Effects of 1% Lidocaine Instillation on Overactive Bladder Induced by Bladder Outlet Obstruction in Rats

Hyo Jin Kang,[1,2] Sang Woon Kim,[1] Yong Seung Lee,[1] Sang Won Han,[1] Jang Hwan Kim[1]*

Purpose: Lidocaine is a common local anesthetic and antiarrhythmic drug that acts via the local anesthetic effect of blocking voltage-gated sodium channels in peripheral neurons. To evaluate lidocaine as a therapeutic agent, we investigated optimal concentrations and effects of intravesical lidocaine instillation in a bladder outlet obstruction (BOO)-induced rat model of overactive bladder (OAB).

Materials and Methods: To determine the therapeutic dosage of lidocaine, 16 female Sprague-Dawley (SD) rats (mean weight = 200 ± 20 g) were divided into four treatment groups: those receiving saline, 0.5% lidocaine, 1% lidocaine, and 2% lidocaine (n = 4 per group). Twenty-four additional SD rats were divided into two groups to investigate the effect of 1% lidocaine treatment in rats with BOO and normal rats (n = 12 per group). Cystometry was performed by infusing physiological saline and lidocaine into the bladder at a slow infusion rate (0.04 mL/min). Cystometric parameters were analyzed using PowerLab®. The expression of c-Fos, a protein expressed by C-fibers in the spinal cord (L6), was investigated via western blotting.

Results: Among the test lidocaine doses, only 1% lidocaine increased the intercontraction interval (ICI) (control mean = 500.56 ± 24.4 s; treatment mean = 641.0 ± 49.3 s; $p < .01$) without changes in threshold pressure and basal pressure. In the BOO-induced OAB group, the ICI increased significantly after instillation of 1% lidocaine (control mean = 135.8 ± 12.87 s; OAB-group mean = 274.2 ± 33.21 s; $p < .01$). Detrusor overactivity and non-voiding contraction were observed in the control group but not in rats with BOO after lidocaine instillation. The expression of c-Fos in C-fibers in the spinal cord (L6) decreased significantly after 1% lidocaine treatment in rats with BOO.
Conclusion: Intravesical instillation of 1% lidocaine improves cystometric parameters without deterioration of contractility by blocking excessive C-fiber activity in the rat model of BOO-induced OAB. Therefore, instillation of 1% lidocaine has minimal effects on normal nerves while blocking nerves that contribute to OAB. Our findings suggest that intravesical instillation of 1% lidocaine is a useful treatment for OAB.

Keywords: bladder outlet obstruction; cystometry; lidocaine; overactive bladder; unmyelinated C-fibers

INTRODUCTION

Overactive bladder (OAB) is a storage and voiding dysfunction related to urinary urgency, with or without urgency incontinence, frequency, and nocturia.[1-4] The OAB symptoms are caused either by obstruction of, or secondary effects of obstruction on the bladder. In some patients, the symptoms are accompanied by uncontrolled contractions of the detrusor muscle during bladder filling, known as detrusor overactivity (DO).[5-7] Prior investigations have shown that myelinated Aδ-fibers and unmyelinated C-fibers of the afferent nerve are important for the regulation of micturition. C-fibers convey input signals from the periphery to the central nervous system; these fibers respond to mechanical, thermal, and chemical stimuli.[8,9] The activation of C-fibers, which are silent in normal bladders, is regarded as a major cause of OAB, triggering micturition in unstable bladders.[10] We surveyed neuroinhibitors that might specifically inhibit only activated C-fibers during OAB. These included lidocaine, a common local anesthetic and antiarrhythmic drug[11-13] that blocks the influx of sodium ions through direct binding of neuronal voltage-gated sodium membrane channels, thereby producing an analgesic effect by inhibiting the excitation of nerve endings or by blocking conduction in peripheral nerves.[14,15] In addition, lidocaine is a widely used local anesthetic because of its rapid onset of action and intermediate duration of efficacy.[12,16] In previous reports, intravesical instillation of lidocaine was shown to provide immediate relief of pain, as well as improve urgency and frequency, in patients with interstitial cystitis/bladder pain syndrome.[13,17] Yokoyama et al. reported that lidocaine blocked the action potentials of small unmyelinated C-fibers more easily than those of large myelinated Aδ-fibers.[14]
The effects of intravesical lidocaine instillation for therapeutic treatment of OAB have not been elucidated. Lidocaine is a candidate drug for OAB treatment because it has already been approved for clinical use as an anesthetic, and its safety has been established[18]. Therefore, we evaluated various doses of lidocaine in normal rats

[1]Department of Urology, Severance Hospital, Urological Science Institute, Yonsei University College of Medicine, Seoul, Korea.
[2]Medical Science Research Institute, Seoul National University Bundang Hospital, Seongnam, Korea.
*Correspondence: Dept. of Urology, School of Medicine, Yonsei University, 134 Shinchon-dong, Seodaemoon-gu, Seoul, Korea, 120-752
Telephone: +82-2-2228-2319. Fax: +82-2-312-2538. E-mail address: jkim@yuhs.ac.
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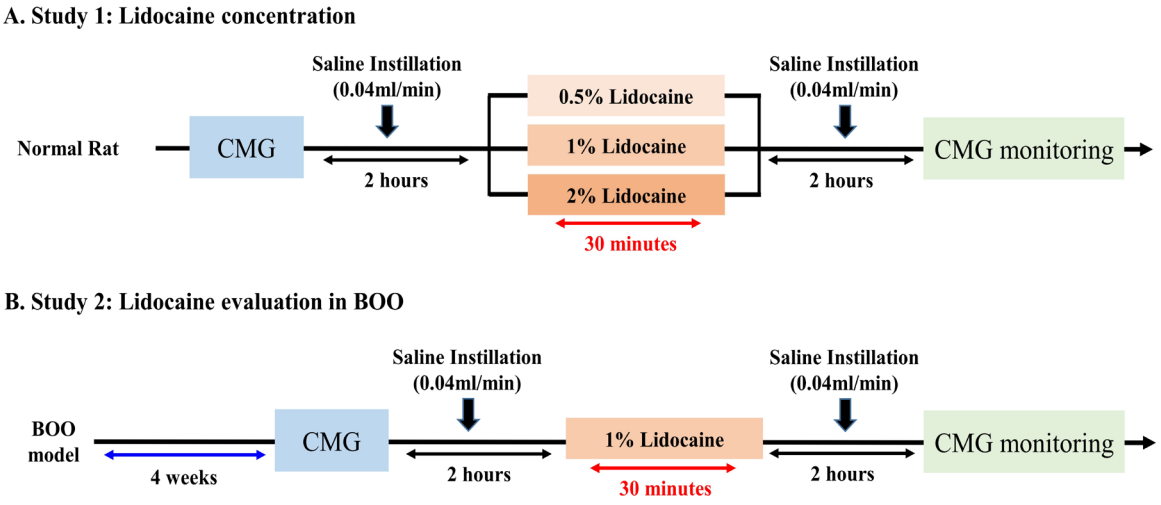

Figure 1. Schematic illustration of the design of the current study.
A) Cystometry for determination of lidocaine concentration. **B)** Cystometry after instillation of 1% lidocaine in rats with bladder outlet obstruction (BOO)-induced overactive bladder (OAB).

to detect concentrations that could inhibit only C-fibers without affecting Aδ-fibers. In addition, we confirmed the therapeutic effect of selected lidocaine doses in a bladder outlet obstruction (BOO)-induced rat model of OAB.

MATERIALS AND METHODS

Animals

Six-week-old female Sprague-Dawley (SD) rats (mean weight = 200 ± 20 g) purchased from Orient Bio (Seongnam, Korea) were cared for in accordance with guidelines of the Association for Assessment and Accreditation of Laboratory Animal Care International. The Institutional Animal Care and Use Committee of Yonsei University College of Medicine (Seoul, Korea) approved these animal experiments.

Sixteen SD rats were divided into the following four groups (n = 4 per group) to determine the optimum lidocaine dose: the control group and groups that received 0.5%, 1%, and 2% lidocaine. Twenty-four additional SD rats were divided into the following two groups (n = 12 per group): the control group with normal rats and the group of rats with BOO. BOO was induced by using methods described in a previous study.[2] Briefly, rats were anesthetized with a mixture of Zoletil (30 mg/kg; Virbac, Carros Cedex, France) and Rompun (10 mg/kg; Bayer Korea Ltd., Seoul, Korea), and the bladder and proximal urethra were exposed via a lower midline abdominal incision. The proximal urethra was carefully freed from the vaginal wall to avoid injury to periurethral blood vessels. A polyethylene-50 (PE-50) catheter (Clay Adams, Parsippany, NJ, USA) with an inner diameter of 1.40 mm was inserted into the urethra. The proximal urethra was then tied loosely with 3/0 silk, thus enabling the catheter to move freely. After the catheter was removed, intramuscular antibiotics were injected postoperatively. The silk ligatures were removed from the rats with BOO before cystometry.

Cystometry

The cystometry study design is shown in **Figure 1**. Two animal experiments were performed: determination of optimum lidocaine concentration and evaluation of effects of 1% lidocaine on BOO. At 4 weeks after BOO surgery, rats were anesthetized with a mixture of Zoletil

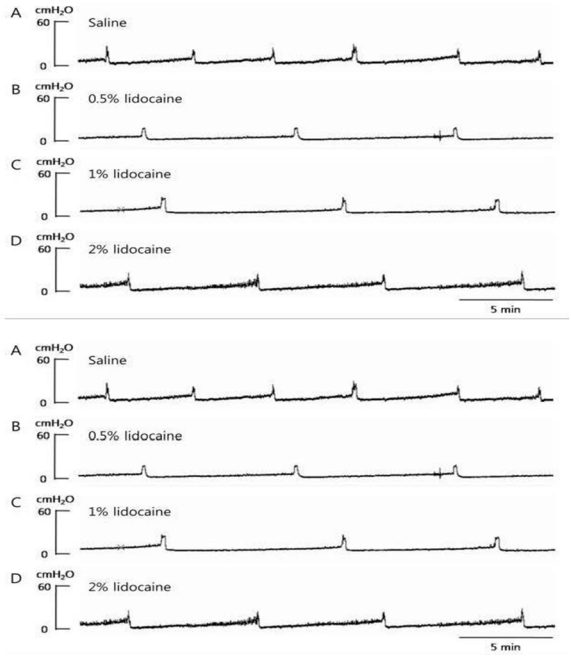

Figure 2. Cystometric analysis of lidocaine dosage in normal rats. Cystometric parameters were analyzed for rats instilled with saline **(A)**, 0.5% lidocaine **(B)**, 1% lidocaine **(C)**, and 2% lidocaine **(D)**. Room-temperature saline or lidocaine was instilled by the intravesical route for 30 min (0.04 mL/min). In the lidocaine-treatment groups, lidocaine was replaced with saline for 2 h. Intercontraction intervals (ICIs) increased in rats instilled with 0.5% **(A)** and 1% lidocaine **(B)**, compared with rats instilled with saline instillation **(C)**; however, BP, TP, and MP values did not differ significantly among groups. **D)** In rats instilled with 2% lidocaine, all cystometric parameters increased relative to those of rats instilled with saline.

Table 1. Cystometric parameters after instillation of various concentrations of lidocaine in normal rats.

	Saline	0.5% lidocaine	1% lidocaine	2% lidocaineCystometric
parameters				
ICI (Intercontraction interval, s)	500.5 ± 24.4	606.3 ± 45.2	641.0 ± 49.3**	598.6 ± 26.4**
BP(Basal pressure, cmH_2O)	3.28 ± 0.19	2.51 ± 0.31	3.49 ± 0.19	5.17 ± 0.40***
TP (Threshold pressure, cmH_2O)	5.83 ± 0.37	6.61 ± 0.85	5.97 ± 0.55	7.45 ± 0.64*
MP (Micturition pressure, cmH_2O)	21.69 ± 0.61	28.73 ± 2.15***	21.09 ± 0.50	18.71 ± 0.74**

Data are shown as the means ± standard deviations. *, $p < .05$ compared with the control; **, $p < .01$; ***, $p < .001$

and Rompun (1 mL/kg), and the bladder was exposed. A PE-50 tube, filled with saline and with its end flared by heat, was inserted into the bladder through the dome and the 3/0 silk ligatures were released. After the abdominal incision was closed, the rats were placed in a restraining cage and allowed to recover from anesthesia for 2–3 h until they awakened. The catheter was connected to a pressure transducer and syringe pump via a three-way stopcock. Cystometry was performed by infusing physiological saline into the bladders of normal rats and rats with BOO at a slow infusion rate (0.04 mL/min). Cystometric variables were measured during saline infusion for 2 h to evaluate bladder function. After a minimum number of stable micturition cycles was analyzed, the saline was replaced with lidocaine hydrochloride (Jeil Pharmaceutical, Daegu, Korea) and infusion was continued for 30 min. The intravesical lidocaine was washed out for 30 min and bladder pressure was immediately monitored using a PowerLab®/LabChart7 instrument (ADInstruments, Bella Vista, Australia). Continuous cystometry was performed, and at least five reproducible micturition cycles were analyzed. Intercontraction intervals (ICIs) were defined as the intervals between large amplitude spontaneous bladder contractions. Threshold pressure (TP) was defined as the bladder pressure immediately prior to micturition, relative to basal pressure (BP; the lowest bladder pressure during filling). Micturition pressure (MP) was defined as the maximum bladder pressure during micturition.

Drug administration

The stock solution of 2% lidocaine hydrochloride (Jeil Pharmaceutical) was neutralized by mixing it with 8.4% sodium bicarbonate solution (Jeil Pharmaceutical) at a 1:1 ratio. To generate 1% and 0.5% lidocaine solutions, 2% lidocaine was diluted with normal saline at 1:1 and 1:2 ratios, respectively. The pH of neutralized lidocaine was between 7.4 and 7.6.

Western blotting

Spinal cord tissues were homogenized using PROPREP lysis buffer (Intron, Seoul, Korea), and the concentration of cellular protein was determined using the Bio-Rad assay reagent (Bio-Rad, Hercules, CA, USA). Briefly, samples with equal concentrations of cellular protein were mixed with 4□ sample buffer (GenDEPOT Inc., Barker, TX, USA), heated at 95°C for 10 min, and separated using electrophoresis on 10% sodium dodecyl sulfate–polyacrylamide gels. Proteins were then transferred onto polyvinylidene difluoride membranes (Amersham Life Science, Arlington Heights, IL, USA) in tris-glycine transfer buffer (InvitrogenTM, Carlsbad, CA, USA). The membranes were blocked for 1 h at room temperature with 5% skim milk in tris-buffered saline with Tween-20. The membranes were incubated at 4°C overnight with anti-c-Fos antibody (Santa Cruz Biotechnology, Santa Cruz, CA, USA), and then incubated with horseradish peroxidase-conjugated anti-mouse IgG (Santa Cruz Biotechnology) for 1 h at room temperature. The membranes were washed and then incubated using a West-Q Chemiluminescent Substrate Plus kit (GenDEPOT Inc.). The intensities of protein bands were determined using Multi Gauge software (version 3.0; Fuji Photo Film, Tokyo, Japan); relative densities were expressed as ratios of control values.

Statistical Analysis

Quantitative data are expressed as the means ± standard deviations. Differences between lidocaine-concentration groups were evaluated using one-way ANOVA analysis of variance followed by Dunnett's T3 and multiple comparison post hoc tests. Paired Student's t-tests were used to compare cystometric parameters before and after 1% lidocaine treatment. Differences with P values < .05 were considered statistically significant. Statistical analyses were performed using GraphPad Prism software (version 5.01; GraphPad Inc., La Jolla, CA, USA).

RESULTS

Cystometry for determination of lidocaine concentration

The ICI increased significantly in rats instilled with 1% and 2% lidocaine, compared with that of rats instilled with saline, indicating that a relatively high concentration of lidocaine delayed micturition. BP and TP increased significantly in rats instilled with 2% lidocaine, compared with those of control rats; BP and TP values in the other groups were nearly identical to those of the control group. The MP trend differed from those of other cystometric parameters-MP increased in rats instilled with 0.5% lidocaine but decreased in rats

Table 2. Cystometric parameters of normal rats and rats with bladder outlet obstruction (BOO) after instillation of 1% lidocaine.

Cystometric parameters	Normal	Normal/lidocaine	BOO	BOO/lidocaine
ICI (Intercontraction interval, s)	358.2 ± 70.02	508.9 ± 71.03**	135.8 ± 12.87	274.2 ± 33.21**
BP (Basal pressure, cmH_2O)	3.56 ± 0.58	3.32 ± 0.63	5.35 ± 0.32	5.71 ± 0.62
TP (Threshold pressure, cmH_2O)	9.02 ± 0.77	11.28 ± 1.59	10.16 ± 0.66	12.86 ± 1.75
MP (Micturition pressure, cmH_2O)	23.36 ± 1.39	24.58 ± 0.65	34.29 ± 5.23	36.98 ± 4.93

Data are shown as the means ± standard deviations. **, $p < .01$.

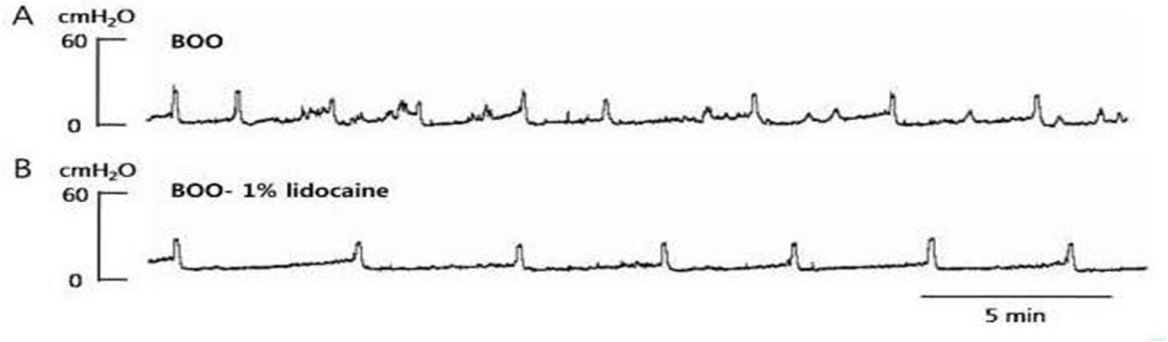

Figure 3. The results of cystometry before and after instillation of 1% lidocaine in rats with BOO.
The mean ICI increased significantly after instillation of 1% lidocaine **(B)** compared with instillation of saline **(A)** in rats with BOO. BP, TP, and MP values remained unchanged. **B)** After instillation of 1% lidocaine, OAB symptoms and non-voiding contractions were absent.

instilled with 2% lidocaine. Furthermore, instillation of 1% lidocaine had no effect on MP (**Table 1; Figure 2**). Thus, instillation of 1% lidocaine had minimal effects on most cystometric parameters in normal rats and only increased micturition interval.

Cystometric parameters in normal rats and the BOO-induced rat model of OAB

At 4 weeks postoperatively, the mean ICI was significantly shorter in rats with BOO, such that the frequency of micturition was more than two times greater than normal in rats with BOO. BP, TP, and MP increased in rats with BOO, but these differences were not statistically significant (**Table 2**).

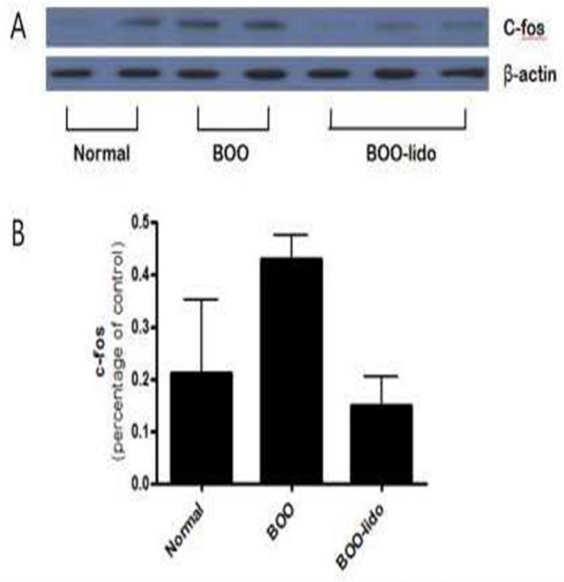

Figure 4. Expression of c-Fos protein in the spinal cords (L6) of normal and BOO rats.
A) According to western blotting analysis, the expression of c-Fos proteins was higher in rats with BOO compared with normal rats. After intravesical instillation of 1% lidocaine, c-Fos expression decreased significantly in rats with BOO. **B)** Blot intensities were analyzed via densitometric scanning, and relative densities were expressed as ratios relative to control values. Data are expressed as the means ± standard deviations.

Cystometry after instillation of 1% lidocaine in the BOO-induced rat model of OAB

After instillation of 1% lidocaine, the mean ICI of the BOO group was significantly longer than that of the BOO group before lidocaine treatment; BP, TP, and MP did not differ significantly between groups (Table 2). Cystometric analysis indicated that instillation of 1% lidocaine induced recovery of frequent micturition. In addition, persistent DO and non-voiding overactivity disappeared after intravesical instillation of 1% lidocaine in rats with BOO (**Figure 3**). Although the instillation of 1% lidocaine seemed to have no effects on BP, TP, and MP according to parametric analysis, it has been shown via graph monitoring to have more influence on these parameters and improve the urination interval.

Expression of c-Fos in the BOO-induced rat model of OAB

Expression of c-Fos was analyzed via western blotting. In this analysis, the intensities of the blots were determined via densitometric scanning, and relative densities were expressed as ratios relative to the control value. The results of western blotting revealed that the expression of c-Fos proteins increased in rats with BOO compared with normal rats. After intravesical instillation of 1% lidocaine, c-Fos expression decreased significantly in rats with BOO (**Figure 4**).

DISCUSSION

Persistent OAB is a urological condition that causes problems with urination and highly prevalent in the general population[19-21]. Prescription drugs for OAB treatment, such as anticholinergics, are moderately effective and cause side effects that include dry mouth, constipation, and drowsiness, which can limit their usefulness[21,22]. Therefore, new therapeutic agents are needed to avoid the side effects of current treatments and address the underlying causes of OAB. The activation of silent C-fibers is regarded as a major cause of OAB, as this process triggers detrusor contraction in unstable bladders[10,14,23]. Blocking C-fiber activation may thus be an effective treatment for OAB patients. Previous studies showed that lidocaine is a non-selective blocker of voltage-gated sodium channels in peripheral neurons, and that unmyelinated C-fibers are more easily affected than myelinated Aδ-fibers[14,24]. Prior investigators reported that intravesical instillation of lidocaine reduces various symptoms of OAB and increases bladder ca-

pacity[10]. However, intravesical instillation of lidocaine has not been established as a clinical treatment option for OAB. Therefore, we investigated lidocaine as a candidate for OAB treatment. In addition, lidocaine has been used as an anesthetic agent; because of its mechanism of action and stability, it may have advantages as a candidate therapeutic agent for clinical application. However, the concentration of lidocaine currently used in clinical applications is intended to induce anesthesia; thus, it simultaneously blocks both Aδ-fibers and C-fibers. To evaluate the feasibility of treating OAB with lidocaine, an adequate concentration is needed to block C-fibers without affecting Aδ-fibers.

We investigated changes in bladder sensation during cystometry after intravesical instillation of 0.5%, 1%, and 2% lidocaine. After the instillation of 2% lidocaine, the ICI, BP, and TP increased significantly, whereas MP decreased. Thus, intravesical instillation of 2% lidocaine may cause serious disturbances in the contraction of bladder smooth muscle; it may block both sensory and motor neurons and is therefore an excessive dose. We propose that instillation of 2% lidocaine should be limited to use as an anesthetic, rather than as a therapeutic agent for treatment of OAB. Following instillation of 1% lidocaine, the results of cystometric analysis revealed that the ICI increased significantly, whereas other parameters did not differ significantly. This suggests that instillation of 1% lidocaine reduces the sensation of bladder filling by blocking sensory neurons. Previous studies have indicated that desensitization of C-fibers does not affect cystometric parameters or bladder capacity in normal individuals[25,26], but we found that cystometric parameters changed after intravesical instillation of lidocaine in our experiment. We presume that our findings were related to the ability of lidocaine to effectively block both myelinated Aδ-fibers and unmyelinated C-fibers because it is a non-selective sodium-channel blocker. Hence, our results suggest that 1% lidocaine blocks the action potentials of sensory neurons and is therefore a suitable concentration for therapeutic treatment of OAB.

To demonstrate the therapeutic effect of intravesical instillation of 1% lidocaine on OAB, cystometry was performed at 4 weeks after BOO induction of OAB in a rat model. The results of cystometric analysis showed that ICIs were significantly longer in rats with BOO treated with lidocaine than in non-treated rats with BOO, whereas BP, TP, and MP did not differ significantly different between groups. Cystometric monitoring showed that the voiding pattern after instillation of 1% lidocaine was very similar to that of normal voiding contractions. Persistent DO and non-voiding overactivity, which were present in the BOO-induced OAB group, disappeared after instillation of 1% lidocaine. Edlund et al. reported that the voiding pattern instability in OAB patients was markedly reduced after intravesical instillation of lidocaine[28]. Therefore, our current results suggest that intravesical instillation of 1% lidocaine is an attractive treatment for OAB based on its ability to block voltage-gated sodium channels in C-fibers. For clinical trials, the establishment of a suitable lidocaine concentration lower than that needed for anesthesia is necessary.

To confirm whether instillation of 1% lidocaine blocks the activation of C-fibers, we investigated the expression of c-Fos protein, a known C-fiber marker, before and after instillation of 1% lidocaine. Western blotting analysis showed that the expression of c-Fos protein increased in rats with BOO, compared with normal rats; c-Fos expression decreased significantly after instillation of 1% lidocaine in rats with BOO. Our results suggested that the activation of unmyelinated C-fibers might be associated with DO in the BOO model, and that instillation of 1% lidocaine might improve DO by blocking voltage-gated sodium channels in unmyelinated C-fibers. The instillation of 1% lidocaine may be an effective treatment option for use in clinical settings. Moreover, the effects of intravesical instillation of lidocaine are limited to the bladder, thereby avoiding the development of side effects associated with current medications used for treatment of OAB. Instillation of lidocaine is relatively inexpensive, which may reduce medical costs for patients with OAB. Notably, patients can perform self-instillation of lidocaine by using clean intermittent catheterization.

Importantly, our study had some limitations. We did not evaluate the duration of the effects of instillation of 1% lidocaine. The frequency of instillation needed for a therapeutic effect is important for patients with OAB. In future studies, it will be necessary to evaluate the tolerance and adverse effects of repeated instillation of lidocaine.

CONCLUSIONS

Lidocaine is widely used in clinical fields as an anesthetic but has not been regarded as a therapeutic agent. In the current study, we investigated lidocaine instillation at various concentrations for OAB treatment and demonstrated its effectiveness. We found that instillation of 1% lidocaine has minimal effects on normal urination and alleviates symptoms of OAB via blocking voltage-gated sodium channels in unmyelinated C-fibers. Although further evaluation is needed to support its use in clinical applications, instillation of 1% lidocaine may constitute a new strategy for OAB treatment.

ACKNOWLEDGMENTS

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CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

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