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Original Article

Repeated intravesical injections of platelet-rich plasma are safe and effective in the treatment of interstitial cystitis/bladder pain syndrome

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Abstract

Objectives: Interstitial cystitis/bladder pain syndrome (IC/BPS) is a challenging chronic inflammatory condition affecting the urinary bladder, with limited treatment options. This study aims to assess the clinical efficacy of repeated intravesical platelet-rich plasma (PRP) injections for promoting urothelial regeneration and reducing inflammation in patients with IC/BPS and investigate its correlation with subjective and objective treatment-related outcomes. **Materials and Methods:** Four monthly intravesical PRP injections were given to 98 patients with non-Hunner-type IC/BPS. Treatment outcomes were assessed using a global response assessment (GRA) score 3 months posttreatment. In addition, clinical symptom scores, pain severity, voiding diary data, uroflowmetry parameters, and GRA scores were compared before and after treatment and between different treatment outcome groups (satisfactory: GRA≥2 unsatisfactory: GRA<2). Baseline urine biomarkers were analyzed to identify potential treatment outcome predictors. **Results:** After four PRP injections, 54 (55.1%) patients reported satisfactory outcomes. Lower urinary tract symptoms, bladder pain, urinary frequency, anxiety, and flow rate significantly improved from baseline ($P < 0.05$) in all patients, regardless of the treatment outcome. All patients experienced improved treatment outcomes and increased maximum bladder capacity with successive PRP treatments, and no major complications were reported. Urine biomarkers indicated elevated inflammation and oxidative stress biomarkers in patients with IC/BPS compared to controls. **Conclusion:** Repeated PRP injections are safe and effective for reducing symptoms and bladder pain and improving bladder capacity in a majority of IC/BPS patients, with better outcomes observed in patients with a mild form of bladder inflammation. These results support PRP as a promising novel bladder therapy for IC/BPS.

Keywords: *Interstitial cystitis/bladder pain syndrome, Novel treatment, Pain, Platelet-rich plasma, Treatment outcomes*

Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a heterogeneous and chronic debilitating disease with symptoms including urinary frequency, nocturia, bladder pain, and psychological stress [1]. IC/BPS has two subtypes: Hunner (HIC) and non-Hunner-type IC (NHIC) [2]. The pathogenesis of IC/BPS is unclear, and current evidence suggests that it is characterized by urothelial damage, increased urothelial cell apoptosis, and upregulation of nociceptive receptors [2,3], inducing epithelial barrier dysfunction, mast cell activation, and ultimately bladder insult, a vicious cycle of perpetuating damage; neural hyperactivity, chronic neuropathic pain, and neurogenic inflammation are also observed [2,3]. A HIC is an inflammatory lesion characterized by ruptured mucosa and submucosa in response to bladder distention with the goal standard therapy of fulguration ulcer lesion. NHIC patients have also demonstrated urothelial dysfunction and chronic inflammation [4]. Notably, central sensitization and inter-organ cross-talk have also been noted in IC/BPS [5].

Cystoscopic hydrodistention, oral medications (amitriptyline, cimetidine, hydroxyzine, pentosan polysulfate, and analgesics), intravesical hyaluronic acid (HA) instillations, dimethyl sulfoxide, botulinum toxin-A (BoNT-A) injections, and neuromodulation are recommended in the treatment guidelines

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[1,2]. However, these treatments are generally short-term and may not be effective for different IC/BPS subtypes. Treatment failures are often attributed to unresolved bladder urothelial dysfunction and persistent chronic inflammation, which remain key underlying factors [2,6]. Regrettably, no customized durable treatments are available for IC/BPS patients owing to a lack of comprehensive understanding of disease pathophysiology [1,7]. Improving the regenerative ability of urothelial progenitor cells might help promote a healthier bladder epithelium and improve bladder symptoms.

Platelet-rich plasma (PRP) treatment uses autologous concentrated plasma containing platelet growth factors and cytokines such as platelet-derived growth factors, transforming growth factors, vascular endothelial growth factors, and tumor necrosis factor (TNF) [8]. PRP is widely used in musculoskeletal injuries and wound care [9], promoting tissue regeneration by stimulating cell growth, differentiation, and angiogenesis while reducing reactive oxygen species (ROS) production and inflammatory reactions [9,10].

Previous studies have shown that repeated intravesical injections of autologous PRP can improve IC/BPS symptoms [3,9,11-13]. However, most published studies have used a small study sample. This study aimed to determine the clinical efficacy of intravesical PRP injections in a large IC/BPS patient cohort and explore the phenotype associated with satisfactory outcomes in patients with IC/BPS.

Materials and methods

Participants

Ninety-eight patients diagnosed with NHIC/BPS between January 2016 and October 2023 and treated with intravesical PRP injections monthly for four times at a single medical center in eastern Taiwan were included in this study [Figure 1]. All patients exhibited bladder wall glomerulations, petechia, or mucosal fissures on cystoscopic hydrodistention.

Before receiving PRP injection, patients were informed about potential complications, such as hematuria, micturition pain, transient urinary retention, or urinary tract infections. Treatment protocols followed established guidelines, incorporating lifestyle adjustments, pain relief strategies, anti-inflammatory and antihistamine medications, cystoscopic hydrodistention, or intravesical HA instillation or BoNT-A injection [1,2]. Nonselective nonsteroidal anti-inflammatories were prohibited during PRP injection courses [14]. This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval for the study was obtained from the Research Ethics Committee (IRB113-068-B, approved date: June 16, 2024) and registered at ClinicalTrials.gov (NCT06339645). The informed patient consent was waived by the Research Ethics Committee. All patients received intravesical injections for 4 consecutive months.

Subjective and objective outcome assessment tool

A 3-day voiding diary, IC symptom index (ICSI), and IC problem index (ICPI) were used to assess IC/BPS symptoms [Figure 1]. Video urodynamic studies were conducted before PRP injection.

For subjective assessment, the primary treatment outcome was patient satisfaction determined by self-reported global response assessment (GRA) scores after each treatment; the primary endpoint was a self-reported GRA score 3 months after the fourth PRP injection. A satisfactory outcome was defined as a GRA of moderate (+2) or marked improvement (+3); conversely, treatment outcomes were deemed unsatisfactory if patients did not achieve this level of improvement [15]. The secondary outcome measures included the ICSI and ICPI assessed by self-reported bladder condition (scored from 0 to 20 points and 0 to 16 points, respectively). Bladder pain severity was evaluated using the 11-point Numerical Rating Scale (NRS); higher scores indicated greater pain severity. Anxiety severity was recorded using Beck's Anxiety Inventory (BAI); a score of 0–18 points indicated mild anxiety and a score of 19–63 points indicated moderate or severe anxiety [16].

Objective outcomes included uroflowmetry examinations before and 3 months after the fourth PRP treatment and assessment of maximum bladder capacity (MBC) and glomerulation grade under cystoscopic hydrodistention. In addition, a 50 mL urine sample was collected on the day of the first PRP procedure (baseline) to determine urinary inflammatory and oxidative stress biomarker levels using the Milliplex® human cytokine/chemokine magnetic bead-based panel kit (Millipore, Darmstadt, Germany); protocols followed were similar to those outlined in a previous study [17].

Intravesical platelet-rich plasma injection procedure

PRP was obtained by drawing 50 mL of whole blood on injection day morning by a nurse and prepared in the hospital's central laboratory. A licensed medical technologist centrifuged with a soft spin centrifugation (190 ×*g*, 20 min, <20°C) separated PRP that was carefully transferred to another tube, avoiding the buffy coat. Further centrifugation with a hard spin (2000 ×*g*, 20 min, <20°C) formed platelet pellets at the bottom of the tube, with the lower portion containing PRP and the upper portion platelet-poor plasma (PPP). Furthermore, 12 mL of sterile PRP was prepared by removing PPP to achieve the desired concentration; 1 mL each was reserved for culture and platelet count, leaving 10 mL for intravesical injections. The concentration of PRP was about 2.5–3.5 times of the peripheral blood platelet count.

PRP injection was administered under intravenous general anesthesia. A total of 20 suburothelial injections of PRP solution were administered to the patients at each treatment session; 0.5 mL of PRP was administered for each injection. During the procedure, a volume of 100 mL was maintained in the bladder to facilitate injection with a 23G cystoscopic injection instrument (Wolf, Knittlingen, Germany). Both the posterior and lateral walls were injected penetrating about 1 mm into the suburothelium. Subsequently, cystoscopic hydrodistention was performed for 15 min with slowly dripping normal saline at a maximum intravesical pressure of 80 cmH_2O. MBC and glomerulation grade were determined after intravesical pressure release, and 14 Fr urethral catheter was left in place overnight after the injection. Patients received oral antibiotics for 7 days (cephradine 500 mg every

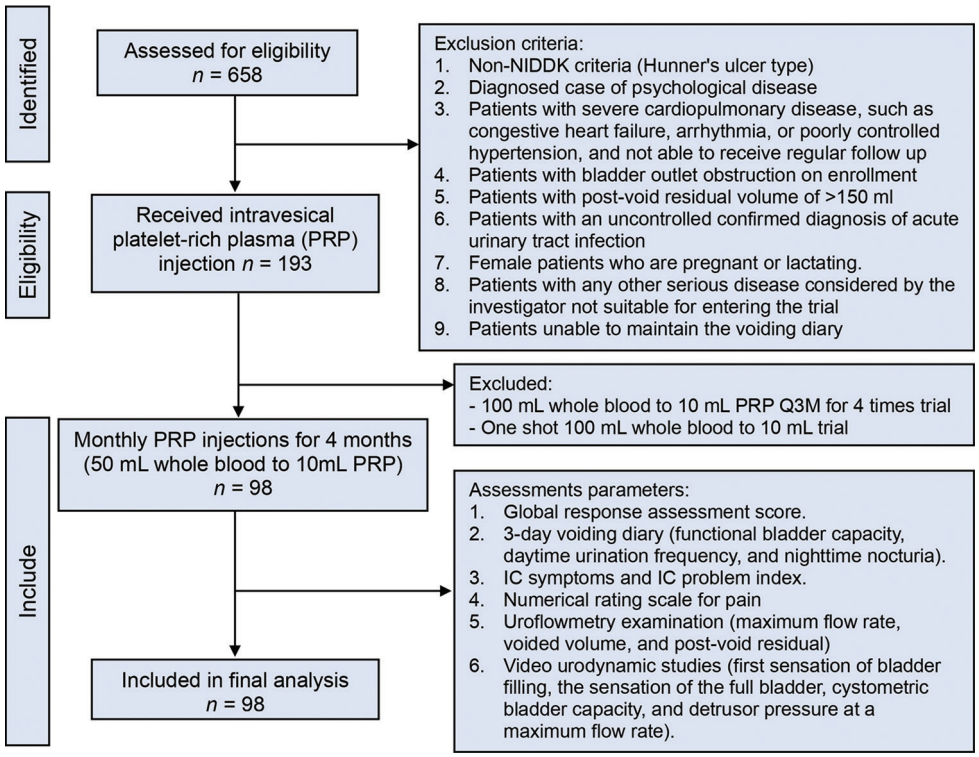

Figure 1: CONSORT flow diagram illustrating the study procedure for patients with non-Hunner's interstitial cystitis/bladder pain syndrome who were treated with intravesical platelet-rich plasma injections at a single medical center in eastern Taiwan between January 2016 and October 2023

6 h) and underwent monthly follow-ups at the outpatient clinic for 3 months post-PRP treatment. Patients could choose to discontinue PRP treatment at any time if satisfied with the results or if they opted not to complete the full course.

Statistical analysis

Statistical analysis was conducted using SPSS (version 25.0; IBM, Armonk, NY, USA) at a significance level of $P < 0.05$. Continuous variables were expressed as mean ± standard deviation and categorical variables as counts and proportions. Patient characteristics and treatment outcomes were assessed descriptively, compared between baseline and after treatment, and then divided into satisfactory (GRA≥2) and unsatisfactory (GRA<2) outcome groups. Categorical variables were compared using Pearson's Chi-square or Fisher's exact tests. For continuous variables (excluding urinary biomarker outliers), within-group subjective and objective parameters were analyzed using paired *t*-tests; between-group comparisons employed independent *t*-tests to determine treatment outcomes. Overall treatment outcome, trends in MBC and glomerulation grade post-PRP, and disparities among outcome groups were examined. Predictive factors associated with intravesical PRP injection leading to satisfactory outcomes in IC/BPS patients were explored, if feasible.

Results

Overall characteristics and treatment outcomes of the study patients

The mean age and IC duration of the 98 patients were 54.3 ± 12.3 years and 12.6 ± 10 years, respectively. Mean MBC was 684.4 ± 174.5 mL; the 3-day voiding diary showed that the average day- and night-time urinary frequency were 13.9 ± 8.9 times and 3.1 ± 1.9 times, respectively. All patients had moderate–severe anxiety before the PRP treatment (mean BAI = 22.4 ± 12.3 points). At the study endpoint, significant improvements were observed in ICSI, ICPI, NRS, urination frequency, nocturia, functional bladder capacity (FBC), anxiety severity, maximum flow rate (Qmax), and voided volume, without an increase in postvoided residual urine (PVR) compared to baseline [Table 1].

Comparison of clinical characteristics and treatment outcomes of interstitial cystitis/bladder pain syndrome patients stratified based on outcome satisfaction

At baseline, satisfactory and unsatisfactory outcome groups had no statistically significant differences in terms of age, IC duration, symptom scores, nocturia, the bladder wall thickness in bladder computer tomography, BAI, urodynamic and uroflowmetry parameters, MBC, and glomerulation grade; however, satisfactory outcome group had a significantly lower baseline urinary frequency (12.1 ± 5.9 vs. 16.0 ± 11.3, $P = 0.031$) and greater FBC (296.5 ± 126 vs. 232.8 ± 125.9, $P = 0.015$).

After PRP treatment, a significant improvement was observed in the ICSI, ICPI, NRS, urinary frequency, nocturia, FBC, BAI, and Qmax for patients in both the satisfactory and unsatisfactory outcome groups. However, upon comparing between patient groups, the satisfactory outcome group showed significant improvements in ICSI (change in ICSI from baseline: −4.87 ± 4.38 vs. −2.72 ± 4.53; $P = 0.020$) and ICPI (change in ICPI from baseline: −4.12 ± 4.17 vs. −2.47 ± 3.95; $P = 0.049$) than the unsatisfactory outcome

Table 1. Overall baseline and after treatment in subjective and objective parameters of patients with non-Hunner interstitial cystitis/bladder pain syndrome with intravesical platelet-rich plasma injection treatment

	Baseline	3rd PRP	3M after 4th PRP
Age (years)	54.3±12.3		
Gender			
Male	16 (16.3%)		
Female	82 (83.6%)		
IC duration (years)	12.6±9.99		
Videourodynamic study parameters			
First filling sensation	128.1±53.4		
Full sensation	203.4±84.5		
Pdet.Qmax	22.3±14.8		
Cystometric bladder capacity	260.1±114.2		
ICSI	10.8±4.43	7.43±4.02$	6.91±4.04*
ICPI	10.6±3.38	7.4±3.86$	7.21±3.94*
Bladder pain severity (NRS)	3.78±3.08	2.15±2.44$	2.02±2.47*
3-days voided diary			
Frequency	13.9±8.9	12.4±10.4$	11.2±5.49*
Nocturia	3.09±1.87	2.18±1.41$	2.08±1.49*
Functional bladder capacity	267.6±129.3	311.4±133.0$	322.0±121.0*
Anxiety severity of BAI	22.4±12.3	16.9±10.5$	17.4±9.83*
Uroflowmetry			
Maximum flow rate	10.9±6.5	15.8±9.5$	18.4±10.7*
Voided volume	205.2±110.7	212.0±112.9$	233.2±114.1*
Post-void residual	46.4±107.1	31.6±72.0$	24.9±53.6

	Baseline	1st PRP	2nd PRP	3rd PRP	4th PRP
MBC	684.39±174.52	715.67±174.93	793.10±144.37	775.86±156.19	785±158.19
Glomerulation	1.58±0.7	1.37±0.8	1.28±0.8	1.46±0.83	1.2±0.77

$Pair *t*-test compare 3rd after treatment vs. baseline,*Pair *t*-test compares three months after 4th treatment vs. baseline. IC: Interstitial cystitis, VUDS: Video urodynamic study, Pdet. Qmax: Detrusor pressure at the maximum flow rate, ICSI: IC symptom index, ICPI: IC problem index, NRS: Numerical Rating Pain Scale, BAI: Beck's Anxiety Inventory, MBC: Maximum bladder capacity, , PRP: platelet-rich plasma.

group. The mean duration after the fourth intravesical PRP injection until the next treatment (BoNT-A injection or repeat PRP injection) due to IC symptom flaring was 304 days in all patients [Table 2].

Baseline urine inflammatory cytokines and oxidative stress biomarkers in interstitial cystitis/bladder pain syndrome patients with different treatment outcomes

Based on the previous studies [10-12], baseline urine biomarkers were compared between IC/BPS patients and controls as well as between IC/BPS patients with satisfactory and unsatisfactory treatment outcomes. Significantly higher levels of inflammatory cytokines (monocyte chemoattractant protein-1, exotoxin, TNF-α, and prostaglandin E2) and oxidative stress biomarkers (8-hydroxy-2-deoxyguanosine and 8-isoprostane) and lower levels of nerve growth factor, interleukin-2, and macrophage inflammatory protein-1 beta were observed in IC/BPS patients compared to controls. However, baseline urine biomarkers did not significantly differ between IC/BPS patients with different treatment outcomes [Table 3].

Overall treatment outcomes and bladder condition after intravesical platelet-rich plasma injections

Overall, the intravesical PRP injection treatment improved symptoms and bladder condition in all patients with IC/BPS; however, we could not identify specific patient characteristics or phenotypes that might predict a satisfactory outcome. With repeated injections, the percentage of patients with a satisfactory outcome increased from 25.5% after the first PRP injection to 46.9% at the third PRP injection and 55.1% at the study endpoint (3 months after the fourth PRP injection). A total of 79.6% of patients reported a slight improvement (GRA ≥1 plus GRA ≥2) after four PRP injections [Figure 2a]. MBC and glomerulation grade were also improved after consecutive PRP treatments. The mean MBC increased from 684.4 mL at baseline to 785 mL at the fourth PRP injection, retrospectively [Figure 2b]; however, the glomerulation grade only slightly improved, albeit not significantly [Figure 2c].

There were minimal treatment-related adverse events after PRP injections. Among the 98 patients and 392 episodes of PRP injections, only one patient experienced dysuria without urinary retention and two patients developed mild hematuria that resolved spontaneously the following day without medication. Three participants withdrew from the clinical trial after reporting marked improvement following the third PRP injection. No participants required extended hospitalization or additional treatment.

Discussion

Study results revealed that repeat autologous PRP intravesical injections effectively reduced IC symptoms, bladder pain, anxiety severity, urinary frequency, and nocturia. In addition, PRP treatment significantly increased FBC and improved voiding parameters without increasing PVR. Nearly

Table 2: Baseline clinical characteristics and treatment outcomes in patients with interstitial cystitis/bladder pain syndrome after platelet-rich plasma injection

	Unsatisfactory outcome (GRA <2) (*n*=44)	Satisfactory outcome (GRA ≥2) (*n*=54)	*P*
Age	53.0±11.9	54.0±12.1	0.698
Gender, *n* (%)			
Male	6 (13.6)	10 (18.5)	0.515
Female	38 (86.4)	44 (81.5)	
IC duration	12.8±8.52	12.6±11.5	0.930
ICSI			
Baseline	11.1±4.7	10.6±4.19	0.613
Δ6 months	−2.72±4.53$^{\$}$	−4.87±4.38$^{\$}$	0.020*
ICPI			
Baseline	10.7±4.41	10.5±3.38	0.743
Δ6 months	−2.47±3.95$^{\$}$	−4.12±4.1$^{\$}$	0.049*
Bladder pain severity (NRS)			
Baseline	3.73±3.09	3.81±3.02	0.888
Δ6 months	−1.22±2.34$^{\$}$	−2.18±2.7$^{\$}$	0.067
3-day voided diary - frequency			
Baseline	16.0±11.3	12.1±5.9	0.031*
Δ6 months	−2.71±6.17$^{\$}$	−1.67±5.0$^{\$}$	0.337
3-day voided diary - nocturia			
Baseline	3.36±2.09	2.87±1.66	0.199
Δ6 months	−1.34±1.52$^{\$}$	−0.8±1.73$^{\$}$	0.146
3-day voided diary - FBC			
Baseline	232.8±125.9	296.5±126.0	0.015*
Δ6 months	73.3±152.9$^{\$}$	18.1±110.3$^{\$}$	0.086
Bladder computer tomography, *n* (%)			
Smooth bladder wall	9 (56.3)	13 (54.2)	0.897
Focal thickness	7 (43.8)	11 (45.8)	
Anxiety severity of BAI			
Baseline	21.7±13.2	22.9±11.7	0.712
Δ6 months	−3.57±11.9$^{\$}$	−4.77±11.3$^{\$}$	0.707
VUDS parameters			
First filling sensation	122.5±47.1	132.5±57.9	0.363
Full sensation	196.9±75.2	208.6±91.5	0.499
Pdet	20.6±14.4	23.7±15.1	0.318
Cystometric bladder capacity	237.2±102.5	278.9±120.6	0.083
Uroflowmetry - Qmax			
Baseline	10.4±6.34	11.3±6.65	0.478
Δ6 months	6.64±10.55$^{\$}$	8.0±10.78$^{\$}$	0.554
Uroflowmetry-voided volume			
Baseline	184.1±111.9	222.2±107.8	0.094
Δ6 months	39.4±138.1	24.3±127.9	0.597
Uroflowmetry - PVR			
Baseline	40.3±81.6	51.2±124.2	0.625
Δ6 months	−15.9±114.4	−29.9±126.3	0.593
MBC	674.3±162.8	692.6±184.6	0.609
Platelet concentration	2.72±1.16	2.59±1.16	0.819
Days until the next treatment	304.2±172.9	304.7±154.9	0.994

*Significant $P<0.05$, $^{\$}$Compare with the baseline. GRA: Global response assessment, IC: Interstitial cystitis, NRS: Numerical Rating Scale, BAI: Beck's Anxiety Inventory, VUDS: Video urodynamic study, Pdet: Detrusor pressure at the maximum flow rate, PVR: Postvoided residual urine, ICSI: IC symptom index, ICPI: IC problem index, MBC: Maximum bladder capacity, FBC: Functional bladder capacity

80% of patients experienced a mild improvement after four PRP injections, with 55.1% of patients reporting moderate to marked improvement. Patients could have a mean remission duration of >10 months before requiring further treatment.

Patients with IC/BPS usually suffer from frequency, nocturia, bladder pain, and anxiety [1,2]. The most commonly accepted pathophysiology of IC/BPS involves chronic inflammation within the bladder wall, increased urothelial apoptosis, impaired urothelial cell proliferation, and activated sensory receptors [18]. Consequently, patients experience irritative bladder symptoms and pain due to urothelial barrier dysfunction [19,20]. The exacerbated bladder inflammation further results in the progression

Table 3: Baseline urine inflammatory cytokines and oxidative stress biomarkers with different treatment outcomes in patients with bladder pain syndrome

	Unsatisfactory outcome (*n*=44)	Satisfactory outcome (*n*=54)	*P*	Control[&] (*n*=31)	PRP versus control (*P*)
IL-8	10.14±12.48	16.87±24.41	0.086	12.44±20.97	0.737
IP10	13.34±26.93	14.47±31.28	0.835	13.81±18.42	0.978
MCP1	335.08±337.73	347.8±635.21	0.907	147.13±109.73	0.001*
NGF	0.17±0.02	0.17±0.02	0.930	0.26±0.07	<0.001*
BDNF	0.52±0.11	0.54±0.13	0.415	0.54±0.11	0.661
Exotoxin	7.67±8.47	8.91±9.04	0.495	4.97±3.7	0.042*
IL-2	0.22±0.08	0.21±0.12	0.727	0.8±0.18	<0.001*
IL-6	15.75±92.07	2.05±3.24	0.281	1.29±1.35	0.551
MIP1β	1.42±2.33	1.44±2.09	0.983	2.52±1.81	0.017*
RANTES	5.86±7.3	4.93±6.3	0.506	6.04±5.15	0.609
TNF-α	1.5±0.45	1.52±0.36	0.869	0.81±0.32	<0.001*
PGE2	308.79±263.89	310.93±221.43	0.966	161.37±105.15	<0.001*
8-OHDG	32.36±24.04	37.25±24.13	0.328	18±13.73	<0.001*
8-isoprostane	54.4±50.76	58.11±75.57	0.785	16.78±11.74	<0.001*
TAC	1670.58±1525.4	1510.51±1721.14	0.637	1077.91±925	0.110

*Significant $P<0.05$, [&]Control group: Health without IC received the sling procedure due to simple stress urinary incontinence. IL-8: Interleukin-8, IP10: Interferon gamma-induced protein 10, MCP1: Monocyte chemoattractant protein-1, NGF: Nerve growth factor, BDNF: Brain-derived neurotrophic factor, IL-2: Interleukin-2, IL-6: Interleukin-6, MIP1β: Macrophage inflammatory protein-1 beta, RANTES: Regulated upon activation, normal T cell expressed and presumably secreted (also known as CCL5), TNF-α: Tumor necrosis factor-alpha, PGE2: prostaglandin E2, 8-OHDG: 8-hydroxy-2-deoxyguanosine, TAC: Total antioxidant capacity, PRP: Platelet-rich plasma.

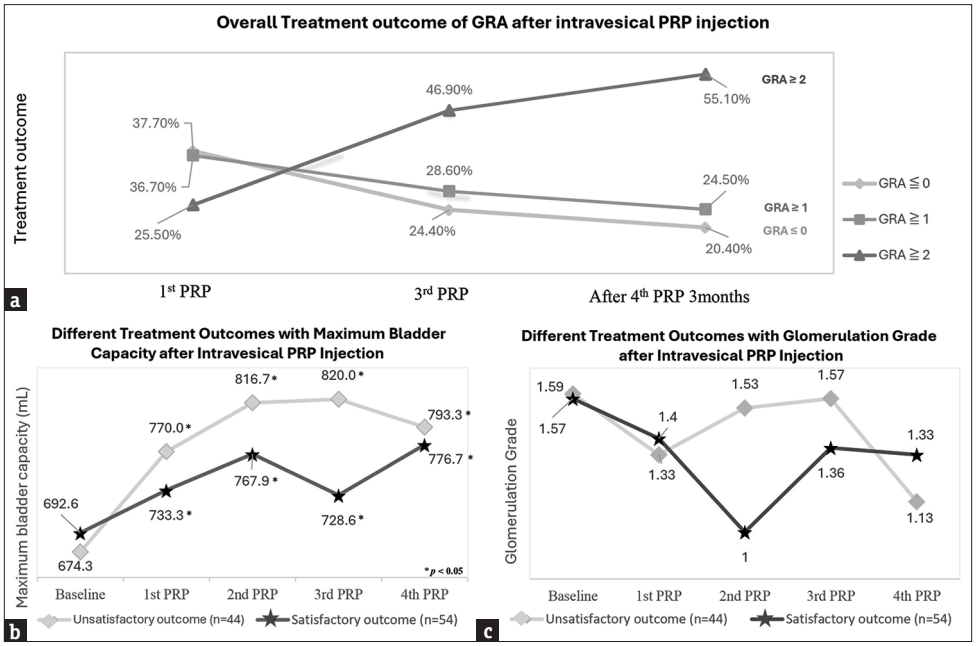

Figure 2: The changes of (a) global response assessment at 3 and 6 months after the first platelet-rich plasma (PRP) injection in patients with different treatment outcomes from baseline to fourth PRP injection in overall patients with interstitial cystitis/bladder pain syndrome, (b) maximum bladder capacity and (c) glomerulation grade between patients with satisfactory and unsatisfactory treatment outcome after intravesical PRP injections. PRP: Platelet-rich plasma, GRA: Global response assessment

of oxidative stress [21]. Current treatments for IC/BPS include cystoscopic hydrodistention, oral medications, and intravesical instillations of HA or dimethyl sulfoxide which could only provide short-term relief in a small portion of patients across different phenotypes [2]. BoNT-A is effective in patients with bladder-pain-predominant IC/BPS by inhibiting sensory neurotransmitter release to limit the secretion of inflammatory mediators [22-24]. Other bladder therapies have not been proven effective in treating the fundamental pathophysiology of IC/BPS.

The rationale for using PRP therapy in IC/BPS treatment lies in its regenerative properties with the availability of diverse growth factors and cytokines to promote tissue repair and angiogenesis, reduce inflammation and oxidative stresses, and enhance urothelial cell regeneration [25]. Clinical trials have demonstrated its ability to improve bladder symptoms and address underlying pathological changes [26]. PRP can also regulate the overproduction of ROS, which helps inhibit apoptosis, resulting in anti-inflammatory and analgesic effects [8]. These therapeutic mechanisms presumably underlie

the success of intravesical PRP injections in improving both subjective and objective parameters in over half of our study patients with IC/BPS. Although this study did not identify a specific phenotype of IC/BPS for a satisfactory outcome, PRP seems promising in addressing the underlying pathological changes and promoting urothelial health.

In addition, elevated oxidative stress biomarkers and inflammatory cytokine levels were found in patients with IC/BPS, indicating exaggerated oxidative stresses and inflammation in the IC/BPS bladder. However, the urinary levels of biomarkers did not differ between patients with satisfactory and unsatisfactory outcomes, indicating that the anti-inflammatory effect of PRP injections might not be completely effective against all pathological processes involved in the IC/BPS. Furthermore, our study patients with satisfactory outcomes had less frequency and larger FBC at baseline, suggesting that patients with mild form of bladder inflammation may have a better response to PRP treatment. Regardless of whether the outcome was satisfactory, all patients showed improvements in urinary frequency episodes and pain and an increase in MBC after PRP treatment, corroborating the efficacy of PRP for all phenotypes of IC/BPS.

Small patient samples and protocol variations have hindered promising results in previous studies on intravesical PRP injections for IC/BPS [11-13]. By including a substantial participant cohort, this study provides valuable real-world insights into the efficacy of PRP on IC/BPS. However, lack of a randomized, placebo-controlled arm limits its applicability. In addition, performing cystoscopic hydrodistention after PRP injection might have influenced outcomes, although its impact has been reported to be minimal [13]. All patients were treated with four monthly PRP injections and followed up for treatment outcomes. We believe that more injections might provide better results if patients do not achieve a satisfactory outcome after four injections.

Growing evidence supports the therapeutic potential of PRP as a modulator of nociception, neurogenesis, and neuroinflammation in IC/BPS [27]. The findings of this study suggest that intravesical PRP injections could increase bladder capacity and improve IC symptoms across different phenotypes. However, the anti-inflammatory role of PRP for IC/BPS patients has yet to be confirmed. A comparison of urinary inflammatory biomarkers at baseline and after PRP treatment should clarify this point in further investigation. Future research should focus on elucidating the underlying therapeutic mechanisms of PRP therapy, refining treatment protocols, and evaluating long-term outcomes to optimize its clinical application. Addressing these knowledge gaps may pave the way for personalized and effective treatments for IC/BPS to improve the outcomes and quality of life in IC/BPS patients.

Conclusion

Four consecutive PRP intravesical injections are safe and effective for reducing urinary symptoms and pain and improving bladder capacity in majority of IC/BPS patients. Our results support further research on PRP as a promising novel therapy for this challenging bladder condition.

Acknowledgments

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Data availability statement

The data sets generated and analyzed during the current study can be obtained from the corresponding author upon reasonable request.

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Conflicts of interest

Dr. Hann-Chorng Kuo and Dr. Yuan-Hong Jiang, the editorial board members at *Tzu Chi Medical Journal*, had no roles in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

References

1. Clemens JQ, Erickson DR, Varela NP, Lai HH. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol 2022;208:34-42.
2. Homma Y, Akiyama Y, Tomoe H, Furuta A, Ueda T, Maeda D, et al. Clinical guidelines for interstitial cystitis/bladder pain syndrome. Int J Urol 2020;27:578-89.
3. Trama F, Illiano E, Marchesi A, Brancorsini S, Crocetto F, Pandolfo SD, et al. Use of intravesical injections of platelet-rich plasma for the treatment of bladder pain syndrome: A comprehensive literature review. Antibiotics (Basel) 2021;10:1194.
4. Jhang JF, Hsu YH, Kuo HC. Urothelial functional protein and sensory receptors in patients with interstitial cystitis/bladder pain syndrome with and without Hunner's lesion. Urology 2016;98:44-9.
5. Lai HH, Gardner V, Ness TJ, Gereau RW 4th. Segmental hyperalgesia to mechanical stimulus in interstitial cystitis/bladder pain syndrome: Evidence of central sensitization. J Urol 2014;191:1294-9.
6. Coelho A, Wolf-Johnston AS, Shinde S, Cruz CD, Cruz F, Avelino A, et al. Urinary bladder inflammation induces changes in urothelial nerve growth factor and TRPV1 channels. Br J Pharmacol 2015;172:1691-9.
7. Mohammad A, Laboulaye MA, Shenhar C, Dobberfuhl AD. Mechanisms of oxidative stress in interstitial cystitis/bladder pain syndrome. Nat Rev Urol 2024;21:433-49.
8. Hermilasari RD, Rizal DM, Wirohadidjojo YW. Potential mechanism of platelet-rich plasma treatment on testicular problems related to diabetes mellitus. Prague Med Rep 2023;124:344-58.
9. Everts P, Onishi K, Jayaram P, Lana JF, Mautner K. Platelet-rich plasma: New performance understandings and therapeutic considerations in 2020. Int J Mol Sci 2020;21:7794.
10. Tammam BM, Habotta OA, El-Khadragy M, Abdel Moneim AE, Abdalla MS. Therapeutic role of mesenchymal stem cells and platelet-rich plasma on skin burn healing and rejuvenation: A focus on scar regulation, oxido-inflammatory stress and apoptotic mechanisms. Heliyon 2023;9:e19452.
11. Jhang JF, Lin TY, Kuo HC. Intravesical injections of platelet-rich plasma is effective and safe in treatment of interstitial cystitis refractory to conventional treatment-a prospective clinical trial. Neurourol Urodyn 2019;38:703-9.
12. Jiang YH, Jhang JF, Lin TY, Ho HC, Hsu YH, Kuo HC. Therapeutic efficacy of intravesical platelet-rich plasma injections for interstitial

cystitis/bladder pain syndrome-a comparative study of different injection number, additives and concentrations. Front Pharmacol 2022;13:853776.

13. Jiang YH, Kuo YC, Jhang JF, Lee CL, Hsu YH, Ho HC, et al. Repeated intravesical injections of platelet-rich plasma improve symptoms and alter urinary functional proteins in patients with refractory interstitial cystitis. Sci Rep 2020;10:15218.
14. Kao DS, Zhang SW, Vap AR. A Systematic Review on the Effect of Common Medications on Platelet Count and Function: Which Medications Should Be Stopped Before Getting a Platelet-Rich Plasma Injection? Orthop J Sports Med 2022; 10:23259671221088820.
15. Tsai CP, Yang JM, Liang SJ, Lin YH, Huang WC, Lin TY, et al. Cystoscopic characteristic findings of interstitial cystitis and clinical implications in women with refractory interstitial cystitis: A prospective, multicenter study. J Chin Med Assoc 2021;84:418-22.
16. Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and hospital anxiety and depression scale-anxiety (HADS-A). Arthritis Care Res (Hoboken) 2011; 63(Suppl 11): S467-72.
17. Yu WR, Jiang YH, Jhang JF, Kuo HC. Use of urinary cytokine and chemokine levels for identifying bladder conditions and predicting treatment outcomes in patients with interstitial cystitis/bladder pain syndrome. Biomedicines 2022;10:1149.
18. Jhang JF, Jiang YH, Kuo HC. Current understanding of the pathophysiology and novel treatments of interstitial cystitis/bladder pain syndrome. Biomedicines 2022;10:2380.
19. Zhang CO, Wang JY, Koch KR, Keay S. Regulation of tight junction proteins and bladder epithelial paracellular permeability by an antiproliferative factor from patients with interstitial cystitis. J Urol 2005;174:2382-7.
20. Yu WR, Jiang YH, Jhang JF, Kuo HC. Cystoscopic characteristic findings of interstitial cystitis and clinical implications. Tzu Chi Med J 2024;36:30-7.
21. Hajam YA, Rani R, Ganie SY, Sheikh TA, Javaid D, Qadri SS, et al. Oxidative stress in human pathology and aging: Molecular mechanisms and perspectives. Cells 2022;11:552.
22. Giannantoni A, Gubbiotti M, Bini V. Botulinum neurotoxin a intravesical injections in interstitial cystitis/bladder painful syndrome: A systematic review with meta-analysis. Toxins (Basel) 2019;11:510.
23. Moore AA, Nelson M, Wickware C, Choi S, Moon G, Xiong E, et al. OnabotulinumtoxinA effects on trigeminal nociceptors. Cephalalgia 2023; 43:3331024221141683.
24. Yu WR, Jhang JF, Kuo HC. Intravesical botulinum toxin injection plus hydrodistention is more effective in patients with bladder pain-predominant interstitial cystitis/bladder pain syndrome. Toxins (Basel) 2024;16:74.
25. Riewruja K, Phakham S, Sompolpong P, Reantragoon R, Tanavalee A, Ngarmukos S, et al. Cytokine profiling and intra-articular injection of autologous platelet-rich plasma in knee osteoarthritis. Int J Mol Sci 2022;23:890.
26. Elmongy NF, Meawad SB, Elshora SZ, Atwa AH, Hammad AM, Mehanna OM, et al. Platelet-rich plasma ameliorates neurotoxicity induced by silver nanoparticles in male rats via modulation of apoptosis, inflammation, and oxidative stress. J Biochem Mol Toxicol 2023;37:e23420.
27. Sánchez M, Anitua E, Delgado D, Sanchez P, Prado R, Orive G, et al. Platelet-rich plasma, a source of autologous growth factors and biomimetic scaffold for peripheral nerve regeneration. Expert Opin Biol Ther 2017;17:197-212.