insertion	15.50±4.30	12.50±4.48	11.76±4.68	8.48±4.24	0.000218*



According to Table No. 7 the IPSS TOTAL SCORESatpre-insertion and POD-1 in groups I to IV were nonsignificant i.ep value was 0.9682 and 0.8642 at pre-insertion and POD-1 respectively. At 2 wks after insertionthere was significant difference in scores(p value was 0.000218) with minimum score in combination therapy and maximum score in control group, thus indicating maximum symptom control in combination therapy.

TABLE NO. 8 : QOL SCORE

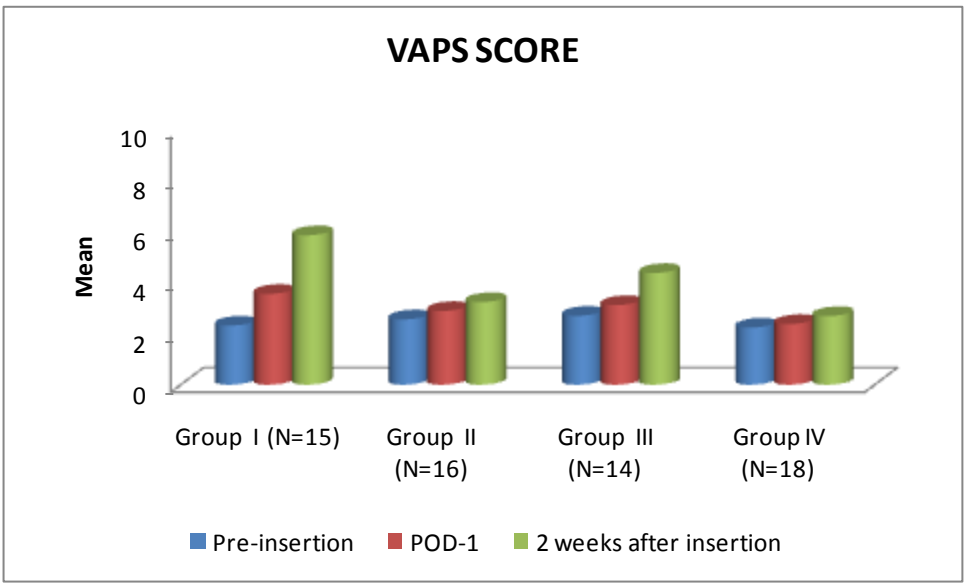
	GroupI (N=15)	GroupII (N=16)	GroupIII (N=14)	Group IV (N=18)	p-value
Pre-insertion	1.80±1.60	1.77±1.72	1.64±1.56	1.78±1.46	0.8679 ^{NS}
POD-1	2.36±1.67	2.44±1.76	2.58±1.84	1.88±1.12	0.68721 ^{NS}
2 weeks after insertion	4.14±1.77	2.82±1.54	3.38±1.78	1.90±1.24	0.000986*



According to Table No. 8 the Quality Of Lifescores at pre-insertion and POD-1 in groups I to IV were nonsignificant i.ep value was0.8679and 0.68721at pre-insertion and POD-1 respectively. At 2 wks after insertionthere was significant difference in scores(p value was 0.000986) with minimum score in combination therapy and maximum score in control group.

TABLE NO. 9 : VAPS SCORE

	GroupI (N=15)	GroupII (N=16)	GroupIII (N=14)	Group IV (N=18)	p-value
Pre-insertion	2.32±1.48	2.56±1.86	2.70±1.48	2.24±1.28	0.67452^{NS}
POD-1	3.56±1.57	2.89±1.48	3.12±1.23	2.38±1.57	0.12473 ^{NS}
2 weeks after insertion	5.86±1.66	3.24±1.24	4.38±1.46	2.69±1.42	<0.05*

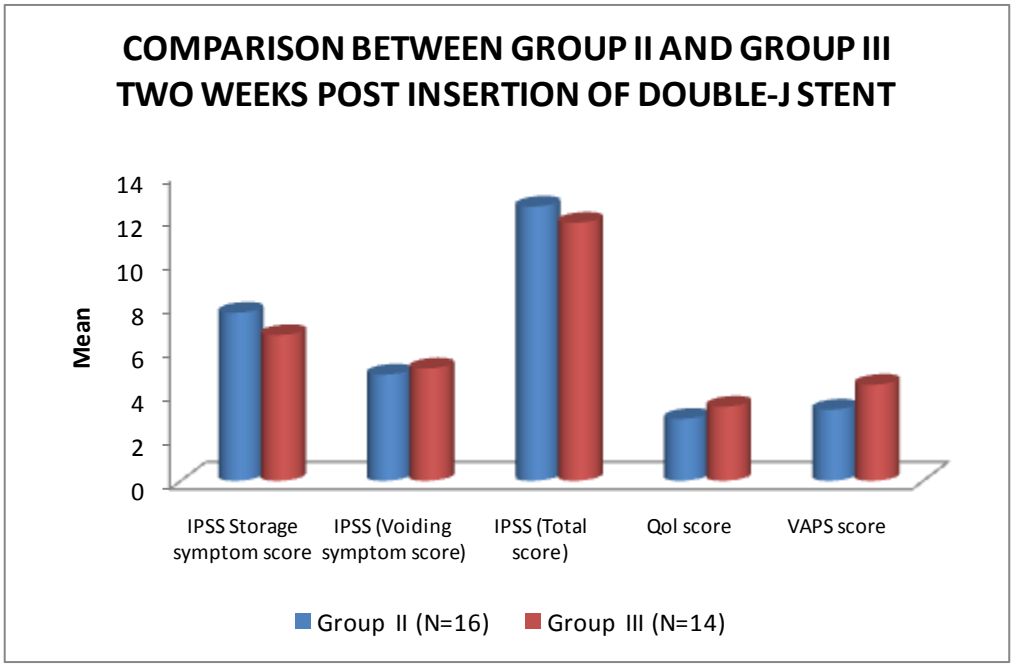


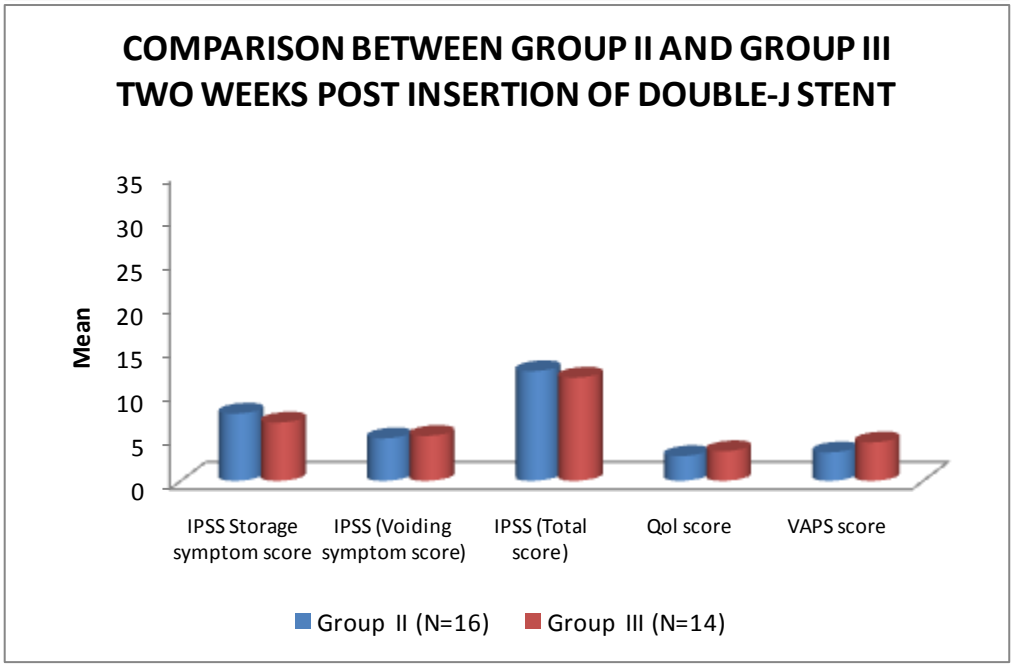
According to Table No. 9the VAPS scores at pre-insertion and POD-1 in groups I to IV were nonsignificant i.ep value was 0.67452 and0.12473at pre-insertion and POD-1 respectively. At 2 wks after insertionthere was significant difference in scores(p value was 0.00236) with minimum score in combination therapy and maximum score in control group.

TABLE NO. 10 : COMPARISON BETWEEN GROUP II AND GROUP III TWO WEEKS POST INSERTION OF DOUBLE-J STENT

	GroupII (N=16)	GroupIII (N=14)	t-value	p-value
IPSS Storage symptom score	7.66±3.64	6.64±3.90	0.7372	0.4674 ^{NS}
IPSS (Voiding symptom score)	4.84±2.64	5.12±2.80	-0.2806	0.7811 ^{NS}
IPSS (Total score)	12.50±4.48	11.76±4.68	0.4408	0.6629 ^{NS}
Qol score	2.82±1.54	3.38±1.78	-0.915	0.3686 ^{NS}
VAPS score	3.24±1.24	4.38±1.46	-2.2875	0.0306 *

***NS**= The two samples are not significantly different.*
**=The two samples are significantly different.*





As seen in Table No. 10the post stentingIPSSscores including Storage symptom, Voiding symptom and Totalscoresat 2 wks post stentingin group II and IIIwerenonsignificantwith p-value0.4674, 0.7811, 0.6629 respectively. Although thestorage symptom score was less in Group III compared to Group II (6.64v/s 7.66) withbetter control of storage or irritative symptoms.

Though thevoiding symptom score difference was statistically nonsignificantbetween Group II and Group III, the score was less in Group II compared to Group III(4.84 v/s5.12).

The difference in post stenting QOL scores at 2 wksbetween group II and III was also non-significant as p value was 0.3686.

Although there was statistically significant difference inVAPSscoresinfavourofgroupII(p value was 0.0306).When comparing poststenting scores among different groups,therewereastatisticallysignificant differencesinallscoresinfavourofgroupsII,III,andIVascomparedtogroup I(*P* value <.005).Howeverwhenwecomp aredeachgroup byone-wayANOVAateachtimepointseparately,therewas no statistically significant difference between groups II and III as regards (total, storage, and voiding) IPSS scores .

GroupIVpatientswhoreceived combination therapy showed a statistically significant difference in all scores as compared to monotherapy (II, III) groups (*P* value < 0.05).This confirmed the superiority of combinationtherapyinovercomingstent-relatedsymptomsascomparedto monotherapy of tamsulosinor solifenacinindividually.

IV. Discussion

The present study was a prospective, randomized and comparative study carried out between January 2013 and November 2014 in the Department of Surgery,S.N. Medical College , Agra to evaluate the effect of tamsulosin, solifenacin and combination therapy of the two agents in improving the lower urinary tract symptoms of patients with indwelling double-J ureteral stents.

A total of70patients were enrolledin the study and 63 patients completed the study (2 patients from group I,2 patients from groupII,2 patients fromgroupIII, and 1 patient from groupIV dropped out).

- **Group 1**(n=15)was the control group and did not take any drugs.
- **Group 2**(n=16)received tamsulosin 0.4 mg once a day every day.
- **Group 3**(n=14) received solifenacin 10 mg once a day every day.
- **Group 4**(n=18) received tamsulosin 0.4 mg and solifenacin 10 mgincombinationdaily.

The results of this prospective, randomized, controlled trial showed that,the combined use of tamsulosin and solifenacin improved the QoL andalleviated LUTS associated with double-J ureteral stents, better thaneither drug alone and well tolerated.

Stent discomfort is believed to affect over 80% of patients[3,4,5,6].Patients with indwelling stents have been known to complain of avariety of stent-related symptoms, typically: storage, voiding, OAB symptoms, haematuria, and pain. These symptoms are believed to beunavoidable and associated with reduced health-related quality of life .

Damiano et al[16]reported that there was no symptoms differencebetween stent with different size, whereas there was a tendency of small diameter stents to dislodge more often. Chew et al[55]reportedthat changing in body position led to movement of distal end within the bladder and induced more trigonal irritation and stent related symptoms.

Lang and associates[56]stated that a possible mechanism of relief ofstent-related symptoms could be smooth muscle relaxation of lowerureter and trigone as well as reducing ureteric motility.

Wang and his colleagues[57]suggested that relaxation of bladderneck/prostatic smooth muscle, with consequent reduction in voidingpressure and urinary reflux, is other possible mechanisms for control ofstent-related symptoms, setting a rationale behind using alpha blockers in overcoming ureteral stent symptoms.

The Quality Of Lifescores at pre-insertion and POD-1 in groups I to IV were nonsignificant i.ep value was0.8679and 0.68721at pre-insertion and POD-1 respectively. At 2 wks after insertionthere was significant difference in scores(p value was 0.000986) with minimum score in combination therapy and maximum score in control group.

The effectiveness of alpha blockers in controlling double-J stent-related symptoms was reported previously by Wang et al. [57]in a prospective randomized study comparing tamsulosin to placebo in 79 patients using (USSQ) reported that tamsulosin improved stent related urinary symptoms, QoL, and they recommended its routine use.

Also Damianoet al.[16]reported that administration of tamsulosin has a positive effecton stent-related urinary symptoms, QoL, and VAPS, although this study was not double-blinded or placebo-controlled. Also, several studies reported that other alpha-blocker alfuzosin improved stent-related symptoms and quality of life and reduced analgesic demand compared to the placebo group [29, 30].

Kuyumcuoglu et al [58]reported in aprospective randomized study that tamsulosin was not different than placebo in controlling stent-related symptoms.Similarly, Lee et al.[46]reported in a prospective, randomized, and placebo-controlled study that postoperative solifenacinuse was effective and well tolerated for the treatment of LUTS, stent-related body pain, and hematuria irrespective of gender in patientsundergoingureteroscopic lithotripsy (URSL) and double-J stent indwelling.

Norris et al[43]reported in a prospective, randomized, and double-blinded placebo-controlled study that there were no differences between oxybutynin and placebo in controlling stent-related symptoms. However, they recommended further study on a large number of patients for optimal management of ureteral stent symptoms. Kuyumcuoglu et al[58]reported that tolterodine SR 4 mg was not different than anti-inflammatory and alpha blocker in controlling stent-related symptoms. In contrast to this data Park etal[41] in a prospective randomized controlled study reported that tolterodine was significantly able to improve pain and urinary symptom index scores when compared with alfuzosin and placebo.

A limitation of our study was the lack of patient homogeneity (as we included patients with different urologic procedures). However, the indications of double-J stent insertion were statistically similar in the four groups, and our main focus was to compare the efficacy of tamsulosinversussolifenacin versus combined treatment as this has been studied in only few literatures. Our findings showed that combined therapy was better than either tamsulosin or solifenacinmonotherapy in reducing stent related symptoms. The superiority of combined tamsulosin and solifenacin therapy was also reported previously by Lim K.T. and his colleagues[59]who reported in nonrandomized, retrospective study that combined use of solifenacin and tamsulosin was significantly better than either drug alone in reducing stent related symptoms. Similar were the results of Shalaby E. and his colleagues.[60]

V. Summary and conclusions

This study was a prospective, randomized and comparative study conducted in Department of Surgery, S.N. Medical College, Agrabetween January 2013 and November 2014 .

Aim of the study was to evaluate the effect of tamsulosin, solifenacin and combination therapy of the two agents in improving the lower urinary tract symptoms of patients with indwelling double-J ureteral stents.

After ethical clearance ,patients were assessed for eligibility and a total of70patients were enrolledin the study and 63 patients completed the study (2 patients from group I,2 patients from groupII,2 patients fromgroupIII, and 1 patient from groupIV dropped out).

- **Group I**(n= 15)was the control group and did not take any drugs.
- **Group II**(n= 16)received tamsulosin 0.4 mg once a day every day.
- **Group III**(n= 14) received solifenacin 10 mg once a day every day.
- **Group IV**(n= 18) received tamsulosin 0.4 mg and solifenacin 10 mgincombinationdaily.

Data was recorded in form of IPSS, VAPS , QoL questionnaire and baseline parameters were compared.Datawas recorded on pre-stenting day,POD-1 and 2 wks after insertion. Statistical analysis was done using appropriate methods.

Ureteral stenting with dj stentwas toleratedwell by majority of our patients andwasa safe procedure. Patientswere compliant in all the groups and there was no treatment withdrawl.

The individual therapy withtamsulosin(Group II)orsolifenacin(Group III)) showedimprovement in theVAS score, IPSS scoreand Quality of Life at 2 wks after insertion,the valuesappearedto be significantly better than the control group(Group I).

The post stentingIPSSscores including Storage symptom, Voiding symptom and Totalscoresat 2 wks post stentingin group II and IIIwere nonsignificantwith p-value0.4674, 0.7811, 0.6629 respectively. The difference in post stenting QOL scores at 2 wksbetween group II and III was also non-significant as p value was 0.3686.

Although there was a statistically significant difference inVAPS scores in favour ofgroupII(p value was 0.0306).

The combination therapy (Group IV) appeared toimprove theVAS score, IPSS scoreand Quality of Lifeatthestent removal day as the values were significantly differentfrom the control group and the individual therapy groups.

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