# Tamsulosin and Sodium Diclofenac as an Effective Therapy to Reduce Pain After Ureteral Stent Removal: A Prospective, Double Blinded Randomized Placebo Controlled Trial

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**Purpose:** This study was conducted to determine the effects of tamsulosin and diclofenac sodium use on patients' pain perception after ureteral stents removal.

**Materials and Methods:** This study was a randomized control trial with double-blinded design. Eighty patients who underwent ureteral stent removal surgery at Kardinah Hospital during January to March 2017 were divided into four groups. The following medications were administered for two days, (A) placebo tid, or (B) diclofenac sodium 50 mg bid, or (C) tamsulosin 0.2 mg sid, or (D) combination of tamsulosin and diclofenac sodium. Analgesic effects were assessed with the Visual Analog Scale (VAS). Relationships among variables were assessed using one-way ANOVA and post hoc tests.

**Results:** The surgical procedure for ureteral stent removal consisted of 48 (60%) male and 32 (40%) female. The average age of group A, B, C, and D were 51.0, 51.9, 47.6, and 47.3 years, and the average stent dwell time was 6.3 weeks. VAS values of the entire experimental group were lower than the control group on the first day until the second day after the stent removal ($p < 0.05$). In the experimental group, there was no difference between group B and C ($p > 0.05$). Group D showed better analgesic effects than group B and C ($p < 0.05$). No severe side effects were observed.

**Conclusion:** The result shows that combination therapy of diclofenac sodium and tamsulosin is better in reducing the pain after ureteral stent removal compared to the admission of a single placebo, tamsulosin, or diclofenac sodium therapy.

**Keywords:** tamsulosin; diclofenac sodium; pain; stent removal

## INTRODUCTION

Ureteral stents are now commonly used by urologists, but the usage of ureteral stents often causes significant morbidity for patients. Some patients experience pain and urinary disorders during stent use.[1] Several studies have been conducted to determine the complications after stent removal. As many as 64% of patients undergoing stent removal reported complaints, including pain, hematuria, frequency, urgency, or fever, with pain as the most common one.[2] Thirty-two percent of patients reported delayed severe pain after they had their ureteral stent removed, and 9% visited the intensive care unit.[3]

Pain management in transurethral postoperative patients is an issue of concern. In general, postoperative regional and local anesthesia have both the advantages and disadvantages for patient morbidity.[4] Therefore, those type of anesthesia is replaced by oral and topical analgesics such as opioids, sedatives and non-steroidal anti-inflammatory drugs (NSAIDs) for irritation and pain management of postoperative urological endoscopy.[5] Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used drugs that have antipyretic and analgesic effects. This drug works in alleviating the postoperative pain by preventing the production and release of prostaglandins.[6] Diclofenac sodium is one of the recommended types of NSAIDs for postoperative urological endoscopy patients.[7] Research on pain perception after stent removal is very limited in number. In a previous study, it was mentioned that the administration of a single dose of the non-steroidal anti-inflammatory drug (NSAID) prevented severe pain after the removal of a ureteral stent.[8] Other studies stated that the combination of silodosin and diclofenac sodium was effective in reducing pain after ureteral stent removal.[9] The combination of tamsulosin and propiverine also decreased irritative voiding symptoms, suprapubic pain and improved the quality of life of the patients with DJ stent.[10-11] Tamsulosin is an $\alpha 1$ selective blocker drug. Alpha 1 receptors distributed in the prostate, bladder, and ureter. The use of tamsulosin can cause a decrease in ureteral contractions, as well as reduce irritation in the trigone area. This is a mechanism for reducing pain in pain caused by ureteric stents in the use of tamsu-

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**Table 1.** Patient characteristic

| Variable | Overall | (A) Placebo | (B) Diclofenac | (C) Tamsulosin | (D) Combination |
|---|---|---|---|---|---|
| Age (year), Mean (SD) | 49.6 (11.7) | 51.0 (13.1) | 51.9 (10.6) | 47.6 (11.4) | 47.3 (11.8) |
| Stent insitu duration (week), Mean (SD) | 6.3 (2.8) | 6.0 (2.4) | 66 (30) | 5.5 (2.5) | 6.9 (3.1) |
| Gender, n (%) | | | | | |
| • Male | 48 (60) | 9 (45) | 11 (55) | 13 (65) | 13 (65) |
| • Female | 32 (40) | 11 (55) | 9 (45) | 7 (35) | 7 (35) |
| Stent location, n (%) | | | | | |
| • Right | 44 (55) | 14 (70) | 10 (50) | 11 (55) | 9 (45) |
| • Left | 36 (45%) | 6 (30) | 10 (50) | 9 (45) | 11 (55) |
| Diagnose, n (%) | | | | | |
| • Renal stone | 26 (32,5) | 6 (30) | 6 (30) | 8 (40) | 8 (40) |
| • Ureteral stone | 54 (67,5) | 14 (70) | 14 (70) | 12 (60) | 12 (60) |
| Previous operation, n (%) | | | | | |
| • Endourology | 43 (53,8) | 11 (55) | 9 (45) | 10 (50) | 10 (50) |
| • Open surgery | 37 (46,3) | 9 (45) | 11 (55) | 10 (50) | 10 (50) |
| VAS score after removal stent, n (%) | | | | | |
| • < 3 | 39 (48,7) | 1 (5) | 13 (65) | 9 (45) | 16 (80) |
| • 3-5 | 38 (47,5) | 18 (90) | 7 (35) | 9 (45) | 4 (20) |
| • >5 | 3 (3,7) | 1 (5) | 0(0) | 2 (10) | 0 (0) |
| Complication | | | | | |
| • Colic Pain | 3 (3,7) | 2 (10) | 1 (5) | 0 (0) | 0 (0) |
| • Hematuria | 4 (5) | 2 (10) | 1 (5) | 1 (5) | 0 (0) |
| • Frequency and urgency | 4 (5) | 4 (20) | 0 (0) | 0 (0) | 0 (0) |
| • No complication | 69 (86,2) | 12 (60) | 18 (90) | 19 (95) | 20 (100) |

losin.[12-14]

The study examined the patient's complaints, and Visual analog score (VAS) score after removal of DJ stents. This study was conducted to determine the effect of tamsulosin and diclofenac sodium use on pain perception of patients after ureteral stent removal

## METHODS

### *Study Design*

This study was a prospective, randomized, double-blind, placebo-controlled trial. The number of samples is determined based on comparative numerical analysis. The study compared the analgesic effects following endoscopic removal ureteral stent surgery. Pain perception was assessed from the first day until the second day following surgery. Analgesic drugs were administered for two days following surgery. The analgesic effects were assessed using the Visual Analog Scale (VAS). All patients above 17 years and below 55 years undergoing unilateral ureteral stenting following renal and ureteric stone surgery were included. No history was presented of psychotic mental illness, organic psychiatric conditions, and other mental illnesses, severe pain-induced illnesses and malignancy. Patients with open surgery conversion, history of peptic ulcer disease, liver impairment, chronic renal failure, coronary artery disease, bleeding diathesis, asthma, urinary tract infections (UTI), chronic painful conditions like arthritis, pregnancy, allergy to medications, significant lower urinary tract symptoms (LUTS) and use of alpha-blockers and residual calculus were excluded. Patients with complications during stent removal like hematuria and mucosal injury were also excluded. The study was initiated after obtaining the approval of the Institutional Ethics Committee at Kardinah Hospital. Ref: 071/001/2017.

Interventions

The patients who underwent endoscopic surgery removal ureteral stent at Urology health center Kardinah Hospital, Tegal from January 2017 to April 2017

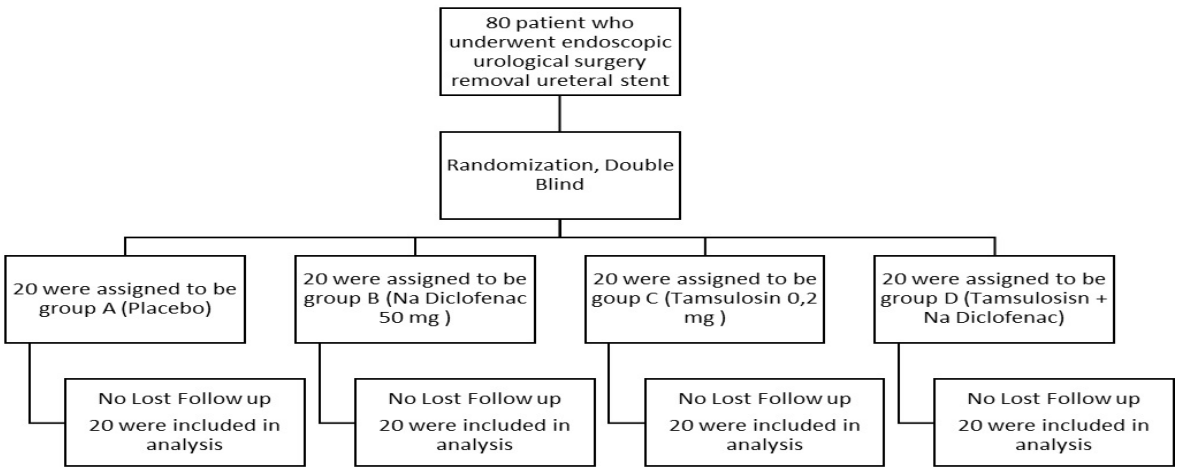


**Figure 1.** Flowchart of randomized control trial study design

**Table 2.** VAS Mean Score Before-After removal stent

| Condition | Placebo | Na Diclofenac | Tamsulosin | Combination |
|---|---|---|---|---|
| Pre-Op | 0,9 | 0,7 | 0,95 | 1,1 |
| Post Op Day 1 | 4 | 2,45 | 2,65 | 1,85 |
| Post Op Day 2 | 2,4 | 1 | 1,15 | 0,55 |

were included. The experimental groups (B, C, and D) consisted of 20 patients in each group, and the control group also (A) consisted of 20 patients.

In control group A, patients were administered vitamin tablet containing folic acid tid for two days. In group B, patients were administered diclofenac sodium 50 mg twice a day for two days. In group C, 0.2 mg of tamsulosin was applied once a day for two days. Group D was administered combination diclofenac 50 mg twice a day and tamsulosin 0,2 mg once a day for two days. All medications were placed in a numbered envelope as per the computer-generated model. All patients received a single dose of levofloxacin 500 mg before stent removal as per our department protocol. All patients and investigators were blinded to the medicine identity and randomization design until the end of the study. Visual analog score (VAS) was taken on a scale from zero to ten, zero meaning no pain to 10, meaning excruciating pain. The surgeon removing the stent was also blinded about the grouping. Stent removal was performed under local anesthesia using 2 % xylocaine jelly under vision with 15 Fr cystoscope. The stent used in this study was a double j stent with a diameter of 5 Fr and a length of 26 cm.

All patients were contacted after 24 h and 48 h. VAS score, additional medications requirement, and site of pain, and any other relevant parameters were recorded.

### *Statistical Analysis*

Age, gender, week of ureteral stenting, stent location (right or left), diagnosis, previous surgery, patient satisfaction, adverse events, patient complaints, and VAS scale for each patient were recorded. Statistical analysis of data that is normal and homogeneously distributed then followed by a one way ANOVA parametric test. However, if it does not meet the requirements for a parametric test, then a non-parametric test, namely Kruskal-Wallis, followed by the Mann Whitney post-hoc analysis to see the differences between treatment groups was employed. A p-value of less than 0.05 was considered to be statistically significant

## RESULTS

In this research, 80 patients who met the inclusion criteria were divided into four study groups. The average age of the entire sample was 49.6 years involving 48 male patients and 32 female patients. Primary data analysis included the length of stents dwell times, stent placement, diagnosis, types of operation, VAS score < 3, 3-5, >5 and complication after up DJ stent were recorded the entire groups. Characteristics of the patients are tabulated in **Table 1**.

In the four groups, the VAS score was analyzed after stent removal. The assessment was performed at 24 hours and 48 hours post-operation. At 24 hours after stent removal, the mean VAS scores in the placebo group were 4.0; diclofenac sodium group was 2.4, tamsulosin group was 2.6, and the combination group was 1.8. Furthermore, at 48 hours after stent removal measurement, the mean VAS score in the placebo group was 2.5, the diclofenac sodium group was 1.0, the tamsulosin group was 1.1, and combination group was 0.5 (**Table 2**). In the post hoc analysis, there was a significant difference in the VAS score of the combination therapy group compared to the entire group (**Table 3**; $p < 0.05$).

## DISCUSSION

Pain management is currently a significant issue among urologists. Unrelieved pain can be a major medical

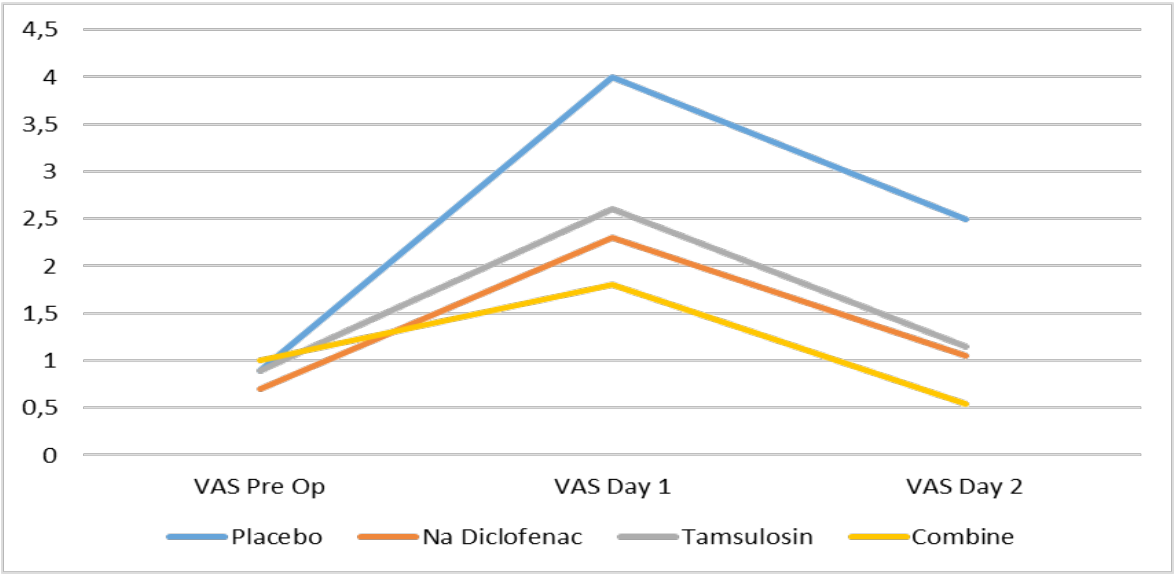


**Figure 2.** Pain scale graphic

**Table 3.** Post Hoc analysis

| | | p value VAS score | |
|---|---|---|---|
| | | Day 1 | Day 2 |
| Combination | Placebo | 0.000 | 0.000 |
| | Tamsulosin | 0.039 | 0.039 |
| | Diclofenac | 0.234 | 0.020 |
| Tamsulosin | Placebo | 0.000 | 0.000 |
| | Diclofenac | 1.000 | 0.951 |
| Diclofenac | Placebo | 0.000 | 0.000 |

problem. In the late 1990s, pain management in the transurethral surgical procedures was established. [6,11] However, many urologists did not understand yet how to address the post-operative acute pain problems in patients undergoing endoscopic surgery. The primary goal of endoscopic post-operative pain management is to overcome the pain with minimal side effects of drugs.[11,15]

The use of a ureteral stent is significantly associated with the pain and discomfort experienced by the patient.[1] In patients with a history of Double-J insertion, the perception of Catheter-Related Bladder Discomfort (CRBD) is less in comparison with patients without such a history.[22]

As many as 80% of patients reported experiencing pain due to stent.[1] In another study, 64% of patients who underwent ureteral stent removal reported complaints, including pain, hematuria, frequency, urgency or fever, and the major complaint was pain.[2] Several studies have been conducted to reduce the pain and discomfort caused by ureteral stent use by using alpha-blocker, anti-cholinergic, and phosphodiesterase inhibitor as well as the design, material and dimension of the stent. [10,16-19] Almost all the existing literature focus on the morbidity of the ureteral stent when the stent is in situ. Frequently, the urologists have patients with colic-like pain after ureteral stent removal, requiring additional analgesic and hospitalization for severe pain cases. Previous studies reported that as many as 32% of patients complained about the delayed severe pain after ureteral stent removal, and 9% returned to the intensive care unit to be treated.[3] In this study, pain assessment was performed using VAS score at 24 hours and 48 hours after ureteral stent removal. The administration of diclofenac sodium, tamsulosin, and the combination of both significantly reduced pain after stent removal compared to placebo ($p < 0.001$). This result lasted up to 24 hours and 48 hours after the operation.

Pain during ureteral stent removal is due to the activation of the nociceptor. Friction between the stent and ureteral mucosa irritates the ureteric smooth muscle, trigonal irritation, and induces pressure changes in the pelvicocalices system.[9] Tamsulosin is a selective α1 blocker drug. Alpha 1 receptors are distributed in the prostate, vesica urinaria, and ureter. The use of tamsulosin may cause a decrease in ureteral contraction as well as reducing irritation in the trigonum area. It is a pain-reducing mechanism for the pain caused by ureteral stent.[18-20] Diclofenac sodium is one recommended type of NSAIDs for post-operative urological endoscopy patients, and it is a standard drug in renal colic. [7] COX inhibitors and Non-selective COX inhibitors, significantly reduce ureteral contraction in the human and porcine ureter.[20] In addition, the use of diclofenac sodium drugs can reduce renal blood flow resulting in analgesic and anti-inflammatory effects.[21]

There was no significant difference in VAS score between the diclofenac sodium group and the tamsulosin group ($p > 0.05$). In the diclofenac group, the mean VAS score was lower than that of tamsulosin. At 24 hours post-operative, VAS score of the diclofenac sodium group was 2.4 and 2.6 in the tamsulosin group. At 48 hours post-operative, VAS score of the diclofenac sodium group was 1.0 and 1.1 in the tamsulosin group. These results were consistent with the previous studies which stated that there was no significant difference in VAS score in the diclofenac sodium group and alpha-blocker silodosin.9 The incidence of pain with VAS score of $\geq 3$- $\leq 5$ was the most prevalent in the placebo group (90%). In the diclofenac sodium group and tamsulosin group, the score was 35% and 55% respectively. While in the combination group, the incidence of pain with a VAS score of $\geq 3$- $\leq 5$ was 20%, and VAS score > 5 was 0%. These results suggest that the occurrence of severe pain can be prevented by providing a combination of diclofenac sodium and tamsulosin.

In this study, the admission of combination therapy was better in reducing the VAS score of 24 hours and

**Table 4.** Comparison of research results [8,9,10]

| Characteristic | Our study | Gangkak et al., 2016[9] | Irfansyah et al., 2016[10] | Tadros et al., 2012[8] |
|---|---|---|---|---|
| Study design | Prospective, double blinded randomized control trial study | Prospective, double blinded randomized control trial study | Prospective, single blinded randomized control trial study | Prospective, double blinded randomized control trial study |
| Regiment | Diclofenac sodium and tamsulosin | Diclofenac sodium and silodosin | Tamsulosin and propiverine HCL | Rofecoxib |
| Total sample | 80 | 240 | 30 | 22 |
| VAS measure | 24 hours dan 48 hours post surgery | 24 hours post surgery | While stent insitu and 24 hours post surgery | 24 hours post surgery |
| Conclusiom | Combination therapy of diclofenac sodium and tamsulosin is better in reducing the pain after ureteral stent removal compared to the admission of single placebo, tamsulosin, and diclofenac sodium therapy | Combination therapy of diclofenac sodium and silodosin did not differ significantly compared to the admission of singe silodosin and sodium diclofenac therapy | Tamsulosin is better compared to Propiverine HCl in reducing pain, but Propiverine HCl is better at increasing QoL and decreasing IPSS score | Rofecoxib single therapy prior to stent release prevents severe pain post-release of ureteral stent |

48 hours postoperatively, compared with other groups ($p < 0.05$). We did not find any significant side effects on the combination therapy of diclofenac sodium and tamsulosin. The most common side effect of the administration of diclofenac sodium was gastrointestinal symptoms. In this study, we did not find any significant gastrointestinal complaints and urinary complaints (colic pain, hematuria, and frequency-urgency) in the use of drug combinations sodium diclofenac 50 mg twice daily and tamsulosin 0.2 mg once daily for two days.

When compared to previous studies, this study did not only evaluate the 24 hours post-operative pain scores, but it continued the evaluation until 48 hours postoperation.[9] The results of combination therapy remained better in reducing the 48 hours post-operative pain of the VAS score. Results and conclusions in this study, compared with other researches, is presented in **Table 4**.

This study, nevertheless, has some disadvantages. First, in this study, the numbers of randomized samples are few, and the population of this study are limited to a district hospital in central java only. Future researches are expected to develop the types of therapy and surgery techniques that can significantly reduce the pain after ureteral removal.

## CONCLUSIONS

Our study showed that the combination therapy between diclofenac sodium and tamsulosin is better in reducing pain after ureteral removal than placebo, tamsulosin, and diclofenac sodium admission.

## CONFLICT OF INTEREST

The authors reported no potential conflict of interest.

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