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Original article

The effect of diclofenac sodium on bladder detrusor contractility and its clinical implication

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Background: Overactive bladder symptom (OAB) seriously influences a person's life including mobility, work-related activities, sleep, domestic, and sexual life. Many patients with OAB symptoms have insufficient improvement from usual treatment.
Objective: To investigate the effects of Diclofenac Sodium **(**DS) on bladder detrusor contractility and on the clinical symptoms associated with detrusor over-activity of patients following prostatectomy.
Methods: Bladders dissected from guinea pigs were used to study the effect of DS on uninhibited bladder contractions *in vitro.* Bladder detrusor contraction was evoked by histamine. The tension of bladder detrusor and the frequency and amplitude of bladder detrusor contraction were measured. *In vivo* efficacy of DS was then measured in patients after prostatectomy by using the symptom scoring system and by detecting the duration of the efficacy.
Results: DS significantly inhibited the contraction of detrusor evoked by histamine in a dose-dependent manner. The inhibition of bladder detrusor contraction by DS was statistically significantly stronger compared to that by normal saline (NS) and was analogous to that by verapamil *in vitro*. The total effective rates of DS were a little higher than intravenous verapamil *in vivo*. The complete remission rate and the mean effect-lasting time of rectal diclofenac were significantly higher than that of intravenous verapamil. No significant side effect was observed in patients with DS treatment.
Conclusion: DS significantly inhibited the contraction of bladder *in vivo* and *in vitro*. DS could act as a useful agent for the relief of overactive bladder symptom post-prostatectomy.

Keywords: Bladder detrusor contraction, diclofenac sodium, guinea pig, overactive bladder symptom, patients following prostatectomy

Uninhibited bladder contractions symptoms, which were defined by the International Continence Society (ICS) as overactive bladder (OAB) symptoms, consist of the presence of urinary urgency, with or without urge incontinence, usually with frequent micturition and nocturnal [1]. The OAB symptoms can directly influence a person's mobility, increase the degree of social isolation, impair work-related activities, disrupt sleep, and impair domestic and sexual life, and result in depression [2, 3]. Diclofenac, derived from benzene acetic acid, is a non-steroidal anti-inflammatory drug (NSAID) that is usually present as sodium or potassium salt with potent anti-inflammatory, analgesic, and antipyretic properties [4]. The mechanism of its action is principally associated with the inhibition of prostaglandin synthesis, especially the inhibition of cyclo-oxygenase [5]. Diclofenac has been demonstrated to be an effective treatment in a series of diseases including acute and chronic arthritis, rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and migraine [6-8]. Reports by Kuznetsova AA et al. showed that administration of diclofenac sodium (DS) before bed-time eliminated episode of nocturnal enuresis in children [9]. Both *in vitro* and *in vivo* experiments have confirmed that it has apparent inhibitive effects on upper urinary smooth muscle contraction [10, 11]. However, little information on its effects on bladder detrusor contraction is available in the literature until recently.

In the present study, we set out to investigate effects of DS on contraction of bladder detrusor. An *in vitro* model for bladder detrusor contraction was developed in bladders from guinea pigs so that the effects of DS on the drop of tension of bladder detrusor and the inhibition of the contraction of bladder detrusor

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were observed. In vivo efficiency of DS on the inhibition of bladder detrusor contraction in patients following prostatectomy was then studied.

Materials and methods

Drugs

DS mucilage (100 mg/piece) with 2% sodium carboxymethyl cellulose as the base was obtained from Lanzhou Medical College Pharmaceutical Factory. Verapamil injection (10 mg/piece) was obtained from and Jiangsu Xinghua Pharmaceutical Factory.

Animal experiment

Forty-eight healthy adult guinea pigs weighing 400 to 500 g were stunned and bled. The bladder was removed, and muscle strips with the size of 10 mm × 3 mm were removed. The muscle strips were suspended in tissue trough filled with oxygenated Krebs solution at 37^{O}C. DS was added when contraction of muscle strip was induced 20 to 30 seconds after 1 ml of 0.02% histamine addition to the tissue. Verapamil and normal saline (NS) were included as positive and blank control, respectively. The muscle strips of 10 guinea pigs treated with 0.075 mg/ml DS were defined as low dose group (LDG). The muscle strips of 10 guinea pigs treated with 0.15 mg/ml DS were defined as medium dose group (MDG). The muscle strips of 10 guinea pigs treated with 0.3 mg/ml DS were defined as high dose group (HDG). The muscle strips of 10 guinea pigs treated with 8.33 μg/ml verapamil were defined as verapamil group (VG). The muscle strips of eight guinea pigs treated with NS were defined as NS group (NSG). One end of the muscle strip was placed on the fixed hook, while another end on the tension transducer. The contractibility of muscle was recorded with a two-channel physiological recorder (LMS-2B, Chengdu Apparatus Manufacturing Ltd., Chengdu, China). No spontaneous contractions were recorded. Tension drop = the tension of the bladder detrusor before the treatment of the drug – the tension of the bladder detrusor after the treatment of the drug. Inhibition rate of contraction frequency (%) = 100 – {the frequency of the bladder detrusor contraction during five minutes after the treatment of the drug (converted to the frequency per unit time) / the frequency of the contraction during five minutes before the treatment of the drug (converted to the frequency per unit time) × 100}. Inhibition rate of contraction amplitude (%) = 100 – {the contraction amplitude of the bladder detrusor after the treatment of the drug / the contraction amplitude of the bladder detrusor before the treatment of the drug × 100}. All experiments performed on animals were approved by the Institutional Animal Care and Use Committee of Shanghai First People's Hospital.

Patient recruitment and therapy

Fifty-eight patients post-prostatectomy aged 52 to 80 years were included in this study. Patients with allergy to aspirin, low blood pressure, cardiac insufficiency, or atrioventricular/bundle branch block were excluded. Of the 58 patients, 46 had routine transurethral resection and 12 suprapubic prostatectomy. All the patients had an indwelling Foley's catheter (Fr 24). All subjects gave informed written consent and the study was approved by the Ethics Committee of the Shanghai First People's Hospital. Single-blind alternative delivery was randomly applied to the patients. 100 mg of DS mucilage was administered rectally. 10 mg of verapamil dissolved in 20 ml of glucose solution was administered intravenously. Alternative use of the two agents was given only if one drug had no effect one hour after treatment. The Drug was applied to patients with relapse or without improvement of OAB symptoms with intervals of one hour. Electrocardiogram and blood pressure measurements were performed before and after the treatment. Symptoms of sense of urinating, bladder spasm, or acute incontinence before and after the treatment of the drug were recorded. Side effects were recorded as well. The symptom scoring system was used for clinical efficacy scoring (**Table 1**). According to changes in the symptoms induced by the drug, the efficacy was divided into three grades; 1) Markedly effective: symptoms disappeared completely after treatment, and the total score after treatment was 0; 2) Effective: symptoms improved after the treatment, and the total score after treatment was less than 50% of that before treatment; and 3) Ineffective: symptoms did not improve after the treatment with that drug, and the total score after treatment was more than 50% of that before treatment

Data analysis

Data were presented as mean value standard deviation (SD). Statistical analyses were carried out using SPSS 13.0 software (SPSS Inc., Chicago, IL). One-Sample *t* test was used to compare differences between groups. $p < 0.05$ was considered significant. Cox regression and χ^2 test were used. All experiments were repeated at least three times.

Table 1. Scoring parameters

Score	Sense of Urinating	Bladder Spasm Pain	Acute Incontinence
0	non	None	None
1	Slight	Slight	Occasionally
2	Obvious	Obvious	Frequently

Results

Diclofenac sodium effectively decreases bladder detrusor tension of guinea pigs

To evaluate the effect of DS on bladder detrusor contractility, adult guinea pigs were treated with a series of doses of DS. Verapamil, reported to have strong inhibitive effect on detrusor contraction [12, 13] and was used as a positive control. Meanwhile, NS acted as a blank control. We measured the tension of bladder detrusor before and after drug treatment and then calculated the drop of tension induced by the drug. As shown in **Figure 1**, DS highly decreased the tension of bladder detrusor in a dose-dependent manner. Even the lowest dose of DS was significantly higher than that induced by NS in reducing tension. The degree of the drop of tension induced by DS was similar to that induced by verapamil.

Diclofenac sodium significantly inhibits the frequency and amplitude of bladder detrusor contraction

To further assess the effects of DS on bladder detrusor contraction, we measured the inhibition of the frequency and amplitude of the bladder detrusor contraction by DS. The contraction of bladder detrusor was induced by histamine and the contractibility of muscle was determined by monitoring by a physiological recorder. As shown in **Figure 2A and 2B**, the inhibition ratios of the frequency and amplitude of bladder detrusor contraction were obvious, and the degree of inhibition was in a dose-dependent way. When compared to NS, the inhibition by DS was statistically significant. Furthermore, the effects of the moderate and low dose of DS were similar to the effect of verapamil.

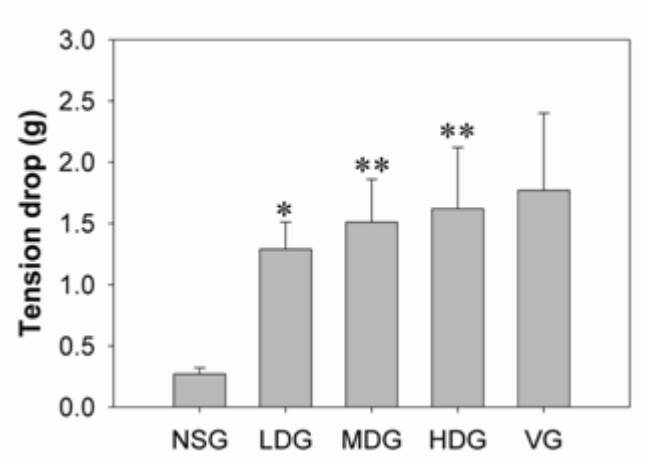


Figure 1. The effect of DS on the drop of tension of bladder detrusor. Tension drops induced by normal saline (NS), a series of doses of diclofenac sodium (DS), and verapamil are shown. DS significantly dropped the tension of bladder detrusor. Significant differences between the effect of DS and NS on the drop of the tension of bladder detrusor were observed (*p <0.05, **p <0.01). NSG, normal saline group; LDG, low dose group (0.075 mg/ml DS); MDG, medium dose group (0.15 mg/ml DS); HDG, high dose group (0.3 mg/ml DS); VG, verapamil group (8.33 μg/ml verapamil)

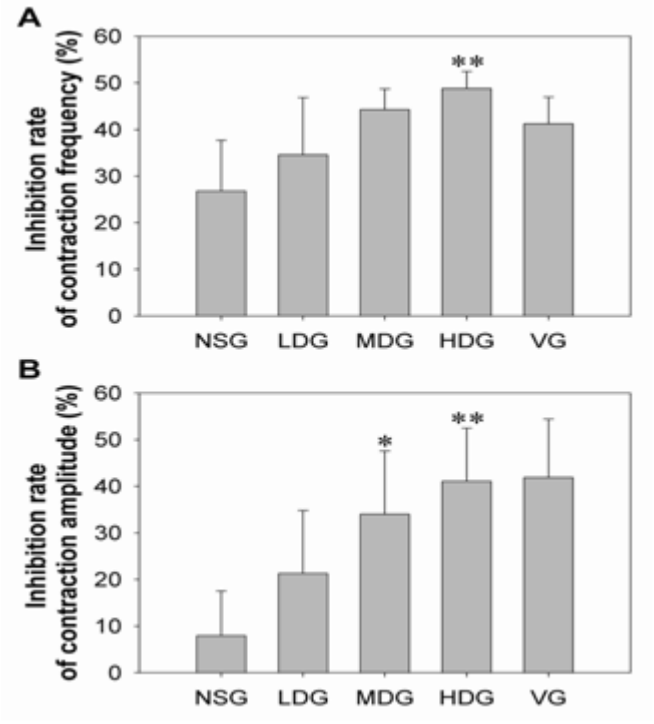


Figure 2. The effect of DS on the inhibition of bladder detrusor contraction**.** Diclofenac sodium significantly inhibited the frequency and amplitude of bladder detrusor contraction. (**A**) Shows inhibition rates of contraction frequency by normal saline (NS), a series of doses of diclofenac sodium (DS), and verapamil. (**B**) Inhibition rate of contractions amplitude by normal saline (NS), a series of doses of diclofenac sodium (DS), and verapamil were shown. There are significant differences between the effect of DS and NS on the inhibition of the frequency and the amplitude of bladder detrusor contraction (*p <0.05, **p <0.01). NSG, normal saline group; LDG, low dose group (0.075 mg/ml DS); MDG, medium dose group (0.15 mg/ml DS); HDG, high dose group (0.3 mg/ml DS); VG, verapamil group (8.33 μg/ml verapamil)

Clinical efficacy of diclofenac sodium in patients post-prostatectomy

To confirm the effects of DS in vivo, we determined efficacy in patients who had undergone prostatectomy. The symptom scoring system was used for the efficacy evaluation (**Table 2**). According to changes in symptoms before and after treatment, the efficacy was divided into three grades; 1) Markedly effective: when symptoms disappeared completely and the total grade was 0; 2) Effective: after treatment symptoms improved with a total score drop of less than 50%; and 3) Ineffective: total scores was less than 50% or the symptoms were not improved. As shown in **Table 2**, DS was effective (markedly effective and effective) in the majority (89.5%) of patients. The ratio of effective (markedly effective and effective) induced by DS was higher than that induced by verapamil (89.5% vs. 77.4%). Furthermore, DS was markedly effective in almost half patients, and the ratio of markedly effective induced by DS was significantly higher than that induced by verapamil (47.4% vs. 16.1%, p <0.01). In addition, efficacy of duration was detected. As shown in **Figure 3**, the efficacy of duration induced by DS was superior to that induced by verapamil (p <0.01). Finally, no obvious changes in electrocardiogram and blood pressure were found in all patients treated with DS or verapamil. No apparent adverse events were observed in patients with DS treatment, however, dizziness and palpitations were observed in 4 cases with verapamil treatment.

Discussion

OAB is a chronic condition of the bladder in the urinary tract that causes sudden urges to urinate. These urges can happen suddenly at any time regardless of the amount of urine in the bladder. OAB affects millions of people throughout the world. One

Table 2. The efficacy of diclofenac sodium and verapamil treatment

Drug	Number of patients	Changes after drug treatment			
		Markedly effective No. (%)	Effective No. (%)	Ineffective No. (%)	Total effective No. (%)
Diclofenac sodium	38	18 (47.4)	16 (42.1)	4 (10.5)	34 (89.5)
Verapamil	31	5 (16.1)	19 (61.3)	7 (22.6)	24 (77.4)

DS: diclofenac sodium

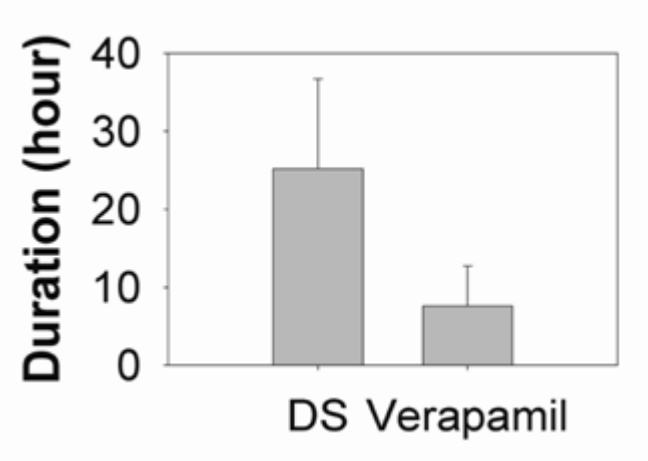


Figure 3. High efficacy of duration induced by DS. Comparison of duration time induced by diclofenac sodium (DS) with that induced by verapamil. The efficacy of duration induced by DS was significantly higher in comparison with that induced by verapamil (p <0.01).

in five adults over the age of 40 is affected by OAB [1]. Approximately 17% of adults more than 18 years old have OAB [20-22]. In the present study, we report a novel role of DS in inhibiting the contraction of upper urinary tract smooth muscle. We show that DS inhibits the histamine-induced contraction of bladder detrusor from guinea pigs and further confirm the clinical implication of DS on the uninhibited bladder contractions in patients following prostatectomy. The mechanisms by which OAB symptoms occur may be associated with prostaglandins release [10, 11]. Secondary factors include indwelling catheters and others [9, 14]. Behavioral and lifestyle interventions are first recommended followed by bladder and pelvic floor muscle training [15]. Pharmacological treatment with spasmolysants including flavoxate and tolterodine are also used to relieve OAB symptoms [16]. Many patients have poor results from these treatments [17]. Recent studies clearly indicate a central role for DS in the inhibition of contraction of upper urinary tract smooth muscle, and in the treatment of the acute renal colic [18]. There are also findings showing that DS reduces agonist-induced contractions in isolated porcine ureters, induced by three potentially important regulators of ureteral motility (5-HT, NE and NKA) in a concentration-dependent manner [19]. In this study, we found that DS had apparent inhibitive effects on bladder detrusor contractions *in vitro* (guinea pigs) in a dose-dependent manner. The inhibitory effect of DS on bladder detrusor contractions was statistically significant in comparison to that of NS. Recently, verapamil, an L-type calcium channel blocker of the Phenylalkylamine class, has attracted attention because of its strong inhibitive effect on detrusor contraction *in vivo* and *in vitro* [12,13]. We now compared the inhibititory effect of DS with that of verapamil and found that the effect of DS was analogous to that of verapamil. Taken together, these data revealed a role of DS in bladder detrusor muscle contraction. It will be important to test the clinical effects of DS in patients with uninhibitive bladder contraction and we subsequently assessed the effect

of DS in patients undergoing prostatectomy. Our findings showed that DS greatly improved or completely relieved symptoms such as strong desire to urinating, bladder spasm pain, and incontinence. The effective (markedly effective and effective) rate of inhibition induced by DS was as high as 89.5%, revealing a clinical inhibitive role of DS on bladder detrusor muscle. The effective rate of inhibition induced by verapamil was 77.4%, consistent with the findings by Yang R et al that verapamil was effective (75%) in treatment of patients with unstable bladder. In addition, the effective rate and duration of efficacy of DS was statistically superior to that of verapamil. Moreover, the duration of efficacy induced by DS was long without apparent side effects.

Conclusion

DS decreased the tension of bladder detrusor and inhibited the frequency and amplitude of bladder detrusor contraction in the *in vitro* model. DS showed marked efficiency after prostatectomy (*in vivo*). This study suggests that DS may be used to treat patients with OAB symptom. This observation needs to be confirmed in a larger prospective study.

The authors have no conflicts of interest to declare.

References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology. 2003; 61:37-49.
2. MacDiarmid S, Sandage BW, Jr., Malhotra BK. The effects of reformulation: improved therapeutic index. Curr Urol Rep. 2008; 9:465-71.
3. Drutz HP, Appell RA, Gleason D, Klimberg I, Radomski S. Clinical efficacy and safety of tolterodine compared to oxybutynin and placebo in patients with overactive bladder. Int Urogynecol J Pelvic Floor Dysfunct. 1999; 10:283-9.
4. Engelhardt G, Homma D, Schlegel K, Utzmann R, Schnitzler C. Anti-inflammatory, analgesic, antipyretic and related properties of meloxicam, a new non-steroidal anti-inflammatory agent with favourable gastrointestinal tolerance. Inflamm Res. 1995; 44: 423-33.
5. Mitchell JA, Warner TD. Cyclo-oxygenase-2: pharmacology, physiology, biochemistry and relevance to NSAID therapy. Br J Pharmacol. 1999; 128:1121-32.
6. Acute treatment of migraine attacks: efficacy and safety of a nonsteroidal anti-inflammatory drug, diclofenac-potassium, in comparison to oral sumatriptan and placebo. The Diclofenac-K/Sumatriptan Migraine Study Group. Cephalalgia. 1999; 19:232-40.
7. McNeely W, Goa KL. Diclofenac-potassium in migraine: a review. Drugs. 1999; 57:991-1003.
8. Karachalios GN, Fotiadou A, Chrisikos N, Karabetsos A, Kehagioglou K. Treatment of acute migraine attack with diclofenac sodium: a double-blind study. Headache. 1992; 32:98-100.
9. Kuznetsova AA, Shakhmatova EI, Prutskova NP, Natochin YV. Possible role of prostaglandins in pathogenesis of nocturnal enuresis in children. Scand J Urol Nephrol. 2000; 34:27-31.
10. Davenport K, Timoney AG, Keeley FX, Jr. Effect of smooth muscle relaxant drugs on proximal human ureteric activity in vivo: a pilot study. Urol Res. 2007; 35:207-13.
11. Chaignat V, Danuser H, Stoffel MH, Z'brun S, Studer UE, Mevissen M. Effects of a non-selective COX inhibitor and selective COX-2 inhibitors on contractility of human and porcine ureters in vitro and in vivo. Br J Pharmacol. 2008; 154:1297-307.
12. Badawi JK, Li H, Langbein S, Kwon ST, Kamp S, Bross S. Inhibitory effects of L- and T-type calcium antagonists on contractions of human detrusor muscle. Eur J Clin Pharmacol. 2006; 62:347-54.
13. Roosen A, Wu C, Sui G, Chowdhury RA, Patel PM, Fry CH. Characteristics of spontaneous activity in the bladder trigone. Eur Urol. 2009; 56:346-53.
14. Batislam E, Nuhoglu B, Peskircioglu L, Emir L, Uygur C, Germiyanoglu C, et al. A prostaglandin synthesis inhibitor, diclofenac sodium in the treatment of primary nocturnal enuresis. Acta Urol Belg. 1995; 63:35-8.
15. Wyman JF, Burgio KL, Newman DK. Practical aspects of lifestyle modifications and behavioural interventions in the treatment of overactive bladder and urgency urinary incontinence. Int J Clin Pract. 2009; 63:1177-91.
16. Andersson KE, Appell R, Cardozo LD, Chapple C, Drutz HP, Finkbeiner AE, et al. The pharmacological treatment of urinary incontinence. BJU Int. 1999; 84: 923-47.
17. Herbison P, Hay-Smith J, Ellis G, Moore K. Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: systematic review. BMJ. 2003; 326:841-4.

18. Roshani A, Falahatkar S, Khosropanah I, Roshan ZA, Zarkami T, Palizkar M, et al. Assessment of clinical efficacy of intranasal desmopressin spray and diclofenac sodium suppository in treatment of renal colic versus diclofenac sodium alone. Urology. 2010; 75:540-2.
19. Iselin CE, Alm P, Schaad NC, Larsson B, Graber P, Andersson KE. Nitric oxide inhibits contraction of isolated pig ureteral smooth muscle. J Urol. 1996; 155: 763-7.
20. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int. 2001; 87:760-6.
21. Stewart W, Herzog R, Wein A. The prevalence and impact of overactive bladder in the U.S.: results from the NOBLE program. Neurourol Urodyn. 2001; 20: 406-8.
22. Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, et al. Prevalence and burden of overactive bladder in the United States. World J Urol. 2003; 20:327-36.