Intravesical Treatment for Interstitial Cystitis

Mei-Yu Jang, M.D., Hann-Chorng Kuo, M.D.[1]

Department of Urology, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; Department of Urology[1], Buddhist Tzu Chi General Hospital and Tzu Chi University, Hualien, Taiwan

Interstitial cystitis (IC) is a syndrome of mystery in urology. IC is characterized by bladder pain associated with urgency, frequency, nocturia, dysuria and sterile urine [1]. The diagnosis of this disease remains unclear and should be based on the exclusion of other diseases. The possible etiologies of IC are (1) a post-infection autoimmune process, (2) mast cell activation induced by inflammation, toxins or stress, (3) urothelial dysfunction and increased permeability of the urothelium, or (4) neurogenic inflammation. The principles for treatment of IC are based on (1) controlling the dysfunctional epithelium by continual replenishment of the glycosaminoglycan (GAG) layer, (2) inhibiting neurological hyperactivity by administration of amitriptyline or imipramine, (3) suppression of allergies with antihistamines, and (4) pain control with non-steroid anti-inflammatory drugs (NSAID), Cox-2 inhibitors or tranquilizers.

Intravesical treatment for IC usually starts with hydrodistention of the bladder. Hydrodistention of the bladder may be recommended as the first treatment choice for patients with IC because it provides relatively high efficacy. However, the short duration of the efficacy requires a second-line treatment option for better management of patients with IC [2]. Intravesical medications such as heparin and heparinoids (e.g. sodium pentosan polysulfate, hyaluronic acid, chondroitin sulphate), dimethyl sulphoxide (DMSO) and vanilloids (capsaicin or resiniferatoxin) have been tried and have shown to be effective in a portion of IC patients.

The advantages of intravesical treatment of IC include: (1) delivery of high drug concentrations into the bladder, (2) low incidence of systemic side effects, (3) reduced oral drug interactions, and (4) direct repair of bladder urothelial deficits.

BLADDER HYDRODISTENTION

For the intravesical treatment of IC, hydrodistention of the bladder is the first choice for diagnosis, biopsy and treatment. Although hydrodistention is effective for relief of bladder symptoms of IC, the symptoms usually recur soon and repeat hydrodistention is necessary [2]. Urine from patients with IC has been shown to inhibit urothelial proliferation through a putative antiproliferative factor and to contain decreased levels of heparin-binding epidermal growth factor-like growth factor (HB-EGF) compared with the control subjects. Bladder stretch increased HB-EGF and conversely reduced antiproliferative factor activity in urine from patients with IC but not in the control subjects up to 2 weeks after distention [3]. Prolonged hydrodistention under epidural anesthesia with intravesical pressure equal to the mean arterial pressure of the patient has been shown to give long-term benefits. Glemain et al treated 65 consecutive IC patients and found this treatment was effective in 60% of patients at 6 months and 43.3% at 1 year [4]. Yamada et al also had similar therapeutic results. In their study, adjuvant hydrodistention under epidural anesthesia was effective for 70% of patients for more than 3 months [5]. Rose et al found that distention with electromotive drug administration (EMDA) in the doctor's office setting was as effective as hydrodistention of the bladder in the operating room [6].

Received: July 9, 2008 Accepted: July 28, 2008
Address correspondence to: Dr. Hann-Chorng Kuo, Department of Urology, Buddhist Tzu Chi General Hospital, 707, Section 3, Chung Yang Road, Hualien, Taiwan
E-mail: hck@tzuchi.com.tw

INTRAVESICAL HEPARIN THERAPY

Heparin is known to mimic the GAG layer structure, and therefore, it is rational to treat IC with intravesical heparin with the aim of replenishing the defective GAG layer in the bladder. Parsons et al treated 48 IC patients with intravesical heparin 10000 IU three times per week for 3 months. They reported 56% of patients had improvement in a 3-day voiding diary and cystometrograms at 3 months. The authors concluded that intravesical heparin controlled symptoms in more than 50% of IC patients [7]. Kuo treated 40 IC patients who had positive KCl test results with intravesical heparin 25000 IU retained for 2 hours, twice per week for 3 months. The symptom scores of 29 (72.5%) patients improved by >50%. Urodynamic study results revealed significant improvement in the first sensation of filling and bladder capacity after heparin treatment [8]. Although there is no consensus on the dose, therapeutic frequency, or the treatment duration in intravesical heparin therapy, it has been suggested that intravesical heparin therapy should start at a high frequency in the acute stage, with a reduced frequency in the subacute stage. Treatment should continue intermittently in the maintenance stage, and should not stop, even in non-responders.

A combination of heparin and alkalinized lidocaine has recently been used to treat IC patients [9]. Parsons et al used 40000 U heparin with 3 mL 8.4% sodium bicarbonate and 1% (Group 1) or 2% lidocaine (Group 2) for intravesical treatment three times per week for 2 weeks. Significant immediate symptom relief after a single treatment was noted in 75% and 94% of groups 1 and 2 patients, respectively, 50% of group 2 patients had symptom relief for 4 hours and 80% of group 2 patients reported significant sustained symptom relief after 2 weeks.

INTRAVESICAL HYALURONIC ACID

Hyaluronic acid is a non-sulfated mucopolysaccharide component of the GAG layer and is believed to be present in subepithelial connective tissue to protect the bladder wall from irritants in the urine. Intravesical treatment with this agent has been investigated in IC patients. Morales et al treated 25 IC patients refractory to any treatment with 40 mg hyaluronic acid weekly for 4 weeks and then monthly.

They found an initial 56% positive response rate at week 4, and a 71% positive response rate at week 12. The response was maintained until week 20, but decreased after week 24 [10]. A recent prospective, non-randomized study with a 3-year follow up in 20 IC patients revealed subjective continuing improvement in pain and frequency, with 55% of patients treated with intravesical hyaluronic acid choosing to continue treatment for symptomatic relief [11].

INTRAVESICAL CHONDROITIN SULPHATE

Chondroitin sulphate is a major component of the GAG layer and comprises 1/3 of the total proteoglycans on the bladder surface. A deficit of chondroitin sulphate proteoglycans on the bladder urothelium has been detected in IC patients [12]. Eighteen IC patients who had positive KCl test results had intravesical instillation of 40 mL of 0.2% chondroitin sulphate once per week for 4 weeks followed by one treatment per month for 12 months. Thirteen of the 18 patients treated (66.7%) had improvement in their lower urinary tract symptoms [13].

INTRAVESICAL PPS TREATMENT

Because the oral pentosan polysulphate (PPS) was effective in treating IC patients, intravesical instillation was investigated to see if better results could be obtained. Bade et al treated 10 IC patients with 300 mg PPS in 50 mL 0.9% saline twice per week for 3 months and 10 patients with a placebo. Four of the treated patients and two control patients had significant symptomatic relief. Eight continued PPS therapy and four without treatment had symptomatic relief [14].

INTRAVESICAL DMSO TREATMENT

DMSO provides an anti-inflammatory effect, analgesia, muscle relaxation, and alteration of the collagen response and has an influence on conduction and neurotransmission in the sensory nerves. At concentrations of 10%, DMSO inhibits mast cell secretion, but an initial increase in mast cell secretion and worsened lower urinary tract symptoms have been noted at a concentration of 50% [15]. Relief of symptoms was reported in 50% of IC patients treated with 50 mL of 50% DMSO retained for 15-20 minutes, given once per week for 2-3 months. However, the relapse rate was 35%-40% during a 24 month follow-up period [16]. The high concentration of DMSO has been thought to harm the bladder wall, resulting in a contracted bladder after repeated instillations. Melchior et al found a 40% concentration of DMSO completely and irreversibly abolished contractions of rat bladders [17].

INTRAVESICAL BCG TREATMENT

Intravesical bacillus Calmette-Guerin (BCG) is an immunological therapy for superficial bladder cancer and is known to stimulate the Th1 cytokine profile. The use of BCG in the treatment of IC aims to modulate immunologic and allergic responses in the IC bladder wall [18]. In a double-blind, placebo-controlled study, 30 IC patients meeting NIDDK criteria received six weekly treatments with Tice strain BCG instillation or a placebo and were followed-up for 8 months. There was a 60% response rate in the treated patients and a 27% rate in the control group [19]. In long-term follow up, 89% of patients who responded favorably after the 6-week BCG treatment continued to have excellent responses at 24-33 months [20]. However, the ICCTG recently reported the results of a multi-center, randomized, double-blind, placebo-controlled trial of intravesical BCG for the treatment of refractory IC. Among 265 patients who received BCG or a placebo and were followed-up for 34 weeks, the response rate was 12% for the placebo and 21% for BCG ($p=0.062$). Only marginal statistical significance was observed in the secondary outcomes (voiding diary, pain, urgency and IC symptom index). Although the safety profile was acceptable, intravesical BCG treatment was considered ineffective in treatment of refractory IC [21].

INTRAVESICAL VANILLOIDS

Vanilloid receptors (VR1) have been found on the urothelial cells, suburothelial sensory afferents and smooth muscle cells. VR1 co-localizes with $P2X_3$ receptors, mediating stretch, pain and noxious stimuli. Desensitization of VR1 receptors may deplete terminal nerve endings and end pain [22,23]. The most popular vanilloid agents used for clinical trials in IC are capsaicin and resiniferatoxin. Thirty-six patients with hypersensitive bladders were randomized to receive intravesical 10 μM capsaicin or placebo twice weekly for 1 month. Significant improvement in frequency and nocturia was noted in the patients treated with capsaicin at the 6-month follow-up examination. Both groups experienced a significant reduction in pain at the end of treatment and at the 6 month follow-up evaluation. However, no improvement in urgency was experienced after capsaicin instillation [24]. Intravesical capsaicin therapy was also investigated in Taiwan. The author treated 10 patients with IC and 10 with hypersensitive bladders. Capsaicin in a 10 μM concentration was instilled intravesically once per week for 6 weeks. There was a short response period in eight patients with hypersensitive bladders (3-5 days) and in two IC patients (2-3 days). Nevertheless, no side effects were reported except for severe irritating symptoms after treatment [25].

Lazzeri et al treated 18 IC patients with single doses of 10 nM resiniferatoxin (RTX) or placebo. Significant improvements in frequency, nocturia and pain scores were noted at 30 days, but therapeutic effects were reduced at 3 months [26]. The same author further treated five women with IC with prolonged intravesical infusion of 10 nM RTX for 10 days. The pain score (6.7 to 3.2) decreased after treatment and remained significantly lower at 3 months. Frequency (11.3 to 8.7) and nocturia (3.6 to 1.9) were also reduced at 3 months [27]. In a preliminary study, Peng and Kuo found that multiple intravesical treatments with RTX 10 nM once weekly for 4 weeks was well tolerated and reduced bladder pain and increased the symptom score in 58% of 12 women with chronic IC [28]. Although these preliminary studies seem promising, a recently reported multi-center, randomized, placebo-controlled trial to assess the efficacy and safety of single-dose RTX to treat IC revealed no significant difference between RTX and the placebo. In 163 IC patients treated with 10 nM, 50 nM, or 100 nM RTX or a placebo in a single intravesical treatment and followed up over 12 weeks, RTX did not improve the overall symptoms, pain, urgency, frequency, nocturia, or average void volume at 12 weeks. The bladder pain induced by RTX instillation increased at the higher doses [29].

Although capsaicin or RTX seems theoretically to be effective on IC, the clinical results do not support their use, possibly due to underlying pathophysiologies other than vanilloid receptor activation in IC patients. IC bladder is likely to have multiple defects and inflammatory

processes, treatment of IC might not be effective when aiming at a single pathology.

CONCLUSIONS

Intravesical treatment with heparin, hyaluronic acid, chondroitin sulphate, BCG, or DMSO for IC is effective for some patients. However, the placebo effect should be weighed and randomized, double-blind trials should be undertaken to demonstrate the actual therapeutic effects of these therapeutic modalities. By far, intravesical heparin remains the treatment of choice for early IC according to the study results. Combined therapies with hydrodilatation, antihistamines, NSAID, and anticholinergics might be beneficial in addition to intravesical treatment. Long-term therapy is needed to ensure a better cure rate for IC.

REFERENCES

1. Tait L: Cure of chronic perforating ulcer by the formation of an artificial vesico-vaginal fistula. Lancet 1870; **2**:738.
2. Inoue R, Takahashi S, Sunaoshi K, Ichihara K, Masumori N, Tsukamoto T: Hydrodistention of the bladder in patients with interstitial cystitis--clinical efficacy and its association with immuno- histochemical findings for bladder tissues. Hinyokika Kiyo 2006; **52**: 765-768.
3. Tsai TC, Zhang CO, Shoenfelt JL, Johnson HW Jr, Warren JW, Keay S: Bladder stretch alters urinary heparin-binding epidermal growth factor and antiproliferative factor in patients with interstitial cystitis. J Urol 2000; **163**:1440-1444.
4. Glemain P, Riviere C, Lenormand L, Karam G, Bouchot O, Buzelin JM: Prolonged hydrodistention of the bladder for symptomatic treatment of interstitial cystitis: Efficacy at 6 months and 1 year. Eur Urol 2002; **41**:79-84.
5. Yamada T, Murayama T, Andoh M: Adjuvant hydrodis-tension under epidural anesthesia for interstitial cystitis. Int J Urol 2003; **10**: 463-468.
6. Rose AE, Azevedo KJ, Payne CK: Office bladder distention with electromotive drug administration (EMDA) is equivalent to distention under general anesthesia (GA). BMC Urol 2005; **5**:14.
7. Parsons CL, Housley T, Schmidt JD, Lebow D: Treatment of interstitial cystitis with intravesical heparin. Br J Urol 1994; **73**:504-507.
8. Kuo HC: Urodynamic results of intravesical heparin therapy for women with frequency urgency syndrome and interstitial cystitis. J Formosan Med Assoc 2001; **100**:309-314.
9. Parsons CL: Successful downregulation of bladder sensory nerves with combination of heparin and alkalinized lidocaine in patients with interstitial cystitis. Urology 2005; **65**:45-48.
10. Morales A, Emerson L, Nickel JC, Lundie M: Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. J Urol 1996; **156**:45-48.
11. Kallestrup EB, Jorgensen SS, Nordling J, Hald T: Treatment of interstitial cystitis with Cystistat: A hyaluronic acid product. Scand J Urol Nephrol 2005; **39**:143-147.
12. Hurst RE, Roy JB, Min KW, et al: A deficit of chondroitin sulfate proteoglycans on the bladder uroepithelium in interstitial cystitis. Urology 1996; **48**:817- 821.
13. Steinhoff G, Ittah B, Rowan S: The efficacy of chondroitin sulfate 0.2% in treating interstitial cystitis. Can J Urol 2002; **9**:1454-1458.
14. Bade JJ, Laseur M, Nieuwenburg A, van der Weele LT, Mensink HJ: A placebo- controlled study of intravesical pentosanpolysulphate for the treatment of interstitial cystitis. Br J Urol 1997; **79**:168-171.
15. Parkin J, Shea C, Sant GR: Intravesical dimethyl sulfoxide (DMSO) for interstitial cystitis--a practical approach. Urology 1997; **49(Suppl 5A)**:105-107.
16. Sant GR: Intravesical 50% dimethyl sulfoxide (Rimso-50) in treatment of interstitial cystitis. Urology 1987; **29**:17-21.
17. Melchior D, Packer CS, Johnson TC, Kaefer M: Dimethyl sulfoxide: Does it change the functional properties of the bladder wall? J Urol 2003; **170**:253-258.
18. Peters KM, Diokno AC, Steinert BW: Preliminary study on urinary cytokine levels in interstitial cystitis: Does intravesical bacille Calmette-Guerin treat interstitial cystitis by altering the immune profile in the bladder? Urology 1999; **54**:450-453.
19. Peters K, Diokno A, Steinert B, et al: The efficacy of intravesical Tice strain baccilus Calmette-Guerin in the treatment of interstitial cystitis: A double-blind, prospective, placebo controlled trial. J Urol 1997; **157**:2090-2094.
20. Peters KM, Diokno AC, Steinert BW, Gonzalez JA: The efficacy of intravesical bacillus Calmette-Guerin in the treatment of interstitial cystitis: Long-term follow up. J Urol 1998; **159**:1483-1486.
21. Mayer R, Propert KJ, Peters KM, et al: A randomized controlled trial of intravesical bacillus calmette-guerin for treatment refractory interstitial cystitis. J Urol 2005; **173**:1186-1191.
22. Brady CM, Apostolidis A, Harper M, et al: Parallel changes in bladder suburothelial vanilloid receptor TRPV1 and pan-neuronal marker PGP9.5 immunoreactivity in patients with neurogenic detrusor overactivity after intravesical resiniferatoxin treatment. BJU Int 2004; **93**:770-776.
23. Smet PJ, Moore KH, Jonavicius J: Distribution and colocalization of calcitonin gene-related peptide, tachykinins, and vasoactive intestinal peptide in normal and idiopathic unstable human urinary bladder. Lab Invest 1997; **77**:37-49.
24. Lazzeri M, Beneforti P, Benaim G, Maggi A, Lecci A, Turini D: Intravesical capsaicin for treatment of severe bladder pain: A randomized placebo controlled study. J Urol 1996; **156**:947-952.
25. Kuo HC: Treatment of hypersensitive bladder and interstitial cystitis by intravesical instillation of capsaicin. Tzu Chi Med J 1994; **6**:239-244.
26. Lazzeri M, Beneforti P, Spinelli M, Zanollo A, Barbagli G, Turini D: Intravesical resiniferatoxin for the treatment of hypersensitive disorder: A randomized placebo controlled study. J Urol 2000; **164**: 676-679.
27. Lazzeri M, Spinelli M, Beneforti P, Malaguti S, Giardiello G, Turini D: Intravesical infusion of resiniferatoxin by a temporary in situ drug delivery system to treat interstitial cystitis: A pilot study. Eur Urol 2004; **45**:98-102.
28. Peng CH, Kuo HC: Multiple intravesical instillations of low-dose resiniferatoxin in the treatment of refractory interstitial cystitis. Urol Int 2007; **78**:78-81.
29. Payne CK, Mosbaugh PG, Forrest JB, et al: Intravesical resiniferatoxin for the treatment of interstitial cystitis: A randomized, double-blind, placebo controlled trial. J Urol 2005; **173**:1590-1594.