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ORIGINAL ARTICLE

Safety and dose flexibility clinical evaluation of intravesical liposome in patients with interstitial cystitis or painful bladder syndrome

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Abstract To present single institution open-label experience with intravesical liposomes (LPs), a mucosal protective agent, in patients with interstitial cystitis/painful bladder syndrome (IC/PBS) and to assess the safety and efficacy on IC/PBS symptoms. A total of 17 symptomatic IC/PBS patients were treated with intravesical LPs (80 mg/40 mL distilled water) once a week for 4 weeks ($n = 12$) or twice a week treatment for 4 weeks ($n = 5$). The primary outcome was the change in the O'Leary-Sant Symptom/Problem score and O'Leary-Sant total Score from baseline to Week 4 and Week 8. Other outcome measurements included the changes in pain scale, urgency scale, voiding log, and patient global assessment. Both weekly and biweekly LP instillation regiments were well tolerated. The incidence of urinary incontinence, retention, or unanticipated adverse changes was not noted at any dose either during the treatment or at the 4-week follow-up. The O'Leary-Sant Symptom/Problem score, O'Leary-Sant total Score, and pain score were significantly improved from baseline at both dose regimens with added benefit with the biweekly regimen. Intravesical LPs treatment is safe and its efficacy has sustained duration. Furthermore large-scale, placebo-controlled studies are warranted to assess the efficacy for this promising new treatment for IC/PBS.
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Introduction

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a clinical diagnosis that relies on symptoms of suprapubic/bladder discomfort related to bladder filling that is accompanied by urinary frequency, urgency, or nocturia, in

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the absence of infection or another pathological condition [1,2]. Although the pathogenesis of IC/PBS is complex and uncertain, a defect in the glycosaminoglycan layer and dysfunctional urothelial barrier has been proposed [3]. A dysfunctional epithelium allows the transepithelial migration of noxious substances in the urine, such as potassium, which can depolarize subepithelial afferent nerves and provoke bladder pain and urinary frequency [4].

The principles for treatment of IC/PBS are based on (1) controlling the dysfunctional epithelium; (2) inhibiting neurogenic inflammation; (3) suppression of allergies; and (4) pain control [5]. The current treatment methods used for IC/PBS include dietary manipulation, oral therapy (pentosanpolysulfate, antispasmodics, anti-inflammatories), or intravesical therapy (dimethyl sulfoxide, heparin-like drugs, resiniferatoxin, and botulinum toxin) [5–7]. However, concerns have been raised about their safety, efficacy, and unfavorable pharmacodynamics. Thus, there is a significant medical need for additional treatment options for those suffering from refractory IC/PBS.

Liposomes (LPs) are vesicles or bubbles of phospholipids filled with water instead of air dispersed in aqueous medium [8–10]. The propensity of LPs to bind water and adhere as a molecular film on cell surfaces has made them a favorite choice for topical drug carriers [8–10]. Studies involving protamine sulfate-mediated bladder injury demonstrated the ability of LPs to act as a bladder protective agent [11]. In addition, anti-inflammatory effect of empty LPs composed of different bioactive phospholipids has been observed in various other tissues, including but not limited to skin, eye membranes, and intestinal tissues [12].

We hypothesized that intravesical administration of LPs in IC/PBS patients will improve the barrier function and result in palliation of symptoms. The previously reported safety and efficacy of LPs compared with oral pentosanpolysulfate prompted the present study to expand and assess the safety and efficacy of LPs at two different dose regiments in IC/PBS patients [13].

Materials and methods

The study was conducted at Chang Gung Memorial Hospital Kaohsiung, with the approval of the institutional review board. Informed consent for the procedure was obtained from all patients. A total of 17 IC/PBS patients were treated with intravesical LP-08 (Lipella Pharmaceuticals, Inc., Pittsburgh, PA, USA; 80 mg/40 mL distilled water) once a week for 4 weeks courses of treatment ($n = 12$) between October 2007 and October 2008 [13], and an additional 5 patients were assessed after twice a week instillation for 4 weeks between November 2008 and May 2009.

Patients were selected for enrollment into the study with a diagnosis of IC/PBS based on a history of symptoms, including number of voids per day (10 or more), average voided volume (50–200 mL), nocturia (at least 1), pain scale (suprapubic or bladder pain, at least 1 on a 0–5 pain scale), and urgency scale (at least 1 on a 0–5 urgency scale), for 6 months or longer. In addition, patients had to have negative urinary cytology studies and cultures, and cystoscopy to rule out other pathological conditions.

Patients were excluded from participation in the study for age less than 20 years, pregnancy or lactation, bleeding diathesis, use of anticoagulant therapy, active bleeding peptic ulcer disease, chronic use of narcotics, obvious neurological impairment, or known allergy to LPs [13].

LPs instillations were performed in the urology clinic using an 8 French catheter for LP-08 instillation. Before inserting the catheter into the urethra, 2% lidocaine hydrochloride jelly was applied to the catheter tip. Then the bladder was drained from any postvoid residual and the LPs was instilled (80 mg LP-08/40 mL distilled water) and retained for a minimum of 30 minutes to a maximum of 60 minutes and bladder contents were ultimately voided out [13]. Treatment outcome measures included the change from baseline to the end of Week 4 and Week 8 in the severity of IC/PBS symptoms measured by the O'Leary-Sant IC symptom index (total score = 20) and O'Leary-Sant IC problem index (total score = 16) [14]. Higher scores indicate more severe symptoms. The pain assessment scale (range: 0–5; 0: no pain, 5: severe pain), urgency scale (range: 0–5; 0: no urgency, 5: severe urgency), and voiding diaries that measure the voiding frequency for a duration of 72 hours were completed at baseline, Week 4, and Week 8. Global assessment of treatment was categorized into worsened, stationary, mildly improved, moderately improved, and excellent at Week 4 and Week 8.

For each treatment group, parameters expressed were mean ± standard deviation at Week 4 and Week 8 and compared with their baseline values and between groups using the Student t test. A p value less than 0.05 was considered statistically significant.

Results

Baseline patient characteristics are presented in Table 1. All cases were classified as moderate IC/PBS case (LPs once a week group: 2 of 12; LPs twice a week group: 1 of 5) or severe IC/PBS cases (LPs once a week group: 10 of 12; LPs twice a week group: 4 of 5) based on O'Leary-Sant IC symptom index cut points of 0–6 as mild, 7–13 as moderate, and 14–20 as severe [13,14].

Primary objective of our study was safety. None of the patients with LP-08 instillation developed urinary incontinence, retention, or infection. There were no unanticipated adverse event and no significant worsening of symptoms in follow-up time period. Two patients in the LPs once a week-treated group and a single patient in the LPs twice a week-treated group reported mild discomfort while holding LP for 30–60 minutes in the bladder that disappeared on voiding. It was most likely because of the IC/PBS characteristic of bladder pain related to bladder distension. None of the patient required oral or systemic analgesics with LP-08.

The O'Leary-Sant Symptom/Problem score, O'Leary-Sant total Score, and pain score showed significantly greater improvement in the biweekly group than the weekly group at the Week 4 (63.0% *vs.* 22.9%, 61.0% *vs.* 18.6%, 62.0% *vs.* 20.8%, 57.9% *vs.* 39.5%; Fig. 1), but there were no significant difference at Week 8 (Fig. 2) and urgency score.

Significant greater decreases in urinary frequency (-4.4 ± 3.3 and -2.5 ± 4.3; 28.2% *vs.* 14.3%) and increases in voided volume ($36.0.1 \pm 41.1$ and 7.1 ± 39.9; 28.0% *vs.* 7.2%)

Table 1 Baseline patient characteristics by treatment group

Baseline characteristics	Mean ± SD	
	LP1 (once a week, $n = 12$)	LP2 (twice a week, $n = 5$)
Patient age (y)	47.8 ± 11.1	44.2 ± 8.1
O'leary-Sant Symptom Score	15.3 ± 2.5	16.2 ± 2.6
O'leary-Sant Problem Score	14.0 ± 1.9	15.4 ± 0.9
O'leary-Sant total Score	29.3 ± 4.0	31.6 ± 3.4
Pain score (0—5)	3.6 ± 1.5	4.4 ± 0.9
Urgency score (0—5)	4.3 ± 0.9	3.8 ± 1.1
Voiding frequency	17.5 ± 6.0	15.6 ± 3.8
Mean voided volume (mL)	98.4 ± 37.1	128.2 ± 68.0
Nocturia	3.1 ± 1.0	3.1 ± 1.6
Qmax (mL/sec)	11.4 ± 5.3	14.3 ± 3.8
RU (mL)	27.1 ± 27.7	44.3 ± 33.0

There were no statistically significant differences in baseline parameters between the two groups.
LP = liposome; Qmax = maximal flow rate; RU = residual urine; SD = standard deviation.

were observed in the biweekly group than the weekly group at Week 4 but not at Week 8 (urinary frequency 14.7% *vs.* 14.9%; voided volume 24.9% *vs.* 27.5%). There were no significant differences in the decreases of nocturia (48.4% *vs.* 32.3% at Week 4 and 41.9% *vs.* 32.3% at Week 8). There were no significant differences in the increases of voided volume (25.0% *vs.* 27.5% for the biweekly and the weekly group) at Week 8.

Of the five patients in the biweekly group, 1, 1, and 2 had a mild, moderate, and excellent response at Week 4 and 1, 2, and 1 had a mild, moderate, and excellent response, respectively, at Week 8. This was not significantly different when compared with the results in the 12 patients in the weekly group, including 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.

Discussion

The goal of IC/PBS therapy is to reduce the symptoms and improve the quality of life. With a 4-week of treatment with LP-08 (80 mg/40 mL distilled water) once a week [13] or twice a week instilled into the bladder, we demonstrated that 6 of 12 patients (50%) and 4 of 5 patients have responded to LPs treatment, respectively. The effect was maintained for 2 months.

The prevailing understanding of IC/PBS considers disruption of the urothelial barrier as a primary cause. Disrupted urothelium allows unrestricted access of noxious substances, such as high concentration of potassium to the submucosal nerve filaments that may initiate a cascade of signaling events leading to associated irritative voiding symptoms and bladder pain. This understanding explains the moderate efficacy of pentosan polysulfate, which is the only oral medication approved by the Food and Drug Administration for IC/PBS. There seem to be a role of neuroinflammation in the pathology of IC/PBS, which is supported by the current clinical testing of nerve growth factor antibody across the world [5,6,15].

The characteristic of LPs to serve as a "lotion" by adhering to a wounded or leaked bladder mucosa prompted us to examine the use of intravesical novel LPs as safe and effective treatment of IC/PBS patients with moderate or severe symptoms. Our previous study showed that the use of intravesical LPs once a week for 4 weeks achieved similar or greater efficacy as oral PPS. The current report suggested that the more frequent treatment (LPs instillation

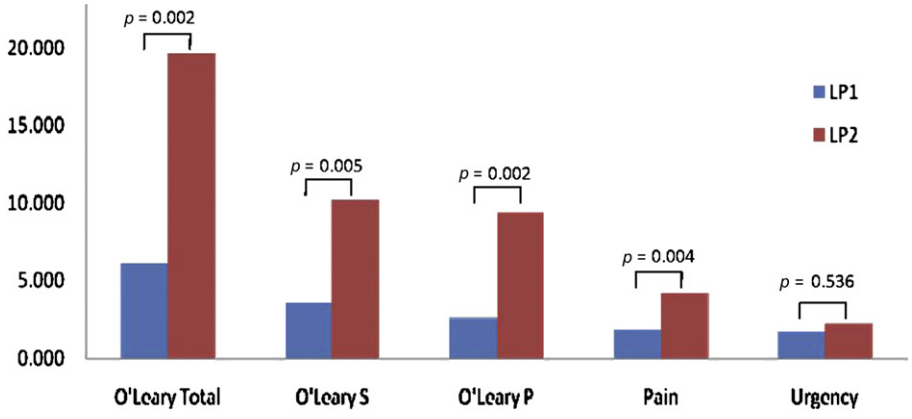

Figure 1. Treatment parameters at Week 4. The O'Leary-Sant Symptom/Problem score, O'Leary-Sant total Score, and pain score showed significantly greater improvement in the biweekly group (LP2) than the weekly group (LP1) at the Week 4. LP = liposome; SD = standard deviation.

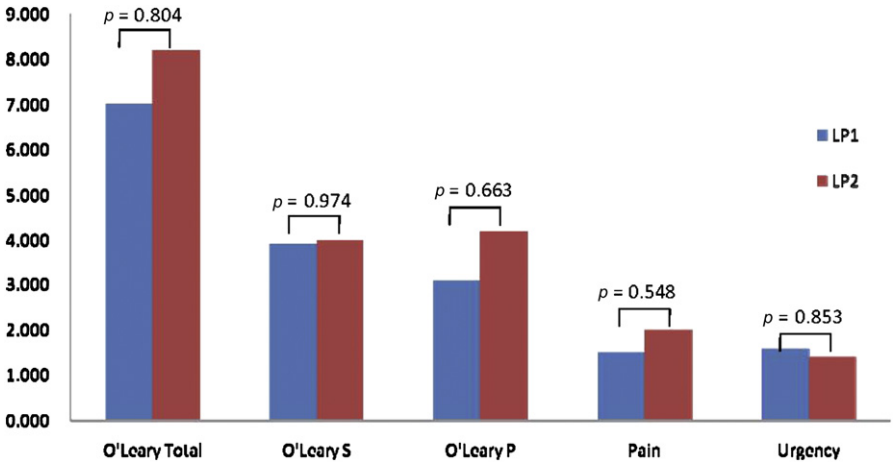

Figure 2. Treatment parameters at Week 8. There were no significant difference in treatment parameters between the biweekly group (LP2) and the weekly group (LP1) at Week 8. LP = liposome; SD = standard deviation.

twice a week) may be more beneficial in selected patients with acute symptoms and may be preferred for episodes of IC/PBS flare-up.

The main drawback of the present study was the lack of placebo control randomization and small sample size. It is difficult to accumulate large sample size with the investigator-initiated study without multiple center study. Further studies using a multi-institutional, placebo-controlled trial to minimize the bias is necessary to elucidate the role of intravesical LPs in IC/PBS treatment. Previous studies have shown that apart from transmembrane uroplakin proteins, the lipids in the apical membrane of the umbrella cells, an uppermost layer of the urothelium, are also an integral component of the permeability barrier in the bladder [16]. They seem to play important roles in reducing the permeability of the apical membrane to water, ammonia, protons, and urea [17]. The therapeutic effect of empty LPs in the IC/PBS patients supports the notion that the dysfunctional urothelium of patients with IC/PBS may also involve deficiency in the lipid structure of the urothelium apart from glycosaminoglycan layer depletion [18].

In conclusion, intravesical LPs instillation is well tolerated and effective, and more frequent instillation may improve efficacy and may be beneficial for symptom flare-up. However, the follow-up period is not enough and the effects after 8 weeks are not clear. Further large-scale, placebo-controlled studies are necessary to evaluate the therapeutic potential of intravesical LPs for IC/PBS.

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