Original Article

Efficacy of Drug Combination for Ureteral Calculi

Efficacy of Danzen DS-Added Tamsulosin Combination Therapy for the Expulsion of Symptomatic Lower Ureteral Calculi

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ABSTRACT

Objective: To know the efficacy of Danzen DS-added tamsulosin for expulsion of the symptomatic distal ureteral stones.

Study Design: Descriptive, cross sectional study.

Place and Duration of Study: This study was conducted at the Outpatient Department of Urology, Sheikh Zayed Hospital, Rahim Yar Khan, Pakistan from June 2016 to February 2017.

Materials and Methods: Eighty-four male/female patients (aged:19-40 years) with single 5-9mm sized lower ureteral stone and colic pain for less than one month were registered using consecutive sampling technique. The subjects were advised to take 10mg tab Danzen DS thrice a day and 0.4mg cap tamsulosin (once a day) for maximum two weeks and visit hospital on 5th, 10th and 15th day for follow up including ultrasonography abdomen for stone positioning.

Results: All the patients (N = 84) adhered with the therapy. The stone expelled in 61 (72.62%) subjects within average time of 11.5 days. Higher stone removal rate was recorded in males than females (75 vs. 68.76, respectively; p = 0.78). There was significant difference in the rate against stone size (75% for 5-7 and 61.36% for 8-9mm; p = 0.01). None of the patients reported significant adverse effects whereas episodes (1-3) of mild colic pain were documented against two participants.

Conclusion: The Danzen DS-added tamsulosin combination therapy shows acceptable efficacy in terms of stone expulsion rate, management time, adverse effects, and episode of pain. The therapy can be used on large scale after validation.

Key Words: Tamsulosin, Danzen, Combination therapy, Symptomatic, Ureteral calculi

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INTRODUCTION

Nephrolithiasis[1] also called kidney stone disease is a worldwide medical issue. It is renamed as ureterolithiasis when the stone stuck in the distal ureter due to gradually increased size. Consequently, there is acute pain beside urine obstruction. Unmanaged recurrent multiple stones can lead to fatal[2] consequences. Unfortunately, the disease is prevalent in Pakistan on account of un healthy life style and genetic tendency.[3]

Hormonal or metabolic abnormalities make the males more prone to the LUS (lower ureteral stone) than females.[2,3] Similarly, risk of the disease is high in early 30's. The pain develops when unblocked α_1 adrenergic receptors of the ureter attempt to push forward the stuck stone from the inflamed region by peristalsis.[4] Finding vitals satisfactory, medical expulsive therapy (MET)[5] is advised for 5-9mm sized LUS.

The noninvasive MET deserves prompt action as any delay increases the size of the stone beyond 9mm where costly surgical intervention becomes inevitable.[5,6] Tamsulosin is the choice of urologists[7] as it not only antagonists the α_1 adrenergic receptors to reverse the mechanism of forced peristalsis but also manages the spasm for early stone expulsion. Whereas, inflammation and pain can be addressed using Danzen DS- a serratiopeptidase[8] with tamsulosin in combination therapy. Similarly, it saves from additional analgesic while discourages adverse effects like tadalafil.[1,5] Like, in combination antibiotics,[9] there is no possibility of drug resistance in the combination MET.

The online published literature is devoid of any evidence on use of Danzen DS-added tamsulosin for expulsion of the LUS. Perceiving its potential, present work was planned to know the efficacy of the combination therapy for the expulsion of the symptomatic LUS. The findings will support the researchers to test it before recommending for

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clinicians in countries like Pakistan[10] where MET is the only readily accessible decision for both, professionals and patients.

MATERIALS AND METHODS

The present descriptive cross-sectional study was conducted between June 2016 and February 2017 at outpatient Deptt. of Urology, Sheikh Zayed Hospital, Rahim Yar Khan, Pakistan subsequent to approval from the hospital ethics committee.

Sample size was seen as 84 using P = 0.32 (derived from a pilot study on Danzen DS-added tamsulosin for expulsion of 5-9mm sized LUS) in a formula Z^2 P (1-P)/d^2. All male/female patients (aged = 19-40 years) with a 5-9mm sized LUS (affirmed by ultrasonography i.e. USG abdomen)[11] and reporting colic pain for less than one month were registered using consecutive sampling technique. However, patients with hydronephrosis (Grade 3 or 4), urinary tract infection, hematuria, previous experience of surgical/ nonsurgical removal of kidney stone(s), single kidney, or elevated serum creatinine (>2.0 mg/dl) were excluded. Finally, those patients were recruited who gave written participation consent.

Sociodemographic information (like age and sex), and clinical manifestations like duration since first episode of pain were documented. Similarly, severity level of the pain on presentation in the study setting was gauged using visual analogue scale[12] ranging no pain (1) to extremely intense pain (10 score). The subjects were asked to take tab 10mg Danzen DS thrice a day and cap 0.4mg tamsulosin (once a day after mealtime) for two weeks while take plentiful fluids. Similarly, they were advised to use purpose-built mesh to detect any expelled whole/pieces of stone on urination and visit hospital on 5th, 10th and 15th day for USG to determine LUS's positioning. They were additionally encouraged to report any adverse effects or pain episode(s).

Data were calculated in terms of mean or frequency. Chi-square test was applied to see any association between stone removal and qualitative variables. The p value ($\leq$ 0.05) was considered as significant in the test. The SPSS ver. 17.0 was used for analyses.

RESULTS

Of 128 patients, 84 were enrolled consecutively for the combination therapy as rest of the cases were excluded on the basis of exclusion criteria and/or refusal to give mandatory participation consent as shown in flowsheet diagram for patient sampling (Fig. 1). Moreover, all the enrolled patients (N = 84) adhered with the therapeutic sessions of combination drugs i.e. Danzen DS-added tamsulosin for maximum 15 days to expel a 5-9mm sized LUS with urine. Not a single case of discontinued drug(s) or loss of follow up was recorded (response rate = 100%) throughout the study.

Data in Table 1 indicate baseline socio-demographic and clinical information of the finally enrolled study subjects. The ratio of male to female population was found to be 1.62:1 (52/32) as per record in predesigned proforma. However, there was not any case of undermined sex/transgender. Statistics of biological age (verified by CNIC, NADRA, Pakistan) were, as: M = 28.82, SD = 4.8 (range 20-40) years. The participants reported stone-related symptoms including pain or burning during urination, smelly urine, and nausea/vomiting for an average about past seven days. The USG abdomen diagnostic technique revealed substantially large-sized stone (M = 7.92mm in larger dimension) in lower ureter (right/left). The patients rated radiating colic pain in the range of 5 (moderate) to 9 (extremely severe) while assessment by duty doctor on 1-10 scored VAS.

Table No.1: Baseline information of the subjects with a LUS

Variable	No. (rate in %age)/ Mean ± SD (min.- max.)
Gender	
Male	52 (61.9)
Female	32 (38.1)
Biological age; years	28.8 ± 4.8 (20-40)
Duration of stone-related symptoms; days	6.6 ± 0.6 (1-12)
Stone size; mm in larger length*	7.9 ± 1.3 (5-9)
Colic pain; severity level**	7.2 ± 1.1 (5-9)

*using USG technique, **self-reporting of patient on VAS

Combination therapy i.e. tamsulosin plus Danzen DS showed its efficacy in expulsion of lower ureteral stones against 61 (72.62% of total 84) non-hospitalized patients within a short time span i.e. M = 11.5, SD = 2.7 (range: 1-15) days under the supervision of research team. However, time was independent of stone size. Comparatively higher stone removal rate was recorded in males than females (75 vs. 68.76, p = 0.78) as displayed in Table 2. Similarly, insignificant association was seen between the rate of the stone expulsion and age groups of the participants (p = 0.55). Surprisingly, the rate was higher i.e. 77.08% (n = 37) in the patients who reported stone-related symptoms for the less than last seven days than one or more than one weeks (66.67%, n = 24). The 75% (n = 34) medium sized (5-7mm) while 61.36% (n = 27) large sized stones (8-9mm) were expelled on use of the medicines. Whereas, the two rates showed statistically significant difference when 2x2 cross tabulation was used in chi-squared test (p = 0.01). Not a single significant adverse effect was reported/ examined in the study population. The episodes of colic pain decreased gradually and ultimately ended except in two patients (less severe than without medicines) where MET failed for LUS.

Table No. 2: Association of stone expulsion rate with information of the subjects

Variable	Stone expulsion; No. (%)		*p*
	Yes	No	
Gender Male Female	39(75.0) 22 (68.7)	13(25.0)10 (31.3)	0.78
Biological age; groups (years) 19-29 30-40	45 (73.8) 16 (69.6)	16 (26.2) 7 (30.4)	0.55
Duration of symptoms; week <one ≥one	37 (77.1) 24 (66.7)	11 (22.9) 12 (33.3)	0.81
Sone size; mm 5-7 8-9	34 (85.0) 27 (61.4)	6 (15.0) 17 (38.6)	0.01*

*significant using chi-square test at 5% level of significance

DISCUSSION

Some patients avoid to give participation consent[13] self-perceiving poor prognosis in the biomedical research. On the other side, strict adherence of the subjects of present work to combination MET for LUS expulsion is exemplary. The adherence ensures quality health care.[14] Approximately double the male than female population of LUS patients remarkably differs (4:1) in a similar Pakistani study[15] (4:1). The responsibility of the deviation apparently goes to differential life styles beside hereditary tendency. Male predominance also exists in hemodialysis.[16] Age of a person in the close proximity of 30 years is crucial towards onset of the ureterolithiasis as endorsed by a published study[5] (33 years). Finding of 8mm-sized stone on the average is frightening because some delay can shift the patients in surgical management. Generally, the combination MET fails in removal of 10mm-sized stone.[17] In the presence of same-sized stone, feeling the pain with more severity than others[14] seems to be a psychophysiological phenomenon.

Our finding on stone expulsion rate (73%) by Danzen DS-added tamsulosin is higher than (64-70%)[5,18] while lower than (84-100%)[7,15,19] using tamsulosin and a supporting drug. Adherence to therapy and reinforcing role of the supporting drug are significant determinants in this context. Moreover, combination MET is save in terms of drug tolerance just like antibiotics combination[9] in the body. Significant effectivity of tamsulosin in low dose has also been reported[10,20] whereas, removal of 5-9mm sized LUS through plentiful oral fluid intake is a surprising outcome.[4,10,20] Consumption of shorter stone expulsion time (i.e. on the average 11 days) than in the study by Jayant and associates is taken positive as the MET is the selection of the patients agreed to awaiting management.[19,21] Contrary to it, poor vigilance at urination for detection of the expelled stone can be held responsible for late expulsion compared to highlighted by Nadim et al.[15] or Erturhan et al.[18] Other combination therapy including terazosin and nifedipine has also shown efficacy (stone discharge rate = 94.5%; time = 7 days) in postoperative treatment of LUS after transurethral ureteroscopic lithotripsy.[22]

Light physical activity[23] by men gives difference in LUS removal rate in sexes: males/females (75/69%). Similarly, decrease in stone expulsion rate with increase in age group can be attributed to unhealthy life style in this career struggling/home establishing stage. Healthy lifestyle prevents from metabolic diseases.[3,24] The higher stone expulsion rate in the patients with less than seven days of symptoms show evident coincidence with the benefits of early diagnosis. The size of the LUS matters in spontaneous[25] or medicine-mediated expulsion as seen in findings of present work. No evidence of adverse effects or need of additional analgesic marks the importance of Danzen DS. Reporting of mild pain by two subjects on the scale[12] makes the combination therapy, acceptable.

CONCLUSION

The MET including Danzen DS-added tamsulosin show acceptable efficacy for LUS in terms of stone expulsion rate, therapy time, significant adverse effects and pain episodes. Better outcomes are recorded against 5-7 than 8-9mm sized stones. There is need to see the therapy with the perspective of cost-effectiveness beside tailoring of dosing regimen. The findings will support the researchers to test it before recommending for clinicians in countries like Pakistan[10] where MET is the only readily accessible decision for both, professionals and patients.

Author's Contribution:

Concept & Design of Study:	Khalid Saeed
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