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Investigation Of Sustain-Release Diclofenac Tablet Effect On Pain Caused By Urethral Dilatation

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Abstract
Objective: The aim of this study was to evaluate the effects of sustained-released Diclofenac on urethral dilatation pain.
Methods & Materials: The present study is a randomized clinical trial that was performed on 40 patients referred to the urology clinic of Ghaem Hospital due to urethral stricture from March 2020 to the end of 2021. Eligible patients were randomly divided into two groups after obtaining informed consent. The intervention group received 100 mg sustained-released Diclofenac tablet the night before urethral dilatation. Patients in the control group also received placebo. Demographic information (age, occupation, etc.), pain (VAS), the need to take analgesic and side effects were collected in a checklist for each patient and using the software SPSS23 for analyzing.
Results: The mean age of patients was 46.18 ± 15.69 years (age range 24 to 72 years). The median of pain score during procedure based on VAS in the intervention group was lower than the control group but not statistically significant (P = 0.11). But, the median of postprocedural pain score based on VAS in the intervention group was lower than the control group and statistically significant (P = 0.03). The difference between the rate of side effects was statistically significant (P = 0.037) in the study groups. 6 patients in the intervention group and 1 patient in control group experienced mild urethral bleeding during the first 24 hours after the procedure.
The need to take analgesic was lower in intervention group than control group and statistically significant (P=0.038)
Conclusion: The results show some effectiveness of sustained-released Diclofenac administration in reducing pain in patients. However, due to the lack of similar studies in this field, it is recommended to conduct more extensive studies with a larger sample size and in a multi-center and with longer follow-up to confirm the results of this study.
Keywords: *urethral stricture, sustained-released Diclofenac, urethral dilatation*

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I. Introduction

Urinary tract obstruction is considered one of the oldest urologic diseases and a common condition with high morbidity (1, 2). Scar in the subepithelial tissue of the urethra leads to stricture formation (3). Urethral strictures can arise from various factors, with the most common causes including prostate surgeries (such as TURP and TURBT), trauma, infections, and congenital factors. Injury to the epithelial tissue of the urethra leads to scar formation and consequently reduces the diameter of the urethra (3). The symptoms of urethral stricture include reduced urinary voiding power, narrowing of the urinary stream, urinary burning, frequent urination, interrupted urinary flow, and a sense of incomplete bladder emptying (4), straining during urination, retention of urine in the bladder, and weak stream, alongside a description of recurrent urinary tract infections or hematuria (5). Moreover, depending on the intensity of the stricture, it can secondarily lead to damage to the bladder wall, pelvic structures, and even kidneys. These injuries may even culminate in kidney failure (6, 7, 8).

Strictures can occur in any part of the passage, from the prostatic urethra to the penile urethra (7). Urethral strictures include two types: anterior strictures and posterior strictures. Anterior strictures in the urethra are mainly due to urethritis in the context of infections such as Neisseria gonorrhoeae, trauma, lichen sclerosis, and a history of hypospadias or urethral surgeries. Posterior strictures in the urethra usually occur following catheterization, treatment of pelvic disease with radiotherapy, prostate surgeries, and pelvic fractures (9). The complications of urethral stricture include recurrent infections of the urethra and bladder, kidney infections, bladder stones, urinary tract stones, urethral diverticulum, incontinence, infertility, bladder irritability, and kidney dysfunction (10).

Retrograde urethrography of the urethra and bladder with a contrast agent assists in assessing the location, length, and intensity of urethral stricture. In the mentioned image, the stricture of the urethra is identified by the narrowing of the urethral lumen at the site of stricture and dilation of the lumen before the stricture. For a more accurate diagnostic procedure, cystoscopy is recommended. Therefore, the diagnosis of urethral stricture is facilitated through radiology or endoscopic tools. Considering that none of the mentioned methods specifically determine the depth of scar tissue, ultrasound and MRI could be useful (5).

The treatment of urethral stricture includes various methods such as direct visual internal urethrotomy, laser internal urethrotomy, repeated dilatation with bougies, long-term catheterization, and injection of drugs such as mitomycin into the urethra after internal urethrotomy. The most definitive and, of course, invasive treatment available is urethroplasty.

In urethroplasty, the narrowed part of the urethra is surgically removed, and healthy mucosa around the stricture is anastomosed. This treatment method yields better results for strictures located at the distal end of the urethra. Its drawbacks include invasiveness, prolonged surgery duration, the need for extensive spinal or general anesthesia, more potential complications associated with the more invasive nature of the surgery, and higher financial costs for the patient. Internal urethrotomy may also have complications such as damage to deep tissues, bleeding from the urethra, and the formation of urethral diverticula. In severe cases, damage to adjacent internal organs such as the rectum is also possible (5). But the most common complication of internal urethrotomy is the recurrence of stricture (11). Additionally, patients with longer strictures are more likely to experience recurrence (12).

Therefore, considering that many patients experience stricture recurrence after internal urethrotomy, they need repeated internal urethrotomy in near future (5, 13). To prevent the need for reoperation and the patient's transfer to the operation room, and the long-term complications of anesthesia and internal urethrotomy, a metallic dilatation of the urethra may be considered as an alternative to internal urethrotomy and more invasive procedures (14, 15).

A considerable number of patients, after undergoing urethral dilatation once, do not return for further visits due to pain and discomfort resulting from the procedure. Often, in the future, they find the need for internal urethrotomy, requiring a return to the operating room (16). The pain associated with this procedure is usually caused by inflammation, direct nerve injury, compression of nerves, and trauma (17) Pain following such procedures can lead to prolonged hospitalization, patient disability, and an increase in healthcare costs. This highlights the importance of attention to postoperative pain (18, 19). In addition to the recurrence of urethral stricture as a medical condition, the quality of life of patients is also significantly affected (7). The sustain-release diclofenac is used as an anti-inflammatory and pain-relieving medication to alleviate pain during and after surgery (20). Therefore, administering a painkiller and anti-inflammatory drug that can control patient pain during urethral dilation can potentially prevent the need for more invasive procedures such as internal urethrotomy, avoiding the transfer of the patient to the operating room and the associated anesthesia complications (5). However, in a meta-analysis study, Patel and colleagues in 2007, based on 9 trials with a total of 817 patients who underwent cystoscopy, investigated the difference in using 2% lidocaine gel and plain gel for patient pain based on the Visual Analog Scale (VAS). Ultimately, the differences were not statistically significant (21). Therefore, we decided to investigate the effect of sustain-release diclofenac on pain resulting from urethral dilation in this study.

II. Method

The study was carried out between February 20, 2020, and March 20, 2022.on patients referring to the Urology Department of Qaem Hospital (AJ) in Mashhad due to urethral stricture. The study was conducted as a Randomized Clinical Trial.

This study has received ethical approval from the Institutional Review Board at Mashhad University of Medical Sciences, and all stages of the study have been conducted based on the specified ethical protocols. the patients' consent to participate in the study was obtained, and written informed consent forms were collected from them to enter the study.

The ethical committee approval code is IR.MUMS.MEDICAL.REC.1398.878, and it was obtained on 2020-01-28. The study has been registered in the Iranian Registry of Clinical Trials (IRCT) with the code IRCT20220711055433N1 on 2022-07-19.

Among the patients who were candidates for urethral dilatation surgery in the Urology Department of Qaem Hospital (AJ) in Mashhad, men over 20 years old with singular urethral strictures measuring less than 1.5 centimeters were included in the study. The exclusion criteria was urethral stricture due to Balanitis Xerotica Obliterans, a history of drug sensitivity to NSAIDs, gastrointestinal problems, liver and kidney diseases, patient withdrawal from continued participation in the study, and the occurrence of intolerable adverse effects due to diclofenac consumption. A total of 40 individuals were included in the study. The urethral strictures in all study participants were confirmed based on medical history, urinary symptoms, and retrograde urethrogram examination.

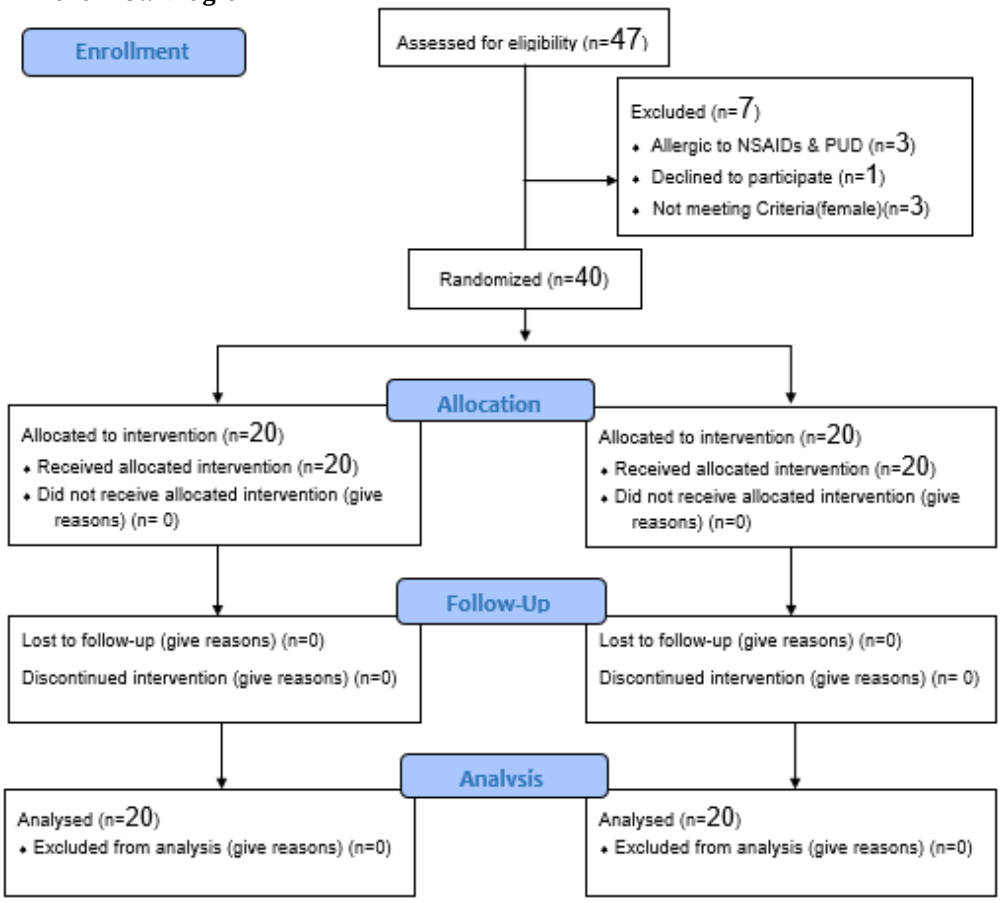
After obtaining informed consent, patients were randomly assigned to the intervention and control groups using a simple random sampling method (utilizing a table of random numbers). Baseline characteristics of patients, including age, occupation, cause of stricture, and duration of the disease, were recorded in a checklist. The patients were provided with information on how and when to take the medication, and the drug was given to them. The intervention group received 100 milligrams of sustain-release diclofenac the night before urethral dilatation, and the control group received a placebo (which was exactly similar in appearance, size, taste, color, and smell to sustain-release diclofenac, produced in coordination with the pharmaceutical company).

The urethral dilation was performed 8 to 10 hours later. This study was conducted as a single-blinded randomized clinical trial, meaning that only the patients were unaware of their group assignment. Patients were assessed for pain during and one hour after urethral dilatation, and the two groups were compared. Additionally, the patients' need for analgesia in the first 24 hours, as an indicator of their pain level, was evaluated along with the Pain-VAS (Visual Analogue Scale) questionnaire.

The Visual Analogue Scale (VAS) is a measurement instrument used to assess the intensity or frequency of various symptoms. It is commonly utilized in clinical and research settings to evaluate subjective characteristics or attitudes that cannot be directly measured. The VAS typically consists of a 10-centimeter line, anchored by two descriptors at each end, representing extremes of the symptom being measured, such as "no pain" and "worst imaginable pain." Patients mark a point on the line that corresponds to their perception of their current state. The distance from the low end of the scale to the patient's mark is then measured in millimeters or centimeters, providing a quantifiable measure of the symptom severity.

Subsequently, the two groups were compared. The study details and flow are presented in the CONSORT flow diagram.

CONSORT 2010 Flow Diagram



Data Analysis

After collecting the data, it was transferred into the SPSS software. Data description was performed using appropriate tables and charts. To compare quantitative variables between the two groups based on the normality or non-normality of their distribution, the independent t-test or Mann-Whitney U test was used. For the comparison of qualitative variables between the two groups, the chi-square or Fisher's exact test was utilized. Statistical significant level was less than 0.05.

The outcome used to calculate the sample size was the pain intensity score in each group. Sample size: Considering the formula for the independent two-sample t-test for a quantitative trait in two independent populations and based on similar studies (22), a total of 40 patients (20 in each group) were included in the study (5, 23, 24).

III. Results

The mean age of the patients was 46.18 ± 15.69 years, with an age range of 24 to 72 years. Other information related to the study patients is also observed in Table 1. There was no statistically significant difference in the age of patients (P=0.55), the frequency of patient occupations (P=0.91), and the frequency of the cause of urethral stricture (P=0.5) between the intervention and control groups. Also, the duration of the disease in the study groups did not show a statistically significant difference (P=0.86).

The pain intensity scores during urethral dilation and one hour afterward (VAS) had a non-normal distribution (P=0.025 and P=0.00, respectively). In the examination of the median pain intensity scores during urethral dilation (VAS), there was no statistically significant difference between the study groups (Table 2).

In the examination of the median pain intensity scores one hour after urethral dilation (VAS), a statistically significant difference was observed between the study groups (Table 3). Additionally, the amount of analgesic consumption showed a statistically significant difference between the study groups (Table 4).

The incidence of side effects in the study groups showed a statistically significant difference (Table 5). In the group of patients who received the treatment (the "intervention group"), six people had a little bleeding from their urethra within the first 24 hours after undergoing dilation with Béniqué. Now, in the control group, only one person had the same complication.

Table1: Basic Characteristic Profile of the Patients

Variable		Value (Percentage)
Mean Age (Years) ± SD		**/69 ± 46/18 15**
Median (Interquartile Range) Pain Intensity Score During Dilatation (VAS)		**(3,6) 5**
Median (Interquartile Range) Pain Intensity Score One Hour After Dilatation (VAS)		**(2/1‹75) 2**
Job	Self-employed	**(%50) 20**
	Employee	**(32/%5) 13**
	Student	**(%10) 4**
	Military	**(7/%5) 3**
Cause of Urethral Stricture	UTI	**(42/%5) 17**
	Surgery	**(%40) 16**
	Trauma	**(17/%5) 7**
Duration of Disease Onset (Years)	**1>**	**(17/%5) 7**
	1	**(%35) 14**
	2	**(%20) 8**
	3	**(%10) 4**
	4	**(%5) 2**
	≤5	**5(12/%5)**

Table2: Pain Intensity During Dilation (VAS) in Study Groups

VAS Pain Intensity	Groups		Total Frequency (Percentage)	P Value
	Cases	Control		
0	**0(0)**	**(0)0**	**(0)0**	**0.11**
1	**(0/0) 0**	**(0) 0**	**(0) 0**	
2	**(%5) 1**	**(%5) 1**	**(%5) 2**	
3	**(%35) 7**	**(%15) 3**	**(%25) 10**	
4	**(%15) 3**	**(%20) 4**	**(17/%5) 7**	
5	**(%20) 4**	**(%15) 3**	**(17/%5) 7**	
6	**(%20) 4**	**(%20) 4**	**(%20) 8**	
7	**(%5) 1**	**(%5) 1**	**(%5) 2**	
8	**(0) 0**	**(%15) 3**	**(7/%5) 3**	
9	**(0) 0**	**(%5) 1**	**(2/%5) 1**	
10	**(0) 0**	**(0) 0**	**(0) 0**	
Total	**(%100) 20**	**(%100) 20**	**(%100) 40**	

The median (interquartile range) of pain intensity during dilation was calculated in the intervention and control groups as 4 (3.5-5.75) and 5 (4-6.75), respectively.

Table 3: Pain Intensity One Hour After Dilatation (VAS) in Study Groups

VAS pain intensity	Groups		Total Frequency (Percentage)	P Value
	Cases	Control		
0	**0)0(**	**0)0(**	**0)0(**	**0.03**
1	**(%60) 12**	**(%25) 5**	**(42/%5) 17**	
2	**(%30) 6**	**(%35) 7**	**(32/%5) 13**	
3	**(0) 0**	**(%30) 6**	**(%15) 6**	
4	**(0) 0**	**(%5) 1**	**(2/%5) 1**	
5	**(%10) 2**	**(%5) 1**	**(7/%5) 3**	
6	**(0) 0**	**(0) 0**	**(0) 0**	
7	**(0) 0**	**(0) 0**	**(0) 0**	
8	**(0) 0**	**(0) 0**	**(0) 0**	
9	**(0) 0**	**(0) 0**	**(0) 0**	
10	**(0) 0**	**(0) 0**	**(0) 0**	
Total	**(%100) 20**	**(%100) 20**	**(%100) 40**	

The median (interquartile range) of pain intensity one hour after dilation was calculated in the intervention and control groups as 1 (1-2) and 2 (1.25-3), respectively.

Table 4: Need for Analgesic Consumption in the Study Groups

Need for Analgesic Consumption	Groups		Total Frequency (Percentage)	P Value
	Cases	Control		
Yes	**(%15) 3**	**(%45) 9**	**(%30) 12**	**038.0**
No	**(%85) 17**	**(%55) 11**	**(%70) 28**	
Total	**(%100) 20**	**(%100) 20**	**(%100) 40**	

Table 5: Side Effects in the Studied Groups

Side Effects	Groups		Total Frequency (Percentage)	P Value
	Cases	Control		
Yes	**(%30) 6**	**(%5) 1**	**(%17.5) 7**	**0.037**
No	**(%70) 14**	**(%95) 19**	**(%82.5) 33**	
Total	**(%100) 20**	**(%100) 20**	**(%100) 40**	

IV. Discussion

The results of this intervention showed that the median pain intensity during dilation (VAS) in the intervention group was less than the control group, but this difference was not statistically significant. The median pain intensity one hour after dilation (VAS) in the intervention group was significantly lower than the control group, and the incidence of side effects in the study groups had a statistically significant difference. Also, the amount of analgesic consumption after dilation showed a significant difference between the two study groups.

In comparison to similar studies, a study conducted by Nadeem et al. in 2016, a double-blind randomized trial, administered diclofenac suppositories one hour before cystoscopy to the intervention group (30 patients), while the control group (30 patients) did not receive any medication. The mean pain intensity score (VAS) between the two groups had a statistically significant difference (P=0.012) (22). Another study by Haq et al. in 2004, a double-blind, randomized study using a placebo on 72 patients, administered diclofenac suppositories 100 mg to the intervention group (36 patients) one hour before transrectal prostate biopsy, while the control group (36 patients) received a placebo one hour before the procedure. The pain intensity score (VAS) in the intervention group was lower than the control group, and this difference was statistically significant (P=0.001) (25).

The strength of the present study lies in its innovative idea and methodology, as there are very few similar studies in this field. Given the limited number of studies in this area, the possibility of a detailed comparison of the results of the current study with other similar studies was not feasible. Another limitation of the present study is that it was conducted in a single center with a relatively small sample size, which may reduce the generalizability of the results.

Therefore, their results align with ours regarding the effectiveness of prescribing diclofenac to reduce pain in urological procedures. However, considering that, based on our knowledge, there have been few similar studies in this field, there is a need for further and more extensive research with larger sample sizes, preferably conducted in a multicenter setting, to corroborate and expand upon these findings.

V. Conclusion

Based on the findings of our study, the median pain intensity scores during dilation (VAS) were lower in the intervention group compared to the control group, but this difference was not statistically significant. Additionally, the median pain intensity scores one hour after dilation (VAS) were significantly lower in the intervention group compared to the control group. Therefore, the results suggest the effectiveness of prescribing

sustain-release diclofenac in reducing pain associated with urethral dilation. It is recommended to conduct more extensive studies with larger sample sizes and longer follow-up periods to confirm the results obtained from this study.

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