Intravesical Liposome Versus Oral Pentosan Polysulfate for Interstitial Cystitis/Painful Bladder Syndrome

Yao-Chi Chuang,* Wei-Chiang Lee, Wei-Chia Lee and Po-Hui Chiang

From the Department of Urology, Chang Gung Memorial Hospital Kaohsiung, Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan, Republic of China

Purpose: We evaluated the safety and efficacy of intravesical liposomes, a mucosal protective agent, compared to oral pentosan polysulfate sodium for interstitial cystitis/painful bladder syndrome.

Materials and Methods: We performed a prospective longitudinal study of the effect of 2 independent treatments (intravesical liposomes and oral pentosan polysulfate sodium) in patients with interstitial cystitis/painful bladder syndrome. Ten possible responses (or measures) to treatment were monitored at 3 time points, including baseline, and weeks 4 and 8. A total of 24 patients with interstitial cystitis/painful bladder syndrome were evaluated in a 1:1 ratio to intravesical liposomes (80 mg/40 cc distilled water) once weekly or to oral pentosan polysulfate sodium (100 mg) 3 times daily for 4 weeks each.

Results: No patient had urinary incontinence, retention or infection due to liposome instillation. There were no unanticipated adverse events and no significant worsening of symptoms during followup. Statistically significant decreases in urinary frequency and nocturia were observed in each treatment group. Statistically significant decreases in pain, urgency and the O'Leary-Sant symptom score were observed in the liposome group. Decreased urgency in the liposome group had the most profound effect of the ordinal measures.

Conclusions: Each glycosaminoglycan directed treatment seemed beneficial. Liposome intravesical instillation is safe for interstitial cystitis/painful bladder syndrome with potential improvement after 1 course of therapy for up to 8 weeks. Intravesical liposomes achieved efficacy similar to that of oral pentosan polysulfate sodium. Further large-scale placebo controlled studies are needed. Intravesical liposomes appear to be a promising new treatment for interstitial cystitis/painful bladder syndrome.

Key Words: urinary bladder; liposomes; cystitis, interstitial; pentosan sulfuric polyester; pain

Abbreviations and Acronyms

GAG = glycosaminoglycan
IC = interstitial cystitis
LP = liposome
PBS = painful bladder syndrome
PPS = pentosan polysulfate sodium
Qmax = maximum urine flow
RU = post-void residual urine

Submitted for publication December 30, 2008.
Study received Chang Gung Memorial Hospital Kaohsiung institutional review board approval.
Supported by Chang Gung Memorial Hospital Kaohsiung CMRPG.

* Correspondence: 123 Ta Pei Rd., Niao Song Hsiang, Kaohsiung Hsien, Taiwan, Republic of China (telephone: 886 7-7317123; FAX: 886 7-7318762, e-mail: chuang82@ms26.hinet.net).

Interstitial cystitis/painful bladder syndrome is a chronic symptom complex of the bladder characterized by suprapubic/bladder discomfort related to bladder filling, accompanied by urinary frequency, urgency or nocturia in the absence of infection or another pathological condition.[1] Although the pathogenesis of IC/PBS is uncertain, it was proposed that dysfunctional epithelium allows the transepithelial migration of solutes such as potassium, which can depolarize subepithelial afferent nerves and provoke sensory symptoms.[2,3] Parsons et al reported that patients with IC/PBS have increased pain with intravesical infusion of potassium compared with that in controls.[4] Together these re-

0022-5347/09/1824-1393/0
THE JOURNAL OF UROLOGY®

Vol. 182, 1393-1400, October 2009
Printed in U.S.A.
DOI:10.1016/j.juro.2009.06.024

sults suggest that dysfunctional epithelium has a major role in IC/PBS cases.

A number of treatments are used for IC/PBS, including dietary modification, medication (PPS, antispasmodics and anti-inflammatories) or intravesical therapy (dimethyl sulfoxide, heparin-like drugs and resiniferatoxin).[5–8] However, these options are often unsatisfactory because of a lack of efficacy, prolonged time to a therapeutic response and response durability. No established treatment approach is recognized as being effective in most patients with IC/PBS. Thus, there is a significant medical need for additional treatment options in those with refractory IC/PBS.

LPs are vesicles composed of concentric phospholipid bilayers separated by aqueous compartments.[9] Because LPs adsorb to cell surfaces and fuse with cells, they serve as vehicles for drug delivery and gene therapy.[10,11] They also create a molecular film on cell surfaces and, therefore, are being tested as possible therapeutic agents to promote wound healing.[11,12] LP based drug products provide a moisture film on the wound and improve wound healing without inflammatory reaction in the neodermal layer. Other groups suggested that LPs could interact with cells by stable absorption, endocytosis, lipid transfer and fusion.[13]

Previous reports showed that patients with IC/PBS have a defect in the urothelial GAG layer.[4] Oral PPS, a Food and Drug Administration approved agent for IC/PBS, has limited efficacy compared to placebo.[5] Therapies such as intravesical heparin, hyaluronic acid or pentosanpolysulfate,[5] which appear to restore the GAG layer on the epithelial barrier surface, may decrease irritant leakage and result in IC/PBS symptom palliation. Similarly LP intravesical administration into the wounded uroepithelium may improve the dysfunctional uroepithelium and be an alternative treatment for IC. We proved these concepts in rat models of hypersensitive bladder, which showed that LP intravesical instillation could decrease the bladder hypersensitivity induced by intravesical potassium chloride or acetic acid.[12] In this study we compared the safety and efficacy of LP topical solution and oral PPS in patients with IC/PBS.

MATERIALS AND METHODS

The experiment was a prospective, longitudinal study of the effect of 2 independent treatments (intravesical LP and oral PPS) in patients with IC/PBS. Ten possible responses (or measures) to treatment were monitored at 3 time points, including baseline, and weeks 4 and 8. A total of 24 patients with IC/PBS were evaluated in a 1:1 ratio to intravesical LP-08 (Lipella Pharmaceuticals, Pittsburgh, Pennsylvania) (80 mg/40 cc distilled water) once weekly or to oral PPS (100 mg) 3 times daily for 4 weeks of treatment each. The study design was approved by the Chang Gung Memorial Hospital Kaohsiung institutional review board.

Five measures were expressed as continuous variables, including urination frequency, nocturia, voided volume, Qmax and RU, and 5 were expressed as ordinal variables, including O'Leary-Sant symptom, problem and total, and pain and urgency scores. Although the study was designed with an active control instead of placebo control, comparison between the LP and PPS groups was not practical since the LP group had a statistically significant higher pain profile at baseline than the PPS group. Comparison of measures at different time points was possible in each treatment group. For each treatment group all 10 parameters at weeks 4 and 8 were compared to baseline. The paired t test was used to compare measures of continuous variables. Pairing added statistical power to the tests since changes in responses of individuals would otherwise have been mixed with those in each group. The paired t test was effectively done by calculating the change in each measure vs baseline and testing whether the mean of the change was sufficiently different from zero, given the SD of the normal distribution of each change. The p values reported for continuous variables represent the probability of obtaining by chance alone the mean difference observed for a given measure. Statistical significance was considered at $p < 0.05$.

Since the magnitude of differences between any given ordinal measure at 2 time points lacks meaning, we used the likelihood ratio chi-square test to determine whether distributions of each ordinal measure for a given group and time point were different than corresponding distributions at baseline. The p values reported for these comparisons represent the probability of obtaining by chance alone a chi-square value greater than what would be calculated if no relationship existed between response and factor. Chi-square was calculated using the contingency table method, that is $(O - E)^2/E$, where O represents the actual observed cell frequency and E represents the expected cell frequency of each cell under the assumption of independence.

Study Patients and Criteria

For study enrollment patients were selected with a diagnosis of IC/PBS based on a history of symptoms, including the number of daily voids (10 or more), average voided volume (50 to 200 cc), nocturia (at least once per night), pain (suprapubic or bladder pain at least 1

Table 1. *Baseline patient characteristics by treatment group*

	Mean ± SD LP	Mean ± SD PPS*
Pt age	47.8 ± 11.1	51.9 ± 14.3
Frequency (No. hrs)	17.5 ± 6.0	16.5 ± 5.7
No. nocturia episodes	3.1 ± 1.1	2.4 ± 1.2
Mean voided vol (ml)	98.4 ± 37.1	135.2 ± 60.1
Qmax (ml/sec)	11.4 ± 5.3	10.8 ± 5.0
RU (ml)	27.1 ± 27.7	28.1 ± 30.3

* No statistically significant differences vs LP.

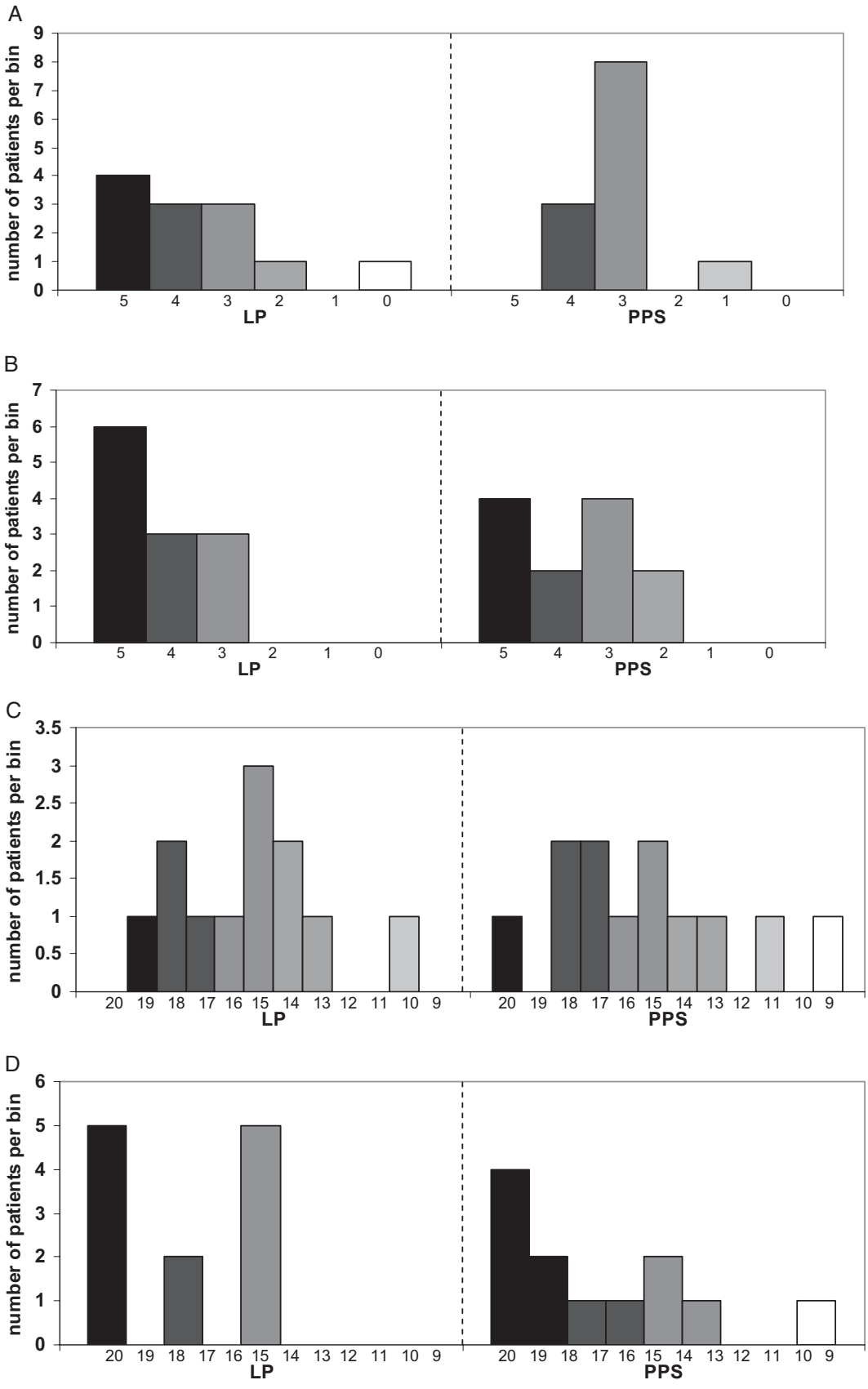

Figure 1. Baseline scores in LP vs PPS groups in 12 patients per group. *A*, pain. *B*, urgency. *C*, O'Leary-Sant symptom. *D*, O'Leary-Sant problem.

on a 0 to 5 pain scale) and urgency (at least 1 on a 0 to 5 urgency scale) for 6 months or longer. Also, patients had negative urine cytology and culture, and underwent cystoscopy to rule out another pathological condition. Patients were excluded from study due to age less than 20 years, pregnancy or lactation, bleeding diathesis, anticoagulant therapy, active bleeding peptic ulcer disease, chronic narcotic use, obvious neurological impairment, or known allergy to PPS or LPs. An informed consent form was signed by each participant.

LP Intravesical Instillation

All instillations were performed at the urology clinic using an 8Fr catheter for LP-08 instillation. Before inserting the catheter into the urethra 2% lidocaine hydrochloride jelly was applied to the catheter tip. The bladder was drained of any RU. LPs were instilled (80 mg LP-08/40 cc distilled water) and retained for a minimum of 30 minutes to a maximum of 60 minutes and voided.

Efficacy Outcomes

The primary outcome was the change from baseline to the end of weeks 4 and 8 in IC/PBS symptom severity, as measured by the O'Leary-Sant IC symptom (total score 20) and problem (total score 16) indexes.[12] Higher scores indicate more severe symptoms. The pain assessment scale (range 0 to 5, including 0—no pain to 5—severe pain), the urgency scale (range 0 to 5, including 0—no urgency to 5—severe urgency) and voiding diaries to measure voiding frequency for 72 hours were completed at baseline, and weeks 4 and 8. Global assessment of treatment was categorized as worsened, stationary, mild improved, moderate improved and excellent at weeks 4 and 8.

RESULTS

Table 1 and figure 1 show baseline patient characteristics. A total of 12 patients completed the study in each group. All cases were classified as moderate IC/PBS, including 2 of 12 in the LP group and 3 of 12 in the PPS group, or as severe IC/PBS, including 10 of 12 and 9 of 12, respectively, based on O'Leary-Sant IC symptom index cutoffs of 0 to 6—mild, 7 to 13—moderate and 14 to 20—severe.[14] Comparison at baseline showed a statistically significant difference in pain distribution between the 2 groups. More severe pain was reported by LP than by PPS treated patients. There was only a 3% probability that the distribution of baseline pain scores in the LP vs PPS groups could have been randomly drawn from 1 population ($p < 0.03$). The baseline ordinal pain score in the PPS group clustered on 3 and that in the LP treated group clustered in the 3 to 5 range (fig. 1).

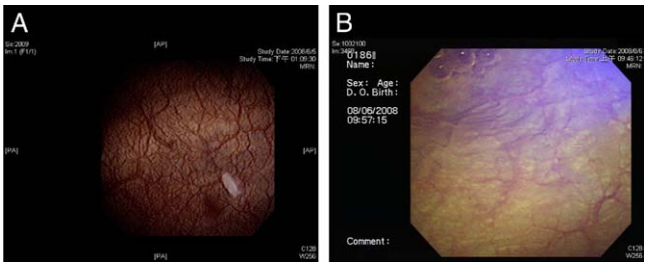

Figure 2. Cystoscopy shows bladder before (*A*) and after (*B*) LP instillation with decreased inflammation and vascularity after treatment.

Table 2. *Parameter changes vs baseline*

Outcomes	Mean ± SD LP		Mean ± SD PPS*	
	Wk 4	Wk 8	Wk 4	Wk 8
Frequency (No./hr)	−2.5 ± 4.3	−2.6 ± 3.4†	−3.6 ± 2.9†	−3.9 ± 3.9†
Voided vol (ml)	7.1 ± 39.9	27.1 ± 50.1	7.2 ± 32.9	14.7 ± 39.6
No. nocturia episodes	−1.0 ± 1.3†	−1.0 ± 1.6	−0.5 ± 0.9	−0.5 ± 0.7†
Qmax (ml/sec)	2.3 ± 2.4†	2.0 ± 4.2	0.8 ± 1.4	0.5 ± 2.4
RU (ml)	−6.1 ± 11.3	−5.2 ± 14.2	0.02 ± 10.1	4.7 ± 15.2

Paired Student's t test $p < 0.05$ vs baseline.

* No statistically significant changes from baseline vs LP (Mann-Whitney U test).

The primary study objective was safety. No patient had urinary incontinence, retention or infection with LP-08 instillation. There were no unanticipated adverse events and no significant worsening of symptoms during followup. There was no adverse event in the PPS group and only 2 patients in the LP group reported mild pain while holding LP in the bladder for 30 to 60 minutes. This discomfort, which disappeared after voiding, was most likely due to the IC/PBS characteristic of bladder pain related to bladder distention. No patient required oral or systemic analgesics with LP-08. Cystoscopy in 3 LP treated patient revealed decreased inflammation at the end of week 8 (fig. 2).

Statistically significant decreases in urinary frequency and nocturia were observed in each treatment group. Statistically significant decreases in pain, urgency and the O'Leary-Sant symptom score were noted in the LP group. Table 2 lists the resulting p values of comparing the treatment effect vs baseline as well as effect size for continuous variables.

Decreased urgency in the LP group had the most profound effect of the ordinal measures. Figures 3 and 4 show urgency and pain score histograms, respectively, in the LP and PPS groups at all 3 periods. There was a statistically significant decrease in the urgency score distribution by week 4 vs baseline but the difference between weeks 4 and 8 was not statistically significant.

The LP group had a significant decrease in the O'Leary-Sant IC total score and symptom index,

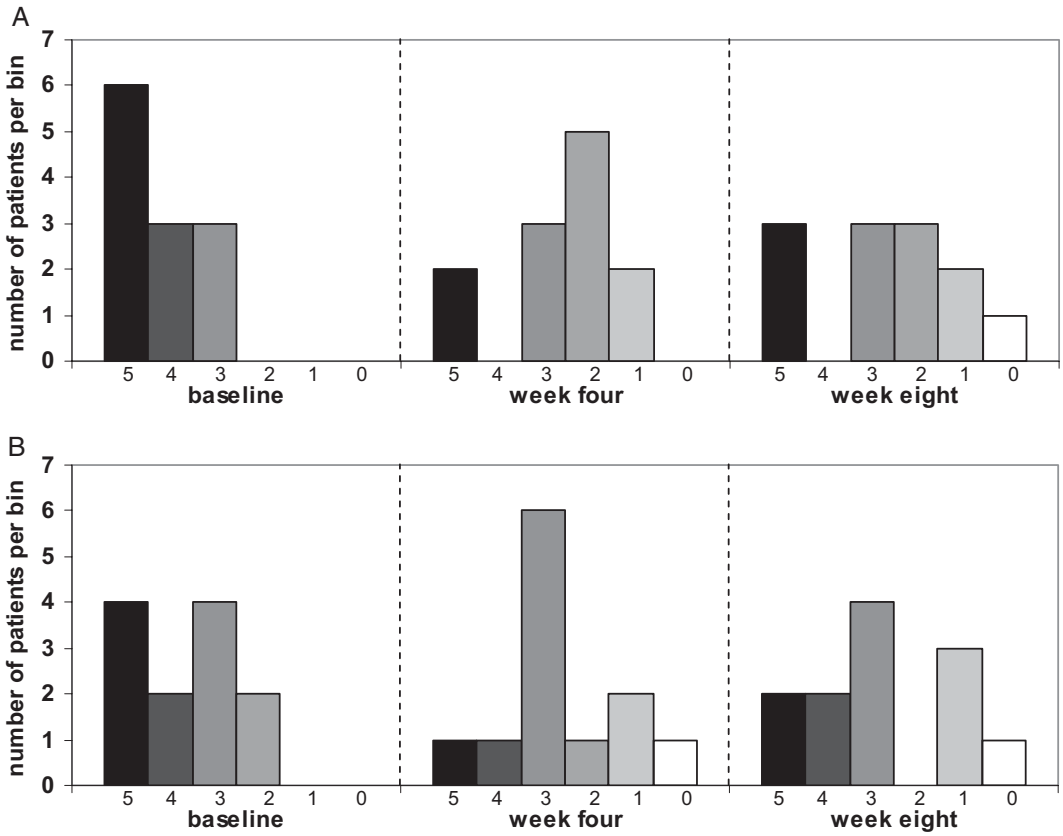

Figure 3. There was statistically significant decrease in urgency scores by week 4 vs baseline but difference between weeks 4 and 8 was not statistically significant. *A*, LP. *B*, PPS.

and pain and urgency scores from baseline to each end point as well as a trend toward other improved parameters (table 3). Although changes in all parameters showed no statistically significant difference between the treatment groups, the LP group had a trend toward a greater decrease in O'Leary-Sant total, pain and urgency scores, and number of nocturia episodes compared to the PPS group (fig. 5). The PPS group showed a trend toward a greater decrease in voiding frequency changes than the LP group, of which the clinical significance is unclear. Of the 12 patients in the LP group 3, 2 and 1 had a mild, moderate and excellent response at week 4, and 4, 1 and 2 had a mild, moderate and excellent response, respectively, at week 8. This was not significantly different vs results in the 12 patients in the PPS group, including 3, 2 and 1 with a mild, moderate and excellent response at week 4, and 4, 1 and 1 with a mild, moderate and excellent response, respectively, at week 8.

DISCUSSION

IC/PBS treatment is meant to alleviate symptoms. The different treatments may be based on hypotheses concerning the cause of IC/PBS. A bladder mucosal barrier defect in the GAG layer is a main cause of IC/PBS.[4,15] With such a defect the submucosal nerve filaments might become accessible to noxious substances in urine, which may explain bladder pain and associated irritative voiding symptoms.[3,16] It is believed that mucosal protective agents may mitigate IC/PBS symptoms. To our knowledge we report for the first time that intravesical LP, a presumptive mucosal protective agent, is safe and achieved efficacy similar to that of oral PPS in patients with moderate or severe IC/PBS symptoms.

IC/PBS symptoms may be partly caused by defective bladder coating. LPs, which are stable fat bubbles filled with water that adhere to a surface, may serve as a lotion for wounded or leaked bladder mucosa. Naked LPs worked as well as those carrying capsaicin to decrease bladder contraction frequency due to hyperactive bladder in rats.[12,17,18] Also, LP intravesical administration appeared to decrease inflammation in IC/PBS bladders (fig. 2). Coating the bladder with LPs may protect against challenges that induce inflammation. The current study showed an approximately 50% response rate

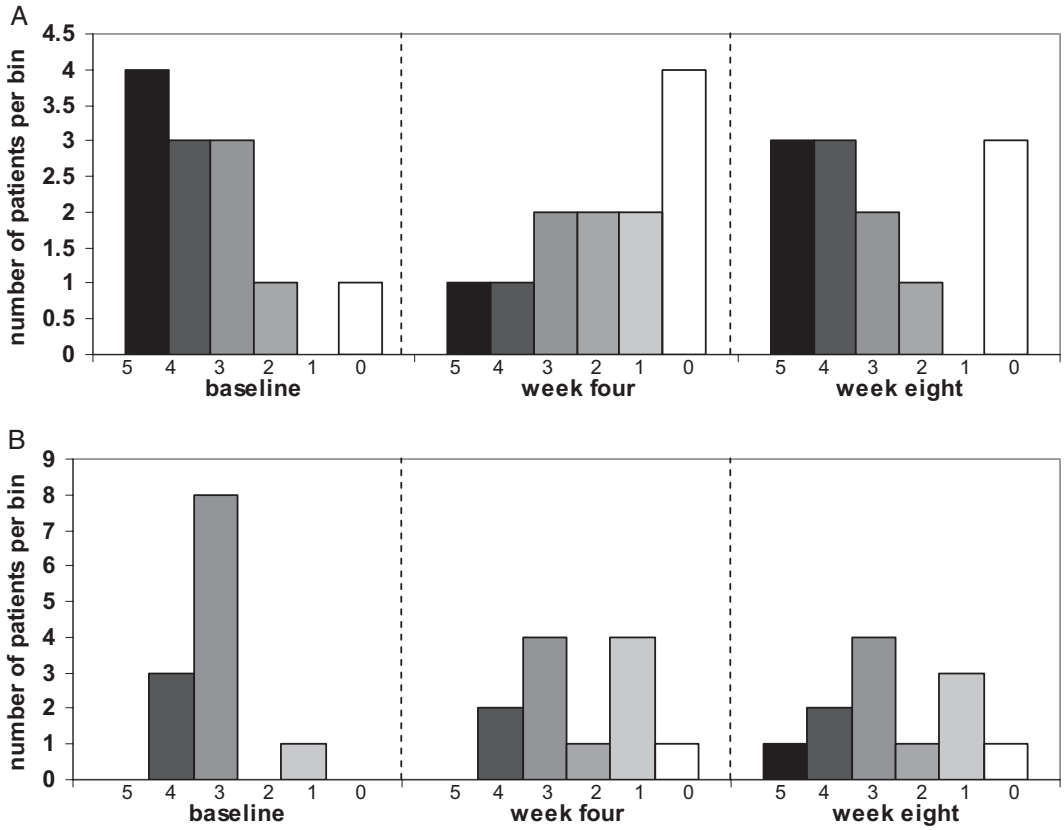

Figure 4. Changes in pain score. *A*, greater number of higher scores at baseline in LP group. *B*, PPS

for 4 weeks of treatment without adverse effects. This treatment is also stable, remaining effective as long as 8 weeks.

Table 3. *Treatment effect vs baseline and effect size*

	LP		PPS	
	Wk 4	Wk 8	Wk 4	Wk 8
Likelihood ratio chi-square test p value (score):*				
Symptom	0.119	0.027	0.267	0.240
Problem	0.120	0.112	0.551	0.182
Total	0.063	0.071	0.169	0.248
Pain	0.145	0.054	0.181	0.239
Urgency	0.003	0.019	0.096	0.109
Paired t test p value (change):*				
Frequency	0.065	0.019	0.001	0.006
Nocturia	0.030	0.055	0.076	0.016
Voided vol	0.549	0.088	0.466	0.226
Qmax	0.007	0.131	0.064	0.491
RU	0.092	0.232	0.980	0.329
Mean change vs baseline:				
Frequency (No./hr)	−2.533	−2.558†	−3.625†	−3.867†
No. nocturia episodes	−0.967†	−1.017†	−0.517	−0.667†
Voided vol (ml)	7.125	26.669	7.167	14.667
Qmax (ml/sec)	2.333†	2.000	0.833	0.500
RU (ml)	−6.083	−5.250	−0.083	4.500

* Probability that change occurred by chance alone.
† Statistically significant.

PPS is the most intensively studied treatment ever proposed for IC/PBS. It is the only oral medication approved by the Food and Drug Administration for IC/PBS. The major mechanism of action of PPS is attributable to the creation of a synthetic layer that protects the bladder wall from attack by irritant elements in urine.[5,19,20] Fritjofsson et al reported that most patients with IC responded favorably with decreased symptoms within only 4 weeks from the start of PPS treatment.[21] Parsons et al noted that 22 of 24 patients with IC responded to PPS treatment within 4 to 8 weeks of treatment initiation and experienced slow, progressive improvement with maintenance of therapy.[22] However, when the drug was terminated, the disease reappeared within 3 to 12 weeks in 80% of these patients.[23] A shortcoming of our pilot study is the limitation of its open level study design. Our results suggest that PPS appears to be well tolerated and beneficial in regard to improving symptoms and global assessment, in accordance with previous reports and similar to the results of Sairanen et al in terms of more than moderate improvement (22%[19] vs 25% in our study).

The main limitation of the current study was the lack of placebo control randomization and

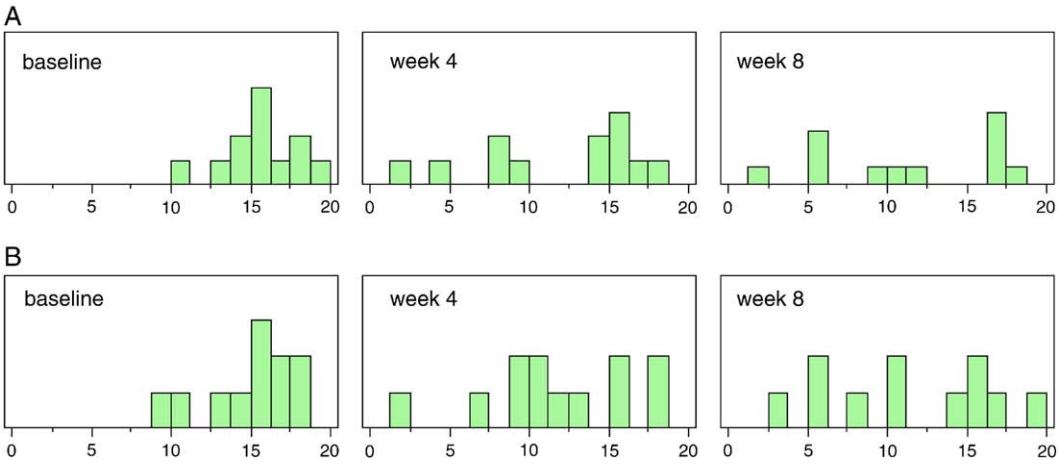

Figure 5. Changes in O'Leary-Sant symptom score. *A*, LP. *B*, PPS

our small sample size. It is difficult to accumulate a large sample without a multiple center study. When the p value was marginal, ie about 0.10, power calculations indicated that a study size of 150 to 200 total patients would be required to achieve a 90% probability of observing a statistically significant effect. Also, the reliability of significance tests would improve with an increased sample size, especially for ordinal measures. Further multi-institutional studies with placebo controls to minimize bias are needed to elucidate the role of intravesical LPs for IC/PBS.

The etiology of IC/PBS likely involves the bladder. Intravesical administration of drug solutions that directly affect the urothelium provides high local drug concentrations in the bladder and a low risk of systemic side effects.[10] Many patients with IC/PBS do not respond to oral medications or are allergic to oral medications. Thus, intravesical treatment is a step between oral and invasive treatments. Various intravesical treatments for IC/PBS, including dimethyl sulfoxide, PPS, heparin, hyaluronic acid and resiniferatoxin,[5] have various results due to the multiple etiologies of IC.

CONCLUSIONS

The response of each group to GAG directed therapy bolsters the belief that mucosal leak is important in IC development, and intravesical therapy to treat the GAG layer is well tolerated and effective. LP intravesical instillation is safe and achieved promising sustained efficacy in patients with IC/PBS in our study. Further large-scale placebo controlled studies are needed to elucidate the real role of intravesical LPs for IC/PBS.

REFERENCES

1. Bogart LM, Berry SH and Clemens JQ: Symptoms of interstitial cystitis, painful bladder syndrome and similar diseases in women: a systematic review. J Urol 2007; **177:** 450.
2. Parsons CL, Rosenberg MT, Sassani P et al: Quantifying symptoms in men with interstitial cystitis/prostatitis, and its correlation with potassium-sensitivity testing. BJU Int 2005; **95:** 86.
3. Chuang YC, Chancellor MB, Seki S et al: Intravesical protamine sulfate and potassium chlorides as a model for bladder hyperactivity. Urology 2003; **61:** 664.
4. Parsons CL, Greenberger M, Gabal L et al: The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. J Urol 1998; **159:** 1862.
5. Chancellor MB and Yoshimura N: Treatment of interstitial cystitis. Urology 2004; **63:** 85.
6. Nickel JC, Downey J, Morales A et al: Relative efficacy of various exogenous glycosaminoglycans in providing a bladder surface permeability barrier. J Urol 1998; **160:** 612.
7. Chancellor MB and de Groat WC: Intravesical capsaicin and resiniferatoxin therapy: spicing up the ways to treat the overactive bladder. J Urol 1999; **162:** 3.
8. Parsons CL, Housley T, Schmidt JD et al: Treatment of interstitial cystitis with intravesical heparin. Br J Urol 1994; **73:** 504.
9. Reimer K, Fleischer W, Brogmann B et al: Povidone-iodine liposomes—an overview. Dermatology, suppl., 1997; **195:** 93.
10. Giannantoni A, Di Stasi SM, Chancellor MB et al: New frontiers in intravesical therapies and drug delivery. Eur Urol 2006; **50:** 1183.
11. Tyagi P, Wu PC, Chancellor MB et al: Recent advances in intravesical drug/gene delivery. Molec Pharmaceut 2006; **4:** 369.
12. Fraser MO, Chuang YC, Tyagi P et al: Intravesical liposomes administration: a novel treatment for hyperactive bladder in the rat. Urology 2003; **61:** 656.
13. Egerdie RB, Reid G and Trachtenberg J: The effect of liposome encapsulated antineoplastic agents on transitional cell carcinoma in tissue culture. J Urol 1989; **142:** 390.
14. O'Leary MP, Sant GR, Fowler FJ Jr et al: The interstitial cystitis symptom index and problem index. Urology 1997; **49:** 58.

15. Parsons CL, Stauffer C and Schmidt JD: Bladder surface glycosaminoglycans: an efficient mechanism of environmental adaptation. Science 1980; **208:** 605.

16. Lucioni A, Bales GT, Lotan TL et al: Botulinum toxin type A inhibits sensory neuropeptide release in rat bladder models of acute injury and chronic inflammation. BJU Int 2008; **101:** 366.

17. Tyagi P, Chancellor MB, Li Z et al: Urodynamic and immunohistochemical evaluation of intravesical capsaicin delivery using thermosensitive hydrogel and liposomes. J Urol 2004; **171:** 483.

18. Tyagi P, Chancellor M, Yoshimura N et al: Activity of different phospholipids in attenuating hyperactivity in bladder irritation. BJU Int 2008; **101:** 627.

19. Sairanen J, Tammela TL, Leppilahti M et al: Cyclosporine A and pentosan polysulfate sodium for the treatment of interstitial cystitis: a randomized comparative study. J Urol 2005; **174:** 2235.

20. Sandhu SS, Goldstraw M and Woodhouse CR: The management of haemorrhagic cystitis with sodium pentosan polysulphate. BJU Int 2004; **94:** 845.

21. Fritjofsson A, Fall M, Fuhlin R et al: Treatment of ulcer and nonulcer interstitial cystitis with sodium pentosanpolysulfate: a multicenter trial. J Urol 1987; **138:** 508.

22. Parsons CL, Schmidt JD and Pollen JJ: Successful treatment of interstitial cystitis with sodium pentosanpolysulfate. J Urol 1983; **130:** 51.

23. Parsons CL and Mulholland G: Successful therapy of interstitial cystitis with pertosanpolysulfate. J Urol 1987; **138:** 513.