

# Intravesical indwelling lidocaine-releasing devices for IC/BPS (Review)

TOMOFUMI WATANABE<sup>1</sup>, TAKUYA SADAHIRA<sup>1</sup>, MASAMI WATANABE<sup>2</sup>,  
YUKI MARUYAMA<sup>1</sup>, KOICHIRO WADA<sup>3</sup>, TAKANORI SEKITO<sup>1</sup>, KOHEI EDAMURA<sup>1</sup>,  
YASUYUKI KOBAYASHI<sup>1</sup>, MOTOO ARAKI<sup>1</sup> and TOYOHICO WATANABE<sup>1</sup>

<sup>1</sup>Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences; <sup>2</sup>Center for Innovative Clinical Medicine, Okayama University Hospital, Okayama 700-8558; <sup>3</sup>Department of Urology, Shimane University Faculty of Medicine, Izumo, Shimane 693-8501, Japan

Received June 8, 2022; Accepted June 27, 2022

DOI: 10.3892/wasj.2022.163

**Abstract.** Since the time the first case of interstitial cystitis/bladder pain syndrome (IC/BPS) was reported, there have been complaints of a decreased quality of life secondary to bladder pain; thus, effective treatment(s) are required. Several treatments have been developed, among which the intravesical instillation of lidocaine is considered one of the most favorable treatments due to the rapid local anesthetic action with minimal systemic side-effects, and even serves as a potential diagnostic tool for IC/BPS. In addition, the anti-inflammatory effects of lidocaine are associated with a longer duration of pain relief as compared to the effects of local anesthetic by breaking the vicious cycle of neurogenic inflammation. However, the main difficulty encountered with this treatment is the low absorption rate and the lack of maintaining a monthly effect. To overcome this difficulty, several approaches, including alkalization or the use of drug cocktails have been attempted. Recently, several indwelling lidocaine-releasing devices have been developed; however, the majority of these devices have not yet entered clinical trials, at least to the best of our knowledge. The only device evaluated in phase II clinical trials to date has failed to demonstrate a statistically significant efficacy compared to the placebo group. If the efficacy is improved and further clinical evidence is collected, the use of IC/BPS as a treatment strategy may become feasible.

---

*Correspondence to:* Dr Takuya Sadahira, Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan  
E-mail: t.sadahira@gmail.com

**Key words:** interstitial cystitis, bladder pain syndrome, urinary bladder, therapeutic

## Contents

1. Introduction
2. Literature selection
3. Overview of IC/BPS
4. Pharmacological effects of lidocaine
5. Diagnostic significance of lidocaine in IC/BPS
6. Therapeutic significance of lidocaine in IC/BPS
7. Intravesical indwelling lidocaine-releasing devices
8. Conclusions and future perspectives

## 1. Introduction

The effective treatment of interstitial cystitis (IC)/bladder pain syndrome (BPS) is mandatory due to severe bladder pain, pressure and discomfort, which in turn negatively affects the quality of life (QoL) of patients (1). Intravesical instillation is considered a promising treatment strategy as intravesical instillation delivers drugs directly and locally to the bladder mucosa; a number of drugs have been tested using this treatment technique (2-4). Specifically, lidocaine has achieved a documented level of success in relieving the symptoms of IC/BPS, and also has the potential to serve as a diagnostic tool for IC/BPS. The main difficulty encountered with the intravesical instillation of lidocaine is the limited duration of the local anesthetic activity; however, several devices have been developed to overcome this issue. The present review article summarizes the mechanisms underlying the intravesical instillation of lidocaine, the current therapeutic and diagnostic evidence, and also provides a comprehensive summary of the published clinical experience to date involving intravesical indwelling lidocaine-releasing devices.

## 2. Literature selection

To evaluate the published clinical trials of indwelling bladder lidocaine-releasing devices for IC/BPS, the PubMed, Google Scholar and the Cochrane Library databases were searched for articles published until May, 2022, with 'interstitial cystitis' OR 'painful bladder syndrome' AND 'intravesical' AND

'lidocaine' AND ('device' OR 'system') as the search terms. Two authors (Tomofumi W and TSA) initially screened the search results independently, then worked together in cases requiring discussion until a consensus was reached. In addition, manual searches of original articles and reviews were performed to identify additional eligible studies.

### 3. Overview of IC/BPS

IC was first reported by Hunner in 1915 in a patient with bladder pain and ulcer (5). Since that time, the definition has changed several times, although IC/BPS is now defined as 'the condition with chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by other urinary symptoms, such as persistent urge to void or urinary frequency in the absence of confusable diseases' (6,7). Patients with a characteristic ulcer (Hunner's lesion) are defined as Hunner-type IC (HIC); the remainder have bladder pain syndrome (BPS) (6,7). IC/BPS is painful, and thus the QoL of patients is markedly decreased (1).

The etiology of bladder pain has not yet been established, although one possible reason is that the loss of bladder urothelial function from various factors leads to the infiltration of urinary substances, such as potassium, which can induce bladder inflammation or nerve sensitization (8). There is another possible theory that claims that the pathogenesis of IC/BPS is an inflammatory change occurring in stromal tissues and involves the stimulation of sensory nerves by neurotransmitters or cytokines (neurologic inflammation). When acute peripheral inflammation activates nociceptors in the dorsal root ganglia, the production and release of neuropeptides, such as substance P, calcitonin gene-related peptide, or nerve growth factor (NGF), are increased (9,10). These neuropeptides lower the activation threshold of the central nerves (central nerve sensitization) and enhance the release of neuropeptides from the peripheral nerves (peripheral nerve sensitization), which trigger the increased permeability of the bladder mucosa and activate immune cells (mast cells) (11). These changes further accelerate peripheral nerve stimulation and inflammation, which may be the origin of unbearable bladder pain (12). Chronic pain syndromes, such as migraines, fibromyalgia, vulvodynia, chronic pelvic pain and irritable bowel syndrome, which are considered to involve central nerve sensitization and often co-exist, are now designated as central sensitivity syndrome (CSS) (13). Some patients with IC/BPS co-exist with CSS, which indicates the association between IC/BPS and CSS (14,15).

IC/BPS is more common among females and is considered a relatively rare clinical entity, with ~10-300/100,000 patients being diagnosed with IC/BPS (16,17). Previous studies have demonstrated that as many as 680/100,000 cases are possible/probable IC, and that ~2.70-6.73% of females meet the diagnostic criteria for IC/BPS (17,18). Thus, the incidence of potential IC/BPS is considered markedly higher than previously considered, highlighting the importance of seeking effective treatment.

A variety of treatments for IC/BPS, including conservative treatment, medical treatment, endoscopic surgery and the intravesical instillation of various drugs [dimethyl sulfoxide (DMSO), silver nitrile, phenol and lidocaine] have

been suggested and tested (2-4). Compared to whole-body administration, intravesical instillation can deliver high concentrations of drugs locally to the bladder with reduced systemic toxicity and side-effects. A number of efforts have been made to maximize the drug concentration and exposure times in clinical studies since *in vitro* experiments involving human bladder cancer cell lines have revealed that the duration of exposure, as well as the concentration of a drug are crucial factors regarding cytotoxicity (19). In the majority of cases, the duration of drug exposure is limited to 2 h, and the instillations are repeated at fixed time intervals to maximize efficacy.

### 4. Pharmacological effects of lidocaine

Lidocaine is a local anesthetic and one of the most popular local anesthetics worldwide. Lidocaine was first synthesized by Löfgren in 1943 (20). Lidocaine demonstrates its anesthetic effects by inhibiting the generation and propagation of action potentials in peripheral nerve cells by non-specifically blocking the sodium channel. In addition, lidocaine suppresses delivery of polymorphonuclear cells to sites of inflammation by influencing the flux of sodium and calcium, which promotes membrane stability (21,22). Moreover, lidocaine reduces the release of pro-inflammatory cytokines, such as tumor necrosis factor- $\alpha$ , interleukin (IL)-1 $\beta$  and IL-8 from immunocytes and microglia (23). It has also been reported that nebulized lidocaine is beneficial in asthma therapy, which prevents eosinophilic inflammation (24). A prolonged nerve block by lidocaine can treat and prevent inflammatory hyperalgesia (25). Based on these results, it can be concluded that lidocaine not only reduces pain, but also exerts an anti-inflammatory effect and breaks the vicious cycle of IC/BPS from interaction between immunocytes and neurocytes by suppressing the migration or activation of immunocytes and by reducing the release of inflammatory cytokines.

### 5. Diagnostic significance of lidocaine in IC/BPS

As intravesical instillation can rapidly improve bladder pain, some studies have focused on the use of lidocaine for diagnostic purposes and for the categorization of IC/BPS. In a retrospective analysis in 2008, Fenton *et al* (26) regarded the pain relief from intravesical instillation of alkalized lidocaine (AL) as a reliable method for selecting patients who required cystoscopy and hydrodistension. They argued that the intravesical instillation of AL lowers the false-positive rate of hydrodistention (26). In fact, that study did not mention the actual false positive in detail (26). Nevertheless, that study still indicates the fact that there is a multidisciplinary chronic pelvic pain referral center that use lidocaine as an important diagnostic tool for IC/BPS (26).

In a retrospective chart review in 2009, Butrick *et al* (27) evaluated the treatment response rate of patients with bladder pain or dysfunction. In their study cohort that included 408 patients, one of the standard treatments was the weekly intravesical instillation of 200 mg non-alkalinized lidocaine, 20,000 units of heparin and 40 mg of triamcinolone (27). The treatment was repeated at least three times and was considered effective in 71% of patients. The intravesical instillation of

lidocaine was most effective in patients whose chief complaint was consistent with a bladder pain disorder (73.7%) and the miscellaneous group (50%), which typically do not have bladder pain (27). In their study cohort, 120 patients who had suspected IC/BPS did not respond to the lidocaine cocktail intravesical instillation, even though 77% had a positive potassium sensitivity test; 51% were finally diagnosed with myofascial pain (27).

Taneja (28) tested a 20-ml intravesical instillation of 2% non-alkalinized lidocaine in 22 women with suspected IC/BPS. In total, 15 patients (68%) reported pain relief, with 11 (50%) claiming complete alleviation of pain (28). Of the 15 responders, 13 (86%) had cystoscopic findings suggestive of IC/BPS (Hunner's lesions, glomerulations and petechial hemorrhages) (28). By contrast, none of the seven non-responders had abnormal cystoscopy findings and were finally diagnosed with other diseases (28).

To evaluate the efficacy and safety of intravesical instillation of a 50% DMSO solution, Yoshimura *et al* (2) enrolled patients who exhibited pain relief with the intravesical instillation of lidocaine in a randomized, double-blind, placebo-controlled trial; the possible use of lidocaine in detecting patients with bladder-centric IC/BPS was also discussed.

The intravesical instillation of lidocaine is beneficial for the diagnosis of IC/BPS, not only by relieving bladder pain, but also by increasing bladder capacity during urodynamic studies. Offiah *et al* (29) reported changes in urodynamic findings and pain before and after the intravesical instillation of AL in 24 women who had previously been diagnosed with IC/BPS. Prior to enrollment, all participants completed the Central Sensitization Inventory (CSI) and Kings Health Questionnaire, and underwent urodynamic assessment. The participants were first asked to report pain during cystoscopy and post-void pain, then received an intravesical instillation of 20 ml 2% AL or normal saline. The solutions were instilled over a period of 20 min, after which pain scoring and the urodynamic study were repeated. Those who received lidocaine treatment exhibited a significant increase in the maximum bladder capacity, and those who failed to respond to treatment had a significantly higher co-morbid rate of CSSs (29). These results indicate that the intravesical instillation of lidocaine can be used to diagnose IC/BPS and evaluate the pathological findings (bladder-centric or originating in the central nervous system); however, additional data are warranted.

## 6. Therapeutic significance of lidocaine in IC/BPS

The intravesical instillation of lidocaine rapidly relieves bladder pain; however, the half-life is relatively short. Thus, considerable efforts have been made to extend the duration of action of lidocaine and increasing the analgesic effects.

Henry *et al* (30) reported the efficacy of the intravesical instillation of AL for IC/BPS and the pharmacokinetics in healthy volunteers and patients with IC/BPS. They reported that the optimal absorption of intravesical lidocaine was achieved when the bladder content pH was ~8.0 (30). Moreover, when considering the acidic pH of urine and lidocaine hydrochloride, the use of AL or a solution containing sufficient sodium bicarbonate is efficient to buffer the urine pH and optimize

the absorption of intravesical lidocaine (30). The decreased mean pain score in 12 patients with IC/BPS and the safety of the intravesical instillation of 5 mg/kg lidocaine were also demonstrated (30). In the majority of clinical trials, lidocaine was administered alkalinized or with sodium bicarbonate, based on these findings (31-35). Nickel *et al* (31) reported the efficacy of the intravesical instillation of AL in a randomized control trial. A total of 102 participants received an intravesical instillation of AL (200 mg) for 5 consecutive days. The safety of the treatment was demonstrated, and daily treatment was shown to significantly decrease pain (31).

In addition to alkalization, in some clinical trials, lidocaine was used in combination with heparin or hyaluronic acid, which are expected to repair the bladder glycosaminoglycan layer defects, and are thus predicted to provide relatively slow bladder pain relief. In 2005, Parsons (32) used lidocaine with sodium bicarbonate and heparin. Both 80 and 160 mg lidocaine exerted a rapid analgesic effect within 20 min of instillation (32). Moreover, a single intravesical instillation with 80 mg lidocaine exerted a durable analgesic effect (>4 h), and in the group treated with 160 mg lidocaine three times per week for 2 weeks, 80% of the patients exhibited a significant improvement in symptoms lasting at least 48 h after the final treatment (32). Symptom relief lasted longer than the duration of the local anesthetic activity of lidocaine, suggesting that the solution suppresses neurologic inflammation. In 2012, Parsons *et al* (33) also demonstrated the efficacy of lidocaine with sodium bicarbonate and heparin in a double-blinded crossover trial. A total of 18 subjects were treated with 200 mg lidocaine, 50,000 IU heparin and sodium bicarbonate. The control group was treated with sodium bicarbonate alone. Compared with the control group, the lidocaine group exhibited a 35% reduction in pain and urinary urgency over a period of 12 h after the instillation (33).

Lidocaine is effective not only in reducing bladder pain, but also in relieving dyspareunia. Welk and Teichman (34) treated 57 patients with IC/BPS with the intravesical instillation of lidocaine, sodium bicarbonate and heparin three times a week for 3 weeks. All primary endpoints, including nocturia, voided volume, the Pelvic Pain Urgency Frequency score, and the Female Sexual Function Index pain domain score were significantly improved (34). Among the 23 participants with dyspareunia, 65% reported a >50% improvement in symptoms, with 13 participants (57%) claiming the resolution of dyspareunia (34).

As noted in the beginning of this chapter, the main difficulty with the intravesical instillation of lidocaine is the limited duration of the local anesthetic activity. Lv *et al* (35) compared treatment with 40 mg hyaluronic acid, 200 mg AL and hyaluronic acid + AL weekly for 8 weeks, then monthly for 4 months. Lidocaine exerted a favorable analgesic effect in the weekly phase of the treatment; however, in the monthly phase, no significant differences were observed in the hyaluronic acid group, and treatment was less effective in the AL group than in the hyaluronic acid group (35). In addition, the majority of the patients (14 of 15) in the AL group failed to complete the monthly treatment (35). That study was conducted over a longer period of time than the aforementioned studies and demonstrated that it was difficult to maintain the effects of

lidocaine on a monthly basis, even though it was effective on a daily or weekly basis (35).

## 7. Intravesical indwelling lidocaine-releasing devices

To achieve a longer anesthetic effect of lidocaine, various indwelling bladder devices have been developed. The present study conducted a literature search as mentioned in the 'Literature selection' chapter above and identified a device (LIRIS™; TARIS Biomedical Lexington, LLC) which is the only indwelling bladder lidocaine-releasing device that has advanced to clinical trials (Table I) (36,37). Prior to LIRIS™, an intravesical indwelling oxybutynin-releasing device (UROS™; Situs Corporation, Houston, TX, USA) was developed (38,39). This horseshoe-shaped device was 10-15 cm in the largest diameter and released oxybutynin at a concentrate rate for up to 28 days (39). In a phase I/II trial, implantation with UROS™ resulted in an increase in bladder capacity of 100% in patients with a neurogenic bladder with a good tolerability (39). There have been no new reports, and UROS™ has not been used clinically to date, at least to the best of our knowledge. It has been suggested that the large device size causes irritation, and LIRIS™ was developed under the concept that the device size should be minimalized to avoid discomfort (36).

In 2011, Lee and Cima (40) developed a prototype device for LIRIS™. This pretzel-form intravesical lidocaine delivery device is comprised of a drug delivery unit and a retention frame and can be implanted and removed during cystoscopy (40). The delivery unit is a water-permeable tube with an orifice that functions as an osmotic pump and the retention frame prevents premature expulsion and irritation by maintaining the shape of the device (40). A total of 2 g lidocaine is crystallized and inserted into the tube (40). In an *in vivo* lidocaine exposure study involving male rabbits, the device was well-tolerated by the animals without any apparent change in voiding behavior, and the lidocaine concentration in the bladder tissue was maintained >0.1 µg/g during the 3-day period of device release, in contrast to the single instillation that exhibited an undetectably low plasma lidocaine level within 24 h (40).

Improving on this device, LIRIS™ was developed and tested in clinical trials (36,37). Its structure was similar to the device aforementioned and it was loaded with solid-formed lidocaine (40). In a single-blind, sham procedure-controlled phase I clinical trial with an empty LIRIS™ 200 mg device, the retention and tolerability of the device alone was tested (36). An empty LIRIS™ 200 mg device was placed in 7 out of 10 healthy participants by cystoscopy and 3 out of 10 participants underwent cystoscopy as a sham procedure (36). The device remained in the bladder for 14 days and exhibited preferable tolerability and safety (36). The majority of adverse events were associated with the cystoscopy procedure, and the most common treatment-related adverse event was dysuria and microscopic hematuria, which was associated with both treatment groups (36). The only severe adverse event was severe dysuria, which was observed in the sham-operated group (36).

To evaluate the safety, tolerability and efficacy of LIRIS™ for patients with IC/BPS, an open-label, ascending-dose phase Ib cohort study with LIRIS™ 200 mg and LIRIS™ 650 mg devices was conducted in women with moderate-to-severe IC/BPS (36). All patients had Hunner's lesions or

glomerulations, and bladder pain (36). The patients were divided into two cohorts [LIRIS™ 200 mg (cohort 1, n=9) and LIRIS™ 650 mg (cohort 2, n=9)]; 2 patients participated in both cohorts (36). The participants kept the LIRIS™ device in the bladder for 14 days and were followed-up until 14 days following its removal. An additional 60-day follow-up of cohort 2 was implemented to evaluate the long-term safety and efficacy. Approximately 90% of the subjects experienced adverse events. The majority of these were mild or moderate in intensity and the most common adverse events were dysuria, bladder pain, hematuria and urethral pain (36). In total, three AEs were severe, although none were that severe to require the discontinuation of the trial (36). Both devices exhibited a clinically-meaningful relief of symptoms, including bladder pain, urgency, voiding frequency and improvement in all disease questionnaires [pain visual analog scale (VAS), urinary urgency VAS, O'Leary-Sant interstitial cystitis symptom index (ICSI) and interstitial cystitis problem index (ICPI)] (36). The cystoscopy findings also revealed the resolution of erythema and Hunner's lesions (5 out of 6 participants) (36). Moreover, 4 participants in cohort 2 experienced pain relief on day 28, and 3 participants reported continuous pain relief on days 60 and 90 (36).

In a 2-center, open-label phase Ib study, a LIRIS™ 400 mg device (not only 200 and 650 mg), also exhibited long-lasting improvement in lesions, pain, voiding frequency and the ICSI/ICPI score with favorable tolerance and safety (41). With these results, two phase II multicenter, randomized, double-blind, placebo-controlled studies were conducted to evaluate the efficacy of a LIRIS™ 400 mg device in female patients with HIC (study 001) and BPS without Hunner's lesions (study 002) (37). Both studies involved two treatment parts. Patients in the treatment 1 part were randomly divided into the LIRIS™ 400 mg device and placebo groups, and all participants who requested additional treatment were eligible to participate in the treatment 2 part, an open-label evaluation of a LIRIS™ 400 mg device as a second treatment at any time point from day 28 of follow-up to week 20 for study 001 and week 22 for study 002 (37). In total, 59 of 72 patients in study 001 were randomly divided and received treatment [LIRIS™/LIRIS™ (n=31), placebo/placebo (n=12) and placebo/LIRIS™ (n=16)]. A total of 11 patients were disenrolled from the study. In addition, 131 patients in study 002 were randomly divided and received treatment 1 [LIRIS™ (n=65) or the placebo (n=66)]. In total, 22 patients discontinued treatment and 98 patients received treatment 2 [LIRIS™ (n=50) or the placebo (n=48)]. In both studies, the frequency of treatment-emergent adverse events (TEAEs) was similar between the treatment groups (37). The most frequently reported TEAEs in the LIRIS™ group were dysuria, urinary tract infections, hematuria and bladder discomfort, and bladder pain in study 001, and dysuria, procedural pain, bladder discomfort, and nausea in study 002 (37). Study discontinuations due to TEAEs were low, and the majority of TEAEs were mild or moderate (37). The mean average bladder numeric rating scale (NRS) pain at week 4, which was the primary endpoint at the primary timepoint did not differ significantly between the groups in both studies. There was numerical pain relief in the LIRIS™ group in study 001 (37). There were no numerical or statistically significant differences between the study 002 groups

Table I. Summary of published clinical trials of intravesical lidocaine-releasing devices for the treatment of IC/BPS.

Author	Year of publication	Phase	No. of subjects	Treatment period	Treatment used	Comments	(Refs.)
Nickel <i>et al</i>	2012	I	10	14 days	LiRIS™ 200 mg device (empty) vs. sham procedure	Single-blind sham-procedure controlled trial. Implantation of LiRIS to healthy participants for 14 days exhibited preferable tolerability and safety.	(36)
Nickel <i>et al</i>	2012	Ib	16	14 days	LiRIS™ 200 mg and LiRIS™ 650 mg	Open-label, ascending-dose cohort study for women with moderate-to-severe IC/BPS. Both devices exhibited clinically meaningful relief in bladder pain, urgency, and voiding frequency with preferable tolerability and safety.	(36)
Evans <i>et al</i>	2021	II	59	14 days	LiRIS™ 400 mg/LiRIS™ 400 mg (n=31) vs. placebo/LiRIS™ 400 mg (n=16) vs. placebo/placebo (n=12)	LiRIS 650 mg led to continuous pain relief. Multicenter, randomized, double-blind, placebo-controlled study for patients with HIC.	(37)
Evans <i>et al</i>	2021	II	131	14 days	LiRIS™ 400 mg (n=65) vs. placebo (n=66)	Numerical, yet not significant improvement in bladder NRS pain, number of Hunner's lesions, and number of micturitions per day. Multicenter, randomized, double-blind, placebo-controlled study for patients with BPS.	(37)
No numerical or significant differences observed in any outcomes.							

IC/BPS, interstitial cystitis/pelvic pain syndrome; HIC, Hunner-type interstitial cystitis; BPS, bladder pain syndrome; NRS, numeric rating scale.

with respect to NRS changes at any timepoint (37). There was a statistically significant decrease in the number of Hunner's lesions following treatment in study 001, although there was no significant difference between the LIRIS™ and placebo groups (37). In addition, the study 001 LIRIS™ group exhibited a greater decrease in the number of micturitions per day, although the difference was not significant (37). No numerical or statistically significant differences between treatments were observed in study 002 (37). There were no statistically significant or numerical differences between the treatments in urgency counts per day changes in either study (37). The authors of that study were of the opinion that the results of study 001 were not statistically significant due to the sample size, which was smaller than originally planned (37). They also believed that the validity of study 002 was unclear as there is no well-established and definitive test to identify the bladder as the source of the pelvic pain (37).

In addition to LIRIS™, several devices have been developed, although the devices have not yet reached clinical trials, at least to the best of our knowledge. In 2021, a three-dimensional-printed elastomer-based intravesical delivery system was developed (42). Using stereolithography, the device obtained complex and precise form with high resolution and lidocaine was added to the liquid resin before printing (42). The solid device with 10 and 30% lidocaine demonstrated first-order release kinetics across 14 days in simulated urine with a shaking water bath (42).

In 2021, Kim *et al* (43) developed a device using another approach [a lidocaine-loaded indwelling urinary catheter (IUC)]. Kim *et al* (43) assembled a thin strand composed of poly(lactic-co-glycolic-acid) (PLGA) and lidocaine with an IUC by wrapping the surface to produce a L\_PLGA\_IUC. L\_PLGA\_IUC exhibited the durable release of lidocaine at pH 7.4 and 6.4. At pH 6.5, L\_PLGA\_IUC released lidocaine (~669.3 µg/cm) during the first day, after which lidocaine was released at a rate of ~5.0 µg/cm until 5 days, which was sufficiently high to demonstrate local anesthetic activity (43). In an *in vivo* animal cystometrogram (CMG) analysis, L\_PLGA\_IUC decreased the bladder pressure and increased the interval of detrusor contractions; the effects were still present 3 days after the IUC insertion (43). In addition, efficacy was demonstrated, even in the cystitis-induced bladder (43). Moreover, the L\_PLGA\_IUC group of rats exhibited a significantly lower expression of pain-related inflammatory markers (NGF, cyclooxygenase-2 and IL-6) in bladder tissues (43).

As all of these devices are still in their infancy, there is limited evidence as regards their efficacy, and thus, they are not the first choice for IC/BPS treatment. If these devices significantly improve or a novel more effective device is developed, and further clinical trials are conducted, these devices may change the IC/BPS treatment strategy.

## 8. Conclusions and future perspectives

The intravesical instillation of drugs is conventionally performed in urology to deliver drugs directly and locally to the bladder mucosa. The diagnosis and treatment of IC/BPS is complex and difficult as it includes not only HIC with marked mucosal damage, but also NHIC (BPS) with no specific findings on cystoscopy and is also associated with

CSS. Lidocaine has the potential to help in evaluating the IC/BPS phenotype, reduce pain through its analgesic effect, and break the pain cycle of neurologic inflammation through an anti-inflammatory effect. Currently, there are two major issues with the use of lidocaine: i) There are a limited number of previous studies describing the diagnostic significance of lidocaine; and ii) lidocaine lacks a long-term analgesic effect. If overcome these difficulties can be overcome with further research and the development of novel indwelling bladder devices, lidocaine may constitute a major advancement in IC/BPS treatment.

## Acknowledgements

Not applicable.

## Funding

No funding was received.

## Availability of data and materials

Not applicable.

## Authors' contributions

TomofumiW and TSa wrote the manuscript. TSa and MW made substantial contributions to the conception and design of the present analysis and were involved in the literature search. TomofumiW, KW, KE and ToyohikoW made substantial contributions to and were involved in the literature search and study selection for the review. TSa, MW, YM, TSe, YK and MA made substantial contributions to the conception and design of the study, provided critical points of discussion and were involved in the completion of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

## References

1. Beckett MK, Elliott MN, Clemens JQ, Ewing B and Berry SH: Consequences of interstitial cystitis/bladder pain symptoms on women's work participation and income: Results from a national household sample. *J Urol* 191: 83-88, 2014.
2. Yoshimura N, Homma Y, Tomoe H, Otsuka A, Kitta T, Masumori N, Akiyama Y, Niimi A, Mitsui T, Nanri M, *et al*: Efficacy and safety of intravesical instillation of KRP-116D (50% dimethyl sulfoxide solution) for interstitial cystitis/bladder pain syndrome in Japanese patients: A multicenter, randomized, double-blind, placebo-controlled, clinical study. *Int J Urol* 28: 545-553, 2021.

3. Sadahira T, Maruyama Y, Watanabe T, Sekito T, Mitsui Y, Wada K, Araki M and Watanabe M: Medical uses for phenol in the urinary tract: A possible forgotten treatment (Review). *Med Int* 1: 13, 2021.
4. Sekito T, Sadahira T, Watanabe T, Maruyama Y, Watanabe T, Iwata T, Wada K, Edamura K, Araki M and Watanabe M: Medical uses for silver nitrate in the urinary tract (Review). *World Acad Sci J* 4: 6, 2022.
5. Hunner GL: A rare type of bladder ulcer in women; report of cases. *Boston Med Surg J* 172: 660-664, 1915.
6. Homma Y, Akiyama Y, Tomoe H, Furuta A, Ueda T, Maeda D, Lin AT, Kuo HC, Lee MH, Oh SJ, *et al*: Clinical guidelines for interstitial cystitis/bladder pain syndrome. *Int J Urol* 27: 578-589, 2020.
7. Abrams P, Andersson KE, Apostolidis A, Birder L, Bliss D, Brubaker L, Cardozo L, Castro-Diaz D, O'Connell PR, Cottenden A, *et al*: 6th international consultation on incontinence. Recommendations of the international scientific committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse and faecal incontinence. *Neurourol Urodyn* 37: 2271-2272, 2018.
8. Parsons CL, Lilly JD and Stein P: Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). *J Urol* 145: 732-735, 1991.
9. Evans AR, Nicol GD and Vasko MR: Differential regulation of evoked peptide release by voltage-sensitive calcium channels in rat sensory neurons. *Brain Res* 712: 265-273, 1996.
10. Herzberg U, Eliav E, Dorsey JM, Gracely RH and Kopin IJ: NGF involvement in pain induced by chronic constriction injury of the rat sciatic nerve. *Neuroreport* 8: 1613-1618, 1997.
11. Lamb K, Gebhart GF and Bielefeldt K: Increased nerve growth factor expression triggers bladder overactivity. *J Pain* 5: 150-156, 2004.
12. Dmitrieva N and McMahon SB: Sensitisation of visceral afferents by nerve growth factor in the adult rat. *Pain* 66: 87-97, 1996.
13. Neblett R, Cohen H, Choi Y, Hartzell MM, Williams M, Mayer TG and Gatchel RJ: The Central Sensitization Inventory (CSI): Establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. *J Pain* 14: 438-445, 2013.
14. Walitt B, Nahin RL, Katz RS, Bergman MJ and Wolfe F: The prevalence and characteristics of fibromyalgia in the 2012 National Health Interview Survey. *PLoS One* 10: e0138024, 2015.
15. Whitehead WE, Palsson O and Jones KR: Systematic review of the comorbidity of irritable bowel syndrome with other disorders: What are the causes and implications? *Gastroenterology* 122: 1140-1156, 2002.
16. Oravisto KJ: Epidemiology of interstitial cystitis. *Ann Chir Gynaecol Fenn* 64: 75-77, 1975.
17. Leppilahti M, Sairanen J, Tammela TL, Aaltomaa S, Lehtoranta K and Auvinen A: Prevalence of clinically confirmed interstitial cystitis in women: A population based study in Finland. *J Urol* 174: 581-583, 2005.
18. Berry SH, Elliott MN, Suttrop M, Bogart LM, Stoto MA, Eggers P, Nyberg L and Clemens JQ: Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. *J Urol* 186: 540-544, 2011.
19. Walker MC, Masters JR, Parris CN, Hepburn PJ and English PJ: Intravesical chemotherapy: In vitro studies on the relationship between dose and cytotoxicity. *Urol Res* 14: 137-140, 1986.
20. Gordh T: Xylocain, a new local analgesic. *Anaesthesia* 4: 4-9, 1949.
21. MacGregor RR, Thorner RE and Wright DM: Lidocaine inhibits granulocyte adherence and prevents granulocyte delivery to inflammatory sites. *Blood* 56: 203-209, 1980.
22. Seeman P: The membrane actions of anesthetics and tranquilizers. *Pharmacol Rev* 24: 583-655, 1972.
23. Su D, Gu Y, Wang Z and Wang X: Lidocaine attenuates proinflammatory cytokine production induced by extracellular adenosine triphosphate in cultured rat microglia. *Anesth Analg* 111: 768-774, 2010.
24. Serra MF, Anjos-Valotta EA, Olsen PC, Couto GC, Jurgilas PB, Cotias AC, Pão CR, Ferreira TP, Arantes AC, Pires AL, *et al*: Nebulized lidocaine prevents airway inflammation, peribronchial fibrosis, and mucus production in a murine model of asthma. *Anesthesiology* 117: 580-591, 2012.
25. Kissin I, Lee SS and Bradley EL Jr: Effect of prolonged nerve block on inflammatory hyperalgesia in rats: Prevention of late hyperalgesia. *Anesthesiology* 88: 224-232, 1998.
26. Fenton BW, Palmieri PA and Fanning J: Receiver operating characteristic curves of symptom scores in the diagnosis of interstitial cystitis/painful bladder syndrome. *J Minim Invasive Gynecol* 15: 601-604, 2008.
27. Butrick CW, Sanford D, Hou Q and Mahnken JD: Chronic pelvic pain syndromes: Clinical, urodynamic, and urothelial observations. *Int Urogynecol J Pelvic Floor Dysfunct* 20: 1047-1053, 2009.
28. Taneja R: Intravesical lignocaine in the diagnosis of bladder pain syndrome. *Int Urogynecol J* 21: 321-324, 2010.
29. Offiah I, Dilloughery E, McMahon SB and O'Reilly BA: Prospective comparative study of the effects of lidocaine on urodynamic and sensory parameters in bladder pain syndrome. *Int Urogynecol J* 30: 1293-1301, 2019.
30. Henry R, Patterson L, Avery N, Tanzola R, Tod D, Hunter D, Nickel JC and Morales A: Absorption of alkalized intravesical lidocaine in normal and inflamed bladders: A simple method for improving bladder anesthesia. *J Urol* 165: 1900-1903, 2001.
31. Nickel JC, Moldwin R, Lee S, Davis EL, Henry RA and Wyllie MG: Intravesical alkalized lidocaine (PSD597) offers sustained relief from symptoms of interstitial cystitis and painful bladder syndrome. *BJU Int* 103: 910-918, 2009.
32. Parsons CL: Successful downregulation of bladder sensory nerves with combination of heparin and alkalized lidocaine in patients with interstitial cystitis. *Urology* 65: 45-48, 2005.
33. Parsons CL, Zupkas P, Proctor J, Koziol J, Franklin A, Giesing D, Davis E, Lakin CM, Kahn BS and Garner WJ: Alkalinized lidocaine and heparin provide immediate relief of pain and urgency in patients with interstitial cystitis. *J Sex Med* 9: 207-212, 2012.
34. Welk BK and Teichman JM: Dyspareunia response in patients with interstitial cystitis treated with intravesical lidocaine, bicarbonate, and heparin. *Urology* 71: 67-70, 2008.
35. Lv YS, Zhou HL, Mao HP, Gao R, Wang YD and Xue XY: Intravesical hyaluronic acid and alkalized lidocaine for the treatment of severe painful bladder syndrome/interstitial cystitis. *Int Urogynecol J* 23: 1715-1720, 2012.
36. Nickel JC, Jain P, Shore N, Anderson J, Giesing D, Lee H, Kim G, Daniel K, White S, Larrivee-Elkins C, *et al*: Continuous intravesical lidocaine treatment for interstitial cystitis/bladder pain syndrome: Safety and efficacy of a new drug delivery device. *Sci Transl Med* 4: 143ra100, 2012.
37. Evans R, Kohan A, Moldwin R, Radecki D, Geib T and Peters KM: Safety, tolerability, and efficacy of LiRIS 400 mg in women with interstitial cystitis/bladder pain syndrome with or without Hunner lesions. *Neurourol Urodyn* 40: 1730-1739, 2021.
38. Chancellor MB: Future trends in the treatment of urinary incontinence. *Rev Urol* 3 (Suppl 1): S27-S34, 2001.
39. Oxybutynin intravesical-situs. I-oxy. *Drugs R D* 3: 82-83, 2002.
40. Lee H and Cima MJ: An intravesical device for the sustained delivery of lidocaine to the bladder. *J Control Release* 149: 133-139, 2011.
41. Peters K, Seifu Y, Cutie C and Radecki D: MP72-16 safety, tolerability, and preliminary efficacy of LiRIS 400 mg in women with ulcerative interstitial cystitis. *J Urol* 195: e958-e958, 2016.
42. Xu X, Goyanes A, Trenfield SJ, Diaz-Gomez L, Alvarez-Lorenzo C, Gaisford S and Basit AW: Stereolithography (SLA) 3D printing of a bladder device for intravesical drug delivery. *Mater Sci Eng C Mater Biol Appl* 120: 111773, 2021.
43. Kim CR, Jang EB, Hong SH, Yoon YE, Huh BK, Kim SN, Kim MJ, Moon HS and Choy YB: Indwelling urinary catheter assembled with lidocaine-loaded polymeric strand for local sustained alleviation of bladder discomfort. *Bioeng Transl Med* 6: e10218, 2021.



This work is licensed under a Creative Commons Attribution 4.0 International (CC BY 4.0) License.