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Comparison of the Efficacy of Combined Therapy with Oral Tamsulosin Plus Oral Diclofenac and Tamsulosin Alone in Time & Rate of Expulsion of Distal Ureteric Stones

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ABSTRACT

Objectives: To compare the effectiveness of combined therapy with Tamsulosin and Diclofenac sodium and Tamsulosin alone in the rate and time of expulsion of distal ureteric stones of size ranging from 5-<9mm.

Methodology: This randomized clinical trial study was conducted at Benazir Bhutto Hospital Rawalpindi and Institute of Kidney Diseases-Hayatabad Medical Complex Peshawar from December 2019 to December 2020. All male and female patients presenting to the urology OPD diagnosed with unilateral distal ureteric stones on X-ray KUB were recruited using systematic random sampling and divided into two groups: Group A (study group) and Group B (control group). Patients with odd numbers were assigned to Group A, while those with even numbers were assigned to Group B. Group A received Tab. Tamsulosin 0.4mg OD and Tab. Diclofenac sodium 75mg BD for 21 days. Group B received Tab. Tamsulosin 0.4 mg OD for 21 days and acetaminophen 500mg SOS.

Results: The clinical trial revealed that in the group of patients receiving Tamsulosin and diclofenac, the rate of expulsion of distal ureteric stones was improved with a statistically significant difference. Time of expulsion of stones in two groups wasn't statistically different.

Conclusions: Tamsulosin and Diclofenac sodium given together have added effect /benefit as compared to Tamsulosin alone in the rate and time of expulsion of distal ureteric stones.

Key Words: Clinical Efficacy Diclofenac Sodium, Medical expulsive therapy (MET), Tamsulosin, Ureters, Urolithiasis.

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Introduction

Active Medical Expulsive Therapy (MET) is an aggressive outpatient approach that reduces pain, increases stone passage, and lowers surgery requirements in nephrolithiasis. MET employs alpha-1 selective blockers like Tamsulosin to relax the ureter and NSAIDs as the first-line pain management therapy. Surgical intervention is reserved for cases where medical treatment is ineffective or unlikely to cure the disease.

Urolithiasis, the formation of urinary tract stones, is an ancient ailment affecting the kidney, ureters, bladder, or urethra. Stones are classified based on size, location, chemical composition, and etiology.[1] The global incidence varies, with higher rates in certain regions due to climate and dietary factors. The prevalence of urolithiasis has increased due to lifestyle changes and global warming. Caucasians have a higher incidence than other populations. Recurrence rates are significant, reaching 75% over 20 years.[2] Various factors contribute to stone formation, including age, gender, diet, dehydration, high vitamin levels, obesity, gastric surgery, drugs, infections, urinary tract factors, genetics, and lifestyle. Water intake plays a crucial role. The formation of calculi involves super-saturation of salts, leading to solid foci that aggregate into stones.

Renal stones are found to be of various types, including calcium oxalate, calcium phosphate, uric acid, struvite, cystine, and protease-related stones.[3] Preventive measures

include adequate water intake and a balanced diet. Specific dietary recommendations target certain types of stones. Pharmacological interventions are considered for high-risk patients.

Common clinical presentations include pain, obstruction, hematuria, and urinary tract infections. Pain severity and location depend on stone position.[4] Management options for ureteric calculi include conservative management, medical expulsive therapy (MET), and surgical intervention. MET, with drugs like alpha blockers and NSAIDs, has become a standard treatment. Alpha blockers like Tamsulosin relax ureteral muscles, facilitating stone passage. NSAIDs provide pain relief and anti-inflammatory effects. Diclofenac sodium is used in acute renal colic, increasing the rate of stone expulsion and as analgesia during shock wave lithotripsy. Acetaminophen is widely used for mild to moderate pain. NSAIDs inhibit COX enzymes, reducing prostaglandin production and providing pain relief. They may have adverse effects on the renal system, affecting potassium excretion and potentially causing nephrotic syndrome.[5]

Acetaminophen, though a popular analgesic, lacks anti-inflammatory properties and can lead to hepatotoxicity and renal tubular necrosis in high doses.

In summary, urolithiasis is a common urinary tract condition with various risk factors and types of stones. Preventive measures, clinical presentations, and management options, including MET with alpha blockers and NSAIDs, play essential roles in its treatment. However, NSAIDs and acetaminophen have potential adverse effects on the renal and hepatic systems, requiring caution in their use. [6]

The main aim of the study was to compare the effectiveness of combined therapy with Tamsulosin and Diclofenac sodium and Tamsulosin alone in the rate and time of expulsion of distal ureteric stones of size ranging from 5-<9mm.

Methodology

An observational study of 12 months was conducted at Benazir Bhutto Hospital, Murree road, Rawalpindi and at Institute of kidney Diseases-Hayatabad medical complex. Peshawar.

Patients diagnosed having ureteric stones measuring 5-9mm. Study design used is Randomized clinical trial. All male and female patients presenting to urology OPD, diagnosed to be having unilateral distal ureteric stone on X-ray KUB are to be recruited. Patients will be selected on systematic Random order (odd and even). The patients assigned are divided into two groups A (study group) & B (control group)

All odds will be assigned to study group “A”, All evens will be assigned to control Group “B”. A total of 50 patients were included in this study, divided into two groups. The sample size for the study was determined using the WHO sample size calculator software, with a level of significance set at 5% and a power of the study test at 90%. Initially, a sample size of 93 was calculated. However, to account for potential loss of follow-up, an attribution bias of 10% was considered. Consequently, the sample size was adjusted to 50 participants. Patients were selected through non probability convenient sampling technique. Every alternate patient, odd and even, fulfilling inclusion criteria were put in group A and Group B respectively. Group A was considered as the Study group while Group B was taken as Control.

Patients of either gender, Patients diagnosed with ureteric stone for the first time, Size of stone estimated 5-9mm.Stones held in distal ureter (unilateral), Patients with only radiopaque stones, Idiopathic stones or stones formed due to any cause, Patients diagnosed with ureteric stones, not willing for surgery were included in the study.

Stone formers (history of recurrent stones), History of any surgical intervention for the same complaints, Children (under 15 years of age), Pregnant females, Patients with history of acid peptic disease, peptic ulcer, Patients with Osteoporosis, Gout, Patients with CVS disease as a comorbid including hypertension, CCF and History of surgery on ureters patients were excluded from the study.

All the male and female patients presenting to urology OPD of Benazir Bhutto hospital, Rawalpindi and diagnosed to be having unilateral distal ureteric stone on XRAY KUB were recruited.

- Total 50 patients were chosen for the study
- XRAY KUB of all the patients were taken at the start of the study
- Patients were selected on non-probability convenient sampling technique. (odd and even)
- First patient was recruited in group A and second reporting patient with the same criteria was included in group B.
- In this way 25 patients were sorted to group A and 25 patients to group B

- The XRAY KUB was repeated for both group A and B weekly for a period of 1 month to assess the rate and time of expulsion of ureteric stones.

All the odds (n=25) with a diagnosis of ureteric stone on XRAY KUB were allotted to group A. Group A was given Tab. Tamsulosin 0.4mg O.D for 21 days and Tab. Diclofenac sodium 75mg B.D for 21 days.

All the evens (n=25) with a diagnosis of ureteric stone on XRAY KUB were allotted to group B. Group B was taken as the control group. Group B were given Tab Tamsulosin 0.4 mg O.D for 21 days and Acetaminophen 500mg SOS for 21 days

Patients were followed up weekly by filling of performas on following parameters.

Frequency of pain episode, History of expulsion/ stones, collected from urine sample, Weekly X-ray KUB for confirmation/diagnosis of stone expulsion, Regular weekly follow-up in OPD / Emergency were done by filling of the Performa's by a trained house officer, medical officer, or trainee and Stone expulsion from the ureter (after 21 days of treatment)

SPSS v.23 was used for data analysis. Frequencies and percentages were calculated for categorical (qualitative) variables. Frequencies were also illustrated through bar and pie charts. Chi-square test was applied between treatment groups A and B and the expulsion of stone (recorded as yes or no). p-value of <0.05 was considered significant. Independent sample t-test was applied to compare the mean day of compulsion among the two groups A and B. Chi square test was applied to compare the rate/frequency of expulsion between the two groups.

Results

The analysis of the data shows that the mean age of the patients in group A included in the study was 29.04 ± 8.2 SD. The mean age of patients in group B was 28.48 with SD ± 4.7. Total of 25 patients were in group A. The mean age was 29.04 with a slandered deviation of 8.25. Two patients were in the range ages of a10-20 years.13 were between age range of 20-30 and 10 were between 30-40 years age. In group B, 4 patients fell in age range of 18-25. 19 patients were between ages 25-35. 2 patients were in 35-40 range of age.

In group A 68% of the patients were male and 32% were female. In group B, 17 patients were male which made them 72%. 8 patients were female, makes 28% of the group.

The severity of pain experienced by the patients is shown in table I.

Table I: Comparative results for severity of pain in treatment groups A & B

VARIABLE	TREATMENTGROUPS	
SEVERITY OF PAIN	Group A	Group B
MILD	14 (56%)	16 (64%)
MODERATE	10 (40%)	8 (32%)
SEVERE	1 (4%)	1 (4%)

The last XRAY KUB taken at day 21 showed the complete expulsion of the renal stone in 23 out of 25 patients in group A, while 2 patients still had stones although the stones had moved down the urinary tract from their original position. The frequency of expulsion of renal stones in group A was 88%.

The last XRAY KUB taken at day 21 in group B showed the persistence of the renal stone in 15 out of 25 patients, while 10 patients showed expulsion of stones. The frequency of expulsion of renal stones in group B was 40%. Chi square test was applied to compare the percentage of patients in the two treatment groups. P value was 0.018 which was statistically significant (Table II)

Table II: Comparative results for severity of pain in treatment groups A & B.

VARIABLE	TREATMENTGROUPS	
SEVERITY OF PAIN	Group A	Group B
MILD	14 (56%)	16 (64%)
MODERATE	10 (40%)	8 (32%)
SEVERE	1 (4%)	1 (4%)

Independent sample T test was applied to compare mean day of expulsion between the two treayment groups.the mean day of expulsion in group A was 16.5 ± 3.23 while in group B, it was 17.33 ± 3.75 .statistically this mean difference was insignificant with a P value of 0.51. (CI -3.22-1.65). (Table III)

Table III: Statistical Analysis for Day of Expulsion of The Stone.

Treatment Groups	MEAN ± S.D	Mean Differece	P value	C I	
				Lower	Upper
Group A	16.55±3.2	-0.788	0.51		
Group B	17.33 ± 3.75			-3.22	1.65

Discussion

Urolithiasis is a troublesome disease effecting the humans all over the globe with an incidence of about 10-15% in the western world reaching to 20-25 % in East. Besides having high recurrence rates of about 50% at 10 years if not dealt with, Renal calculi can result in complications

like severe infection, renal failure or in some cases can be fatal. For the above reasons, prompt aggressive management is a compulsion for cases of urolithiasis. Calculi can form throughout the urinary tract, majorly in kidneys. Passage of the stone from the kidneys into the ureters refers to be the cause of acute ureteric obstruction. The pain experienced is the most severe pain one can ever experience. Surgical intervention used to be the eventual treatment of choice for all types of stones in past. In modern day urology practice, Adjuvant pharmacological intervention during conservative therapy with routine analgesics has been tried to facilitate passage of stone as well as a symptomatic therapy for relief of unbearable pain.

According to the investigation directed by Frolich J and partners, as in association with the benchmark group the animals that had received NSAIDs had considerable growths in the dieresis in addition to natriuresis which showed that Diclofenac and Indomethacin medications increment the urinary production through PG inhibition.[7] After different researches, it was estimated that the reduction in contractile activity of smooth muscles was the result of medicines. However, the contraction was antagonistic to PGs administration. The PGs indicate an upgrade of the rate and force of contraction in ureteric smooth muscle when applied alone.[8] In the study of Sivrikaya and colleagues, the diclofenac was seen to create considerable relaxation of the uterine smooth muscles and it was reasoned that it had viability in both renal colic along ureteric stone removal.[9,10]

According to the research, the use of NSAIDs in the test group has better results in the removal of the renal stones as compared with the control group.[11] As results demonstrated that in contrast with the increase in peristalsis, ureteric relaxation is a prevalent method because peristalsis expansion irritates muscles which eventually stimulate peristalsis irregularly. As a result, difficulties were observed in the removal of renal stones.

Outcomes of this research supports Borofsky and colleagues who led an examination on dog samples on the impact of NSAIDs on renal GFR. Results indicated that a 35% reduction was observed in the renal GFR after fifteen minutes of Toradol (NSAIDs) application as well as a decrease in pressure of ureters.[12]

Conclusion

Medical expulsive therapy does show promising results in patients with distal ureteric stones. Tamsulosin and Diclofenac both are helpful to decrease the number of patients undergoing surgical intervention hence decreasing the morbidity& the workload on the urology unit.

Diclofenac in recommended doses is a safe NSAID which reduces the episodes and severity of pain well, as helps in expulsion of stone. Tamsulosin increases the rate of expulsion of stones through its action on alpha 1a receptors causing the relaxation of smooth muscles of the ureter by decreasing the basal tone, preventing the spasm, thus increasing the outflow. Diclofenac sodium has anti-inflammatory effect through inhibition of Cyclooxygenase and Lipoxygenase pathway. It can increase the efficacy of other drugs used in MET by the anti-inflammatory, anti-edema action. Tamsulosin and Diclofenac given together have an additive effect in expulsion of ureteric stones.

Recommendations: The comparative studies need to be confirmed and consolidated in large sample randomized controlled research. The research can be further supplemented by the evaluation of the role of other NSAIDs in MET. Areas for the research for the drugs which can be helpful in expulsion of stones in proximal or middle ureter should be explored. Drug development program for new drugs selective for ureteric receptors should be carried out.

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