Role of Anticholinergic, Uroselective α 1D/1A Blocker, Combination of Two Drugs and Placebo in Treatment of Ureteral Stent Related Discomfort and Urinary Symptoms

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ABSTRACT

Introduction: The ureteral stent placement has become a part of urological clinical practice to relieve ureteral obstruction caused by variety of urological condition since 1967. Study aimed to access the role of anticholinergic (Tolterodine), uroselective α 1D/1A blocker (Naftopidil) alone and in combination to evaluate DJ stent related discomfort or pain, lower urinary tract symptoms and impact on quality of life.

Materials and methods: This was a randomized double blind placebo controlled comparative prospective clinical study conducted between May 2013 to February 2015 to access the role of anticholinergic (Tolterodine), uroselective α 1D/1A blocker (Naftopidil) alone and in combination to evaluate DJ stent related discomfort or pain, lower urinary tract symptoms and impact on quality of life.

Result: Total of 280 patients were enrolled for the study. 33 patients were excluded. We found Naftopidil and combination to be significanty better for pain score, combination being more effective for storage symptoms, voiding symptoms and quality of life scores.

Conclusion**:** Combination of Tolterodine and Naftopidil can be recommended for relief of stent related discomfort and urinary symptoms.

Keywords: Ureteral Stent, Urinary, Storage, Voiding, Urgency, Frequency, Intermittency

INTRODUCTION

There are many indications for ureteral stent placement of which the emergency ones include obstructive pyelonephritis, intolerable acute ureteral or renal colic. The other common indications are suspected ureteral trauma or perforation, post ureterorenoscopic ureteral edema following ureterorenoscopy or percutaneous nephrolithotomy in a solitary kidney, prior to shock wave lithotripsy in solitary renal unit, transplant kidney, post lithotripsy steinstrasse or larger ureteral stone burden, long standing impacted ureteral stone, passive dilatation of ureter or ureteric orifice, prolonged endoscopic manipulation, recent history of urosepsis or infection and occasionally in pregnancy to treat renal obstruction due to calculus.[1-4]

The indwelling use of DJ stent (Double J) can produce varying degree of discomfort, pain and lower urinary tract symptoms,varying from one patient to other and believed to affect 80% of patients.[5,6] Joshi et al[7] in his study of 120 cases evaluating the quality of life(QOL) and analysis outcome based on International Prostatic Symptom Score(IPSS), International Continence Society(ICS), Bristol Female Lower Urinary Tract Symptoms(BFLUTS) Scoring concluded that 80% of patients have wide range of urinary tract symptoms that affects the quality of life. The storage symptoms, bladder pain and hematuria were the major bothersome symptoms.[8,9]To improve these stent related symptoms attempts have been made by pharmacological agents which were investigated in vitro and in vivo for a decade.[10.11]

Several studies have been done in the past to use pharmacological agents like intravesical oxybutynin, alkalized lidocaine, ketorolac, oralalfuzosin/tamsulosin (alpha-blockers), tolerodine /solifenacin (anti-cholinergics) both alone and in combination to relieve these symptoms.[12-15] The present prospective randomized controlled double blinded comparative clinical study was undertaken to access the role of anticholinergic (Tolterodine), uroselective α 1D/1A blocker (Naftopidil) alone and in combination to evaluate DJ stent related discomfort or pain, lower urinary tract symptoms and impact on quality of life. Naftopidil has three times more antagonistic property for α 1D than α1A as compared to other α 1D/1A blocker. Not much literature support the use of Naftopidil for stent related dysurias.

MATERIAL AND METHODS

This was a randomized double blind placebo controlled comparative prospective clinical study conducted at department of Urology and Renal transplant at Institute of Kidney Diseases and Research Centre, Gujarat between May 2013 to February 2015. All patients between 18 to 55 years of age who underwent indwelling endoluminal DJ stenting after endourological procedure for urolithiasis (URS,

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PCNL, RIRS), stenting before SWL or after laparoscopic pyeloplasty or ureteric reimplantation were included in the study. Patients having contraindications to Tolterodine, Naftopidil, or on drugs interfering with lower urinary tract symptoms, patients having bladder outlet obstruction, overactive bladder, neurogenic bladder, pregnant females, renal transplant patients were excluded from the study. Demographic details of all the included subjects were recorded. The patients were divided into four groups. Group 1 included patients on Tolterodine 4mg sustained release (SR), Group 2 on Naftopidil 50 mg, Group 3 combination of both and Group 4 on placebo as control. Evaluation of stent discomfort, urinary symptoms and quality of life assessment were done by assessing score based on Visual Analogue Score (VAS), IPSS, IPSS-QOL respectively. The patients were followed on day 7 and 14. Statistical analysis was performed using SPSS version 12.0. one tailed unpaired Student was used for comparison of continuous variables. Categorical variables were compared using ANOVA and Chi square test. P value less than 0.05 was considered as statistically significant.

RESULTS

Total of 280 patients were enrolled for the study. Patients were randomized using random allocation software. 33 patients were excluded as 20 had delayed follow up with lost questionnaire form, 2 had early stent removal, 8 did not take study group medications and 3 had post procedural sepsis and prolonged hospital stay. For final analysis 247 were taken into account of which Group 1 had 57, Group 2 had 63, Group 3 had 63, and group 4 had 64 patients. Of the total patients 171 (69.23%) were males and 76 (30.76%) were females. 128 (51.28%) had stent on the right side and 119 (48.17%) had on the left side with no difference among all the groups (p value 0.4058).

Group comparison	t-test value	p value
Placebo vs Tolterodine	0.6788	0.249
Placebo vs Naftopidil	6.96	< 0.00001
Placebo vs Combination	10.37	< 0.00001
Tolterodine vs Naftopidil	7.066	< 0.00001
Tolterodine vs Combination	11.09	< 0.00001
Naftopidil vs Combination	4.64	< 0.00001

Table-1: Intergroup comparison of mean IPSS score (1st week)

Group comparison	t-test value	p value
Placebo vs Tolterodine	0.63	0.264
Placebo vs Naftopidil	9.71	< 0.00001
Placebo vs Combination	11.22	< 0.00001
Tolterodine vs Naftopidil	8.73	< 0.00001
Tolterodine vs Combination	10.20	< 0.00001
Naftopidil vs Combination	2.58	0.005

Table-2: Intergroup comparison of mean QOL score (1st week)

Group comparison	t-test value	p value
Placebo vs Tolterodine	4.01	0.000052
Placebo vs Naftopidil	8.99	< 0.00001
Placebo vs Combination	10.64	< 0.00001
Tolterodine vs Naftopidil	5.94	< 0.00001
Tolterodine vs Combination	7.88	< 0.00001
Naftopidil vs Combination	1.64	0.051

Table-3: Intergroup comparison of mean VAS pain score(2nd week)

At the end of 1st week maximum VAS pain score was in placebo group 4.96 ± 1.79 and least VAS score was in combination group 2.43 ± 1.34, Naftopidil had mean VAS score of 2.87 ± 1.82 and Tolterodine had 4.14 ± 1.27. On intergroup comparison tolterodine, naftopidil and combination were significantly better than placeboin relieving pain at end of 1st week. Naftopidil and combination were significantly better than tolterodine. Though combination had least pain score but did not reach statistical significance when compared with naftopidil.

At the end of 1st week in placebo group, patients had predominantly storage symptoms, such as frequency, urgency and nocturia, incidence of which ranged from 60-80%. In voiding domain they experienced intermittency (80%) and straining (60%).

Patients taking tolterodine had almost similar incidences of frequency and urgency (77-84%) as that of placebo group but with less degree of nocturia (35%). Predominantly voiding symptoms were straining (93%), intermittency (81%) and incomplete emptying (65%).

In naftopidil group patients predominantly had storage symptoms, frequency (85%), uregency (81%) and nocturia (80%). Voiding symptoms were intermittency (46%) and straining (8%).

In contrast to all these findings, combination group had less than 50% of storage symptoms, frequency(44%), urgency(40%) and nocturia (50%) and more incidences of voiding symptoms of straining (27%), intermittency (48%) and incomplete emptying(36%).

In tolterodine group frequency, intermittency, urgency and straining had score more than 1, rest had value less than 1.

In naftopidil group only storage symptoms had score more than 1, voiding symptoms had mean score ≤ 0.50.

In patients taking both drugs had mean value of each IPSS component less than 1.

In placebo group predominant symptoms of frequency, urgency, intermittency and nocturia with mean score value ranging from 1.12-2.14.

IPSS and QOL score were significantly different between groups at end of 1st week. (Table 1, 2). Combination group had least IPSS mean value of 2.76 ± 2.12 and best QOL of 1.12±0.9 with majority of patients were pleased. Placebo had highest mean IPSS score of 8.79± 4.10 and QOL towards dissatisfaction. Mean value of IPSS among groups in increasing order was combination < naftopidil < tolterodine < placebo.

With respect to VAS, naftopidil and combination were significantly better than tolterodine (Table 3). Mean value of IPSS in increasing order was combination< naftopidil < tolterodine <placebo (Table 4). Tolterodine was better to placebo in improving luts at the end of second week (Table

	IPSS 2nd week Mean ± SD	IPSS 2nd week Range (Mode)	QOL 2nd week Mean ± SD	QOL 2nd week Range (Mode)
Tolterodine	4.79 ± 2.30	0-11 (5)	1.89± 0.82	0-4 (2)
Naftopidil	3.74 ± 1.66	0-6 (4)	1.32±0.7	0-3 (1)
Combination	1.03 ± 0.98	0-3 (0)	0.38±0.63	0-2 (0)
Placebo	8.96 ± 3.95	0-16 (10)	2.9±0.83	1-5 (3)

Table-4: Total IPSS and QOL score (2nd week)

Group comparison	t-test value	p value
Placebo vs Tolterodine	6.30	< 0.00001
Placebo vs Naftopidil	9.40	< 0.00001
Placebo vs Combination	14.65	< 0.00001
Tolterodine vs Naftopidil	3.61	0.00022
Tolterodine vs Combination	11.84	< 0.00001
Naftopidil vs Combination	10.03	< 0.00001

Table-5: Intergroup comparison of mean IPSS score (2nd week)

Group comparison	t-test value	p value
Placebo vs Tolterodine	6.73	< 0.00001
Placebo vs Naftopidil	11.70	< 0.00001
Placebo vs Combination	19.25	< 0.00001
Tolterodine vs Naftopidil	4.19	0.00027
Tolterodine vs Combination	11.40	< 0.00001
Naftopidil vs Combination	7.92	< 0.00001

Table-6: Intergroup comparison of mean QOL score (2nd week)

Group comparison	t-test value	p value
Placebo vs Tolterodine	9.81	< 0.00001
Placebo vs Naftopidil	17.81	< 0.00001
Placebo vs Combination	27.98	< 0.00001
Tolterodine vs Naftopidil	8.59	< 0.00001
Tolterodine vs Combination	20.54	< 0.00001
Naftopidil vs Combination	10.00	< 0.00001

Table-7: Intergroup comparison of mean analgesic requirement

5). Out of all, combination had significantly better QOL at the end of 2nd week (Table 6).

Requirement of analgesic in decreasing order was combination > naftopidil > tolterodine > placebo and difference was significant in between groups for analgesic need (Table 7).

With respect to side effects eight patients in tolterodine group had dry mouth and skin, three had constipation and nine had dyspepsia. In Naftopidil group seven had nausea and four experienced light headache. Combination group patients had dryness of mouth and skin, light headache, constipation and dyspepsia. Placebo group patients experienced dyspepsia with other less common constipation.

DISCUSSION

Ureteral stent related discomfort has been a constant trouble for urologists since years. Damiano R[13] compared tamsulosin with no tamsulosin and found tamsulosin to be helpful in reducing stent related pain and European QOL VAS ath the end of first week. Kim GN[14] compared placebo, tamsulosin and combination of tamsulosin and tolterodine and found combination to be better with respect to pain and IPSS. Beddingfield R[16] found Alfuzosin to decrease painful urination as compared to placebo. We found naftopidil and combination had similar efficacy for relieving stent related discomfort at the end of 1st week and there was no added advantage of tolterodine with naftopidil.

We observed that those taking Tolterodine had better control of storage symptoms, naftopidil had better control of voiding symptoms and mean score of both storage and voiding symptoms was low for combination. Patients in placebo group had predominantly storage symptoms and intermittency at the end of 1st week. Kin GN[14] found frequency to be better in tamsulosin and tamsulosin plus tolterodine as compared to none. Similarly irritative domain of IPSS and VAS score was also better in both the groups. Nazim et al[17] found alfuzosin to decrease storage symptoms as compared to placebo. QOL score was also better in alfuzosin group.

With respect to VAS,at the end of 2nd week we found naftopidil and combination had similar efficacy for stent related discomfort and added advantage was not found of adding tolterodine to naftopidil. Develiotis[12] found Alfuzosin to be better than placebo for pain.

Combination group at 2nd week was significantly better from all other groups for improving sense of incomplete emptying. Naftopidil alone was also better than Tolterodine. Intermittency was maximum in Tolterodine group and minimum in combination group. Frequency was also less in Tolterodine and combination group than in the other two groups. Urgency was significantly low in the combination group whereas straining was minimum in Naftopidil group. On the other hand nocturia was maximum in Naftopidil group and least in combination group and the best QOL was seen in the combination group. Beddingfield et al[16] Alfuzosin was significantly better than placebo with respect to frequency of pain killer use and pain interfering with life and sleep. Park SC[18] reported mean body pain score significantly lower in patients taking Alfuzosin and Toloterodine ER. We found patients on combination to have the least analgesic requirement as compared to the rest and none of the patients discontinued medication for side effects.

The anticholinergic drug Tolterodine was found effective in relief of storage symptoms while urselective alpha blocker Naftopidil was found to be more effective in relieving voiding symptoms than storage symptoms. The combination of these drugs significantly relieved both voiding and storage symptoms. Also the quality of life was better and analgesic requirement was the least in the combination group.

Our study speaks of safety, efficacy and superiority of

combining anticholinergics with uroselective α 1D/1A blocker for stent related discomfort, urinary symptoms and quality of life.

CONCLUSION

Combination of Tolterodine and Naftopidil can be recommended for relief of stent related discomfort and urinary symptoms. Further studies will authenticate our opinion on use of Naftopidil alone or in combination with Tolterodine.

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