

# Efficacy of preprocedural diclofenac in men undergoing double J stent removal under local anesthesia: A double-blind, randomized control trial

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## ABSTRACT

**Introduction:** Double J (DJ) stents are often removed under local anesthesia using a rigid cystoscope. Patients experience significant pain during this procedure and also continue to have discomfort during voiding for a few days. We assessed the efficacy and safety of preemptive oral diclofenac in pain relief in patients undergoing DJ stent removal (DJSR) by rigid cystoscopy compared to placebo.

**Methods:** Consecutive consenting male patients undergoing DJSR under local anesthesia between March 2014 and July 2015 were enrolled. Patients were randomized to receive 75 mg oral diclofenac (Group A) or placebo (Group B) 1 h before procedure by double-blind randomization. Intraurethral 2% lignocaine gel (25 ml) was used in both groups. Pain during rigid cystoscopy, pain at the first void, and at 24 h after cystoscopy was assessed using visual analog scale (VAS) (0–100). Adverse reactions to diclofenac and episodes of acute urinary retention, if any, were assessed (Trial registered at [clinicaltrials.gov](http://clinicaltrials.gov): NCT02598102).

**Results:** A total of 121 males (Group A [ $n = 62$ ]; Group B [ $n = 59$ ]) underwent stent removal. The median (Interquartile range) VAS during the procedure in Group A was 30 (30) and Group B was 60 (30) ( $P < 0.001$ ), at first void was 30 (30) and 70 (30) ( $P < 0.001$ ) and at 24 h postoperatively was 20 (20) and 40 (20) ( $P < 0.001$ ). The incidence of epigastric pain, nausea, vomiting, and acute urinary retention was comparable in the two groups ( $P > 0.05$ ).

**Conclusions:** A single oral dose of diclofenac administered 1 h before DJSR using rigid cystoscope under intraurethral lignocaine anesthesia decreases pain significantly during and up to 24 h postprocedure with minimal side effects.

## INTRODUCTION

Double J (DJ) stents are frequently removed under local anesthesia using a rigid cystoscope. Patients experience significant pain during the procedure and discomfort during voiding for few days. Lignocaine gel during this procedure has not been found to very effective.<sup>[1–5]</sup> Zaltoprofen during check cystoscopy after transurethral resection (TUR) of bladder tumor (TURBT) has been proven to be more effective than lignocaine intraurethral analgesia.<sup>[5]</sup> Numerous reports exist on the effect of local anesthesia against cystoscopy-associated

pain, but so far there has been no objective evaluation of the preemptive analgesic effect of nonsteroidal anti-inflammatory drugs (NSAIDs).<sup>[1,2]</sup> Hence, this study was undertaken to assess the effect of preemptive oral diclofenac in pain relief in patients undergoing DJ stent removal (DJSR) by rigid cystoscopy when compared to placebo and to assess the safety of oral diclofenac.

## METHODS

### Trial design

This was a hospital-based, double-blind, randomized, placebo-controlled trial, performed in 121 patients

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undergoing DJSR using rigid cystoscope in the department of Urology. After obtaining approval from the Institute Research Review Board and Ethics Committee, the study was conducted from March 2014 to August 2015. This trial was retrospectively registered in clinicaltrials.gov (NCT02598102) in March 2015.

### Participants

All consecutive male patients aged more than 18 years, undergoing DJSR under local anesthesia (2% lignocaine gel), were eligible for the study after providing a written informed consent. DJ stents were inserted under anesthesia for renal calculi for extracorporeal shockwave lithotripsy or after percutaneous nephrolithotomy or ureterorenoscopy for ureteric calculi. The exclusion criteria were age <18 years, inability to understand visual analog scale (VAS) for pain, lower urinary tract symptoms (LUTS) before initial surgery, prostatitis or urethral stricture during cystoscopy, renal failure (serum creatinine >1.5 mg/dl), concomitant usage of nephrotoxic drugs, history suggestive of or known case of peptic ulcer disease or upper gastrointestinal bleed or upper abdominal surgeries, patients undergoing bilateral DJSR, and loss to follow-up at 24 h of DJSR.

### Randomization, allocation concealment, and blinding

Patients were randomized to receive oral diclofenac 75 mg or placebo by block randomization (block size of 10) performed using Microsoft Excel 2010. Allocation concealment was performed using serially numbered opaque sealed envelope technique. Randomization and sealed envelopes were prepared by a person independent of the investigators, and the urologist involved in patient care. Envelopes were opened on the day of surgery outside the operating room by a nursing staff not involved in the research. The drug was placed in sealed envelope with the code, and the drug and placebo were of similar color and size. The patient and the investigator who assessed the outcome (pain) were also blinded. Hence, the study was double-blind. At the end of the study, the groups were decoded and analyzed [Figure 1].

### Intervention

A standard protocol was used for all our patients. All patients were administered the drug or placebo 1 h before the scheduled procedure. A 17.5F cystoscope (Richard Wolf Medical Instruments Corporation, United States) was used for DJSR in all patients. 25 ml of 2% lignocaine gel was injected intraurethraly and was allowed to act for 10 min. Cystourethroscopy was performed using the standard technique. The bladder was partially filled with 0.9% normal saline irrigant, and the DJ stent was visualized and removed with a flexible DJSR forceps. Postoperative pain intensity was evaluated with the 100-point VAS.<sup>[6,7]</sup> VAS was assessed at DJSR, first void, and 24 h after DJSR. The presence of nausea, vomiting, epigastric pain, and urinary

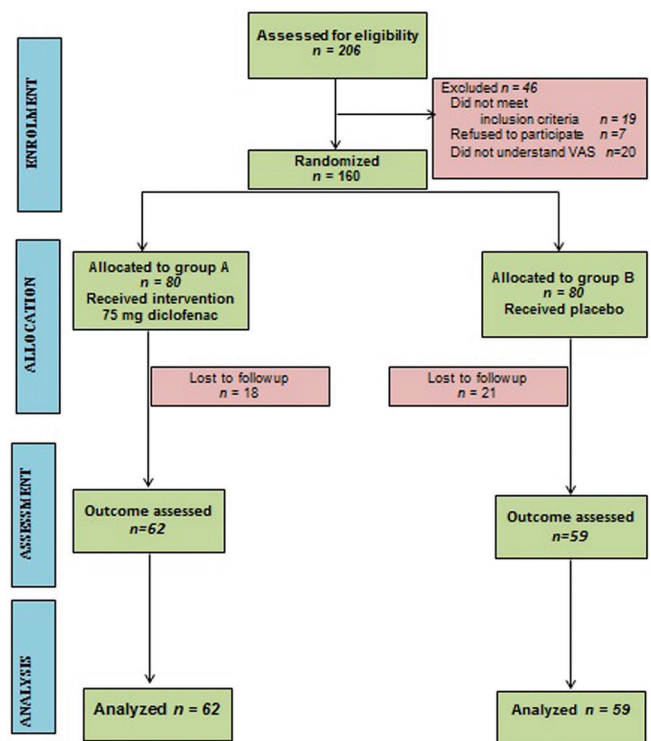


Figure 1: CONSORT diagram for the trial. VAS = Visual analog scale, A = Patients receiving diclofenac, B = Patients receiving placebo

retention was recorded. Complications of the procedure and to the drug were studied.

### Outcomes

The primary outcome variable was the VAS pain scores at various time intervals. The secondary outcome variables were side effects to drug and urinary retention. Other parameters studied included patient-related factors such as demographic data, side of DJ stent (left or right), and duration of stent and surgery-related factors such as duration of procedure.

### Statistical analysis

Statistical analysis was performed using SPSS version 20 for Windows (IBM Corp., Armonk, NY, USA). The variables were summarized using mean and standard deviation, median with interquartile range (IQR), and percentages based on the characteristics of the variable. Independent samples *t*-test or Mann–Whitney *U*-test as appropriate was used based on the normality of the distribution. Chi-square/Fisher's exact test was used for categorical variables. The  $P < 0.05$  was considered statistically significant.

## RESULTS

For the purpose of tabulation and analysis, the groups were denoted as Group A receiving 75 mg of oral diclofenac and control Group B receiving placebo. The baseline patient characteristics such as age, side, weight, duration of stent, and operative time were comparable [Table 1].

## Pain

The median VAS was lower in the Group A during, at first void, and 24 h after DJSR using rigid cystoscope. Using Mann–Whitney U-test, statistically significant difference was observed between Groups A and B [Table 2].

## Adverse reactions

The incidence of epigastric pain, nausea and vomiting were slightly higher in the patients receiving diclofenac. None of the patients developed acute urinary retention. Using Chi-square test, there was no statistically significant difference between proportions of patients developing complications in both the groups [Table 3].

## DISCUSSION

Rigid cystoscopy is still commonly used in office urology mainly due to its lower cost than flexible cystoscopy. This study was performed to assess if diclofenac is effective in reducing pain during DJSR using rigid cystoscopy to standardize conditions and its application can possibly be extrapolated to surveillance in bladder cancer.

Pain associated with surveillance cystoscopy has been reported to be less than that of DJSR. However, with plain gel, median (IQR) VAS of 38 (36) with maximum of up to 80 has been reported for flexible cystoscopy.<sup>[1]</sup> Improving analgesia during cystoscopy can improve the compliance for surveillance in bladder tumors. Preemptive analgesia before

cystoscopy under local anesthesia should be considered as the standard of care to reduce pain experienced by the patient, as patients undergoing repeated procedures do not develop tolerance. However, in patients undergoing cystoscopy for diagnostic purpose or in check cystoscopy following TUBRT, it may be difficult to standardize the procedure and timing of the procedure because of preexisting LUTS, dysuria, and voiding difficulties, stricture urethra which may need additional procedure and other problems.

We identified a unique cohort of patients who usually have undergone an endoscopic procedure in the form of ureteroscopy, DJ stenting, or percutaneous nephrolithotomy and had a DJS placed within 1 month before stent removal and did not have any other lower urinary tract pathology. We also excluded patients with prostatitis, LUTS after the initial surgery, or a stricture during the DJSR. This was done to ensure comparability between patients and to minimize confounding factors.

Zaltoprofen has been used in follow-up cystoscopy after TURBTs for nonmuscle invasive bladder cancers.<sup>[5]</sup> They found no correlation between pain score and number of TURs or time from the surgery. Repeated cystoscopy for postoperative follow-up has not found to increase of the patient's tolerance to the pain.<sup>[5]</sup> More effective anesthesia is necessary to improve their tolerability during the procedure and maintain the quality of life. Lignocaine gel has obviously not been more useful than plain gel.<sup>[2-4]</sup> Numerous reports on the effect of local anesthesia against cystoscopy-associated pain, but so far there has been no objective evaluation of the preemptive analgesic effect of NSAIDs.<sup>[2,5]</sup>

Significant decreases of the pain score with zaltoprofen as compared with lignocaine gel alone during insertion of the rigid cystoscope into the urethra, viewing inside the urinary bladder, and the first urination after cystoscopy. No significant decreases were seen in the pain felt during injecting 2% lignocaine gel into the urethra and during the first urination in the following morning at home when analyzed using the data from all patients. Pain score during insertion of the cystoscope was largest, followed by the first and second urination after cystoscopy, during the cystoscopy itself, injection of gel, and urination the day after cystoscopy.<sup>[2]</sup> We found that oral diclofenac was effective in reducing pain during stent removal and up to 24 h after the procedure in our patients.

Nitrous oxide inhalation via entonox or air was used in flexible cystoscopy in men <55 years and all procedures were done under intraurethral 2% lignocaine gel.<sup>[8,9]</sup> Patients receiving entonox had lesser pain scores, however with more complications but transient. Patients receiving air needed significantly more analgesia and general anesthetic if repeat cystoscopy was needed. Lignocaine gel has been shown to have minimal effect in many studies in flexible

**Table 1: Baseline patient and operative characteristics**

Patient characteristics	Groups		P
	A (n=62)	B (n=59)	
Age, mean±SD (years)	47.5±9.76	46.05±9.12	0.22
Right:left (n)	41:21	30:29	0.47
Duration of stent, mean±SD (days)	20.93±5.36	21.36±5.45	0.87
Weight, mean±SD (kg)	51.35±10.12	51.75±10.49	0.18
Duration of procedure, mean±SD (min)	2.30±1.20	2.50±1.31	0.63

SD=Standard deviation

**Table 2: Visual analog pain scores during and at first void and 24 h after double J stent removal**

Timing	Visual analog scale		P
	A (n=62)	B (n=59)	
Pain during procedure, median (IQR)	30 (30)	60 (30)	<0.001
Pain during first void, median (IQR)	30 (30)	70 (30)	<0.001
Pain after 24 h, median (IQR)	20 (20)	40 (20)	<0.001

IQR=Interquartile range

**Table 3: Proportion of patients developing adverse reactions after double J stent removal**

Adverse reactions	Number of patients, n (%)		P
	A (n=62)	B (n=59)	
Epigastric pain	10 (16)	6 (10)	0.08
Nausea and vomiting	8 (13)	5 (8.5)	0.06

cystoscopy.<sup>[10,11]</sup> Ureteroscopic stent removal of mildly upmigrated DJ stents (below pelvic brim) was performed under 2% intraurethral lignocaine gel or no anesthesia.<sup>[12]</sup> They showed that ureteroscopy was similarly painful in males and females. Flexible cystoscopy was more painful in men. This was attributed to longer urethra in males. We took only males in this study as we wanted to avoid the effect of urethral length in assessing the efficacy of diclofenac.

Dexmedetomidine-remifentanyl and midazolam-remifentanyl have been tried in postoperative cognitive functions in cystoscopy under monitored anesthesia care (MAC) in a day care setting.<sup>[13]</sup> Dexmedetomidine-remifentanyl combination was observed to affect the cognitive functions lesser than midazolam-remifentanyl and with shorter recovery times. However, sedation may result in unresponsiveness, respiratory depression which may be more with benzodiazepines. Pethidine and alfentanil have also been used in the past for cystoscopy.<sup>[14,15]</sup>

Pain prevention was introduced into clinical practice by Crile in 1913 and further developed by Wall and Woolf.<sup>[16,17]</sup> Preemptive analgesia is an antinociceptive treatment that prevents the establishment of altered central processing of afferent input which amplifies postoperative pain.<sup>[18]</sup> It has been defined as analgesic intervention provided before surgery to prevent or reduce subsequent pain.<sup>[19]</sup>

Surgical trauma induces cyclooxygenase-2 (COX-2) enzyme causing release of prostaglandins, which sensitize the peripheral nociceptors and produce localized primary hyperalgesia. This resultant central sensitization produces pain hypersensitivity in the surrounding uninjured tissue.<sup>[19]</sup> After nociception, central sensitization induces c-Fos expressed in spinal dorsal neurons which augments the nociceptive sensitivity. Wind-up is the mechanism of central sensitization, mainly by the activation of N-methyl-D-aspartate (NMDA) and neurokinin receptors. Preoperative NSAIDs before tissue trauma set in prevent the development of hyperalgesia.<sup>[19]</sup>

NSAIDs, by inhibiting the early production of prostanoids before surgical trauma more effectively, prevent the development of both peripheral and central sensitization and hyperalgesia. They also block the nociceptive impulses, increase the threshold of nociceptive neurons by opioids, block the wind-up using NMDA receptor antagonists, and suppress local inflammation. It is possible to produce a painless postsurgical state with NSAIDs.<sup>[18-20]</sup>

Diclofenac and zaltoprofen have similar pharmacokinetic profiles. They are orally absorbed and highly protein bound. They are highly protein bound and metabolized by UGT2B7 and CYP2C9. Most of the drug is biotransformed to glucuroconjugated, and sulfate metabolites which are inactive, and only a small fraction is eliminated in urine in its

unchanged form. Diclofenac and zaltoprofen have found to have no local effect in the urinary tract.<sup>[21,22]</sup> However, in this study, only diclofenac was used. Diclofenac is a nonspecific COX inhibitor. Since patients are preemptively treated with diclofenac, inflammation incited by the stent removal procedure is lesser, and consequently, pain incited is lesser. In our study, pain assessment by VAS was done up to 24 h.

### Limitations

DJSRs in our study were not done by a single surgeon as it was a teaching institute. However, procedure time was taken into account to counteract this, and the procedure time was similar in both groups. Use of 2% lignocaine gel was a possible confounder. The studies have proven lignocaine alone to be ineffective, and an equal amount of gel was used in both groups thus they were comparable.

### CONCLUSIONS

A single oral dose of preemptive diclofenac administered 1 h before DJSR performed using rigid cystoscope under intraurethral lignocaine anesthesia decreases pain significantly during and up to 24 h postprocedure with minimal side effects and can be safely prescribed for office DJSR procedures.

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