Effects of intravesical cocktail instillation on outcomes and serum pain factors of patients with bladder pain syndrome

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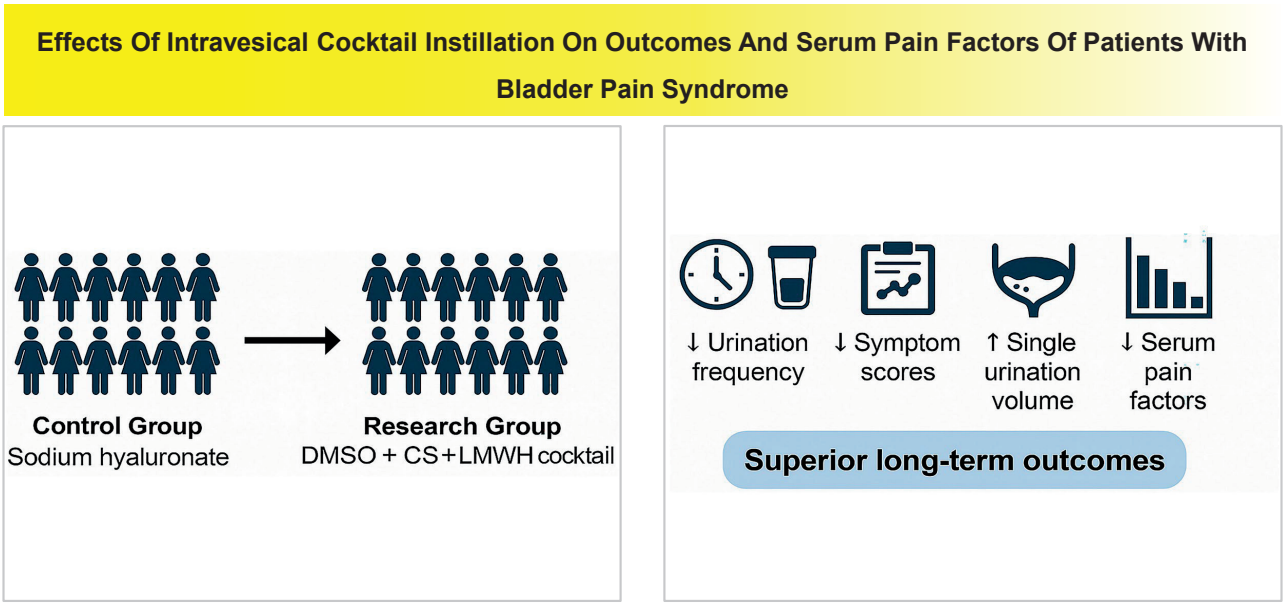
Aims. We aimed to assess the effects of intravesical cocktail instillation on the outcomes and serum pain factors of patients with bladder pain syndrome (BPS).
Methods. The clinical data of 86 female BPS patients hospitalized between March 2017 and March 2024 were collected for retrospective analysis. All patients were treated with oral medication (amitriptyline) + local intravesical instillation of drugs, and then assigned to a control group (sodium hyaluronate intravesical instillation) and a research group [intravesical instillation of dimethyl sulfoxide (DMSO) + chondroitin sulfate (CS) + low-molecular-weight heparin (LMWH) cocktail].
Results. The research group (n=43) had lower urination frequency in 24 h, Pelvic Pain and Urgency/Frequency Patient Symptom Scale score, and O'Leary-Sant interstitial cystitis symptom index and interstitial cystitis problem index, as well as larger single urination volume than those of the control group (n=43) after 3 and 6 months of treatment ($P<0.05$). In the serum, the levels of substance P (SP), 5-hydroxytryptamine (5-HT), prostaglandin E_2 (PGE_2), neuropeptide Y (NPY), β-endorphin (β-EP), and dopamine (DA) declined in the two groups after 1 month of treatment in comparison to the pre-treatment levels. The levels of SP, 5-HT, PGE_2, and NPY were lower, while the levels of β-EP and DA were higher in the research group than those in the control group ($P<0.05$).
Conclusion. The intravesical instillation of DMSO + CS + LMWH cocktail is superior in long-term outcomes. It is more conducive to improving the levels of serum pain factors, with a good safety profile and without increasing adverse reactions.



Key words: bladder pain syndrome, cocktail, intravesical instillation, outcome

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INTRODUCTION

Bladder pain syndrome (BPS), alternatively called interstitial cystitis (IC), is a difficult and complicated urological disease that frequently affects women aged 30–60 years old, and patients may suffer from lower urinary tract symptoms such as urinary frequency, urinary urgency and dysuria, and lower abdominal pain. Further, some patients may develop anxiety and depression due to long-term chronic symptoms, seriously impacting their quality of sleep and life[1,2]. Over the past years, it has been difficult to conduct a clinical evaluation on BPS due to the complicated and diversified symptoms. Hence researchers of urinary surgery from various countries have been dedicated to researching the gold standards for the clinical diagnosis of the disease. For example, the European Society for the Study of Interstitial Cystitis formally named BPS as BPS/IC and clarified its classification and exclusion criteria in 2008. As studies are continuously deepened, the American Urological Association in 2015 and the Canadian Urological Association in 2016 further determined the diagnosis and treatment system of BPS/IC based on the European Society for the Study of Interstitial Cystitis studies[3-5]. Although the pathogenic mechanism of BPS/IC is complex and has not yet been fully defined, most believe that the loss of bladder mucosal glycosaminoglycan (GAG) layer is not only the main pathogenesis of chronic inflammatory diseases of the bladder including BPS/IC but also an important factor in accelerating their clinical progression. It can cause destruction or partial destruction of bladder mucosa and in turn increase the bladder epithelial permeability, ultimately enhancing bladder sensitivity and bladder mucosal dysfunction[6,7]. Therefore, the BPS/IC treatment regimen focusing on the GAG layer repair can improve the clinical benefit of patients to some extent.

Currently, drug therapy remains the preferred regimen in the treatment guidelines of BPS/IC recommended by the American Urological Association and Canadian Urological Association, mainly including oral medication and local intravesical instillation of drugs. Among them, amitriptyline is an oral therapeutic drug recommended by the Japanese Urological Association[8], American Urological Association, Canadian Urological Association, etc., and it is also a tricyclic antidepressant with antihistaminic and central sedative effects, which is conducive to relieving patients' anxiety and depression and thus reducing neuropathic pain[9]. In the meantime, amitriptyline can exert some inhibitory effect on the reuptake of norepinephrine (NE) and 5-hydroxytryptamine (5-HT) by blocking the active transport system of presynaptic nerve terminals, thereby exciting the bladder detrusor muscle, improving the bladder storage function, and promoting the improvement of clinical symptoms in patients[10]. Single oral administration of amitriptyline can rapidly ameliorate the symptoms of urinary urgency and frequency, but it fails to effectively alleviate chronic bladder pain and meet the clinical expectation of long-term outcomes, so the combination regimens need to be considered.

Increasingly more attention has been paid to drug intravesical instillation regimens in the clinical treatment of BPS/IC owing to their direct action on the bladder mucosa. As a kind of drug for intravesical instillation, sodium hyaluronate is a linear glycan formed by alternating connection of the reaction between the disaccharide units of N-acetylglucosamine and glucuronic acid, thus repairing the GAG layer of bladder epithelial cells[11,12]. The treatment of BPS/IC is a time-consuming and repetitive process, and SH is fairly expensive and certainly limited in clinical application, so it is of positive significance to explore an economical, safe and effective replacement therapy for improving the outcomes of BPS/IC. Being drugs for intravesical instillation as well, dimethyl sulfoxide (DMSO), chondroitin sulfate (CS), and low-molecular-weight heparin (LMWH) are characterized by relatively low prices and minor limitations in clinical application, but there are few studies and reports on the treatment of BPS/IC with intravesical instillation of DMSO + CS + LMWH cocktail.

Thus, the intravesical instillation of DMSO+CS+ LMWH cocktail was applied to the treatment of BPS/IC patients in the present study, and its effects on the levels of serum pain factors were observed, aiming to provide references for the selection of clinical regimens.

PATIENTS AND METHODS

Subjects

The clinical data of 86 female BPS patients hospitalized for treatment from March 2017 to March 2024 were collected for a retrospective analysis. All the patients were treated with oral medication (amitriptyline)+local intravesical instillation of drugs, and then they were allocated to a control group (sodium hyaluronate intravesical instillation) and a research group (intravesical instillation of DMSO+CS+LMWH cocktail).

Inclusion and exclusion criteria

The inclusion criteria were determined as follows: 1) patients meeting the diagnostic criteria for BPS/IC published by the American Urological Association or Canadian Urological Association and definitely diagnosed with BPS/IC through cystoscopy, therapeutic hydrodistention[4,5], and urine cytology, 2) those with complete clinical data, 3) newly diagnosed females aged 25–60 years old, 4) those with typical symptoms lasting for > 6 weeks, and 5) those without other abnormalities of the urinary system detected by B-mode ultrasound.

The following exclusion criteria were adopted: 1) patients complicated with pelvic inflammatory diseases, urinary calculi, sexually transmitted diseases, endometriosis, vaginal or urinary tract infections, bladder tumors, urethrocele, or lower urinary tract obstruction, 2) those clinically diagnosed with chemical cystitis, cystitis tuberculosa, radiation cystitis, bacterial cystitis, or other types of cystitis, 3) those with maximum functional bladder capacity >350 mL in the awake state, daytime urination

frequency <8 times or nocturia frequency <2 times, 4) those without a strong desire to urinate even when the bladder was filled with 150 mL of fluid, 5) those complicated with mental disorder or cognitive dysfunction, or 6) those unable to cooperate with the completion of surveys with scales or other tasks.

Treatment methods

Both groups of patients were orally administered with amitriptyline (Hunan Dongting Pharmaceutical Co., Ltd., strength: 25 mg×100 tablets) at an initial dose of 25 mg/time×3 times/d, and the dose was gradually increased to 50–75 mg/time×3 times/d according to patients' tolerance. There was no difference in final dose between the two groups.

In the control group, sodium hyaluronate (Mylan Institutional Inc., Ireland, strength: 40 mg/50 mL) intravesical instillation was carried out on the basis of oral medication. Specifically, the perineum of the patients in the lithotomy position was routinely disinfected. Then a disposable single-lumen catheter was inserted into the bladder *via* the urethral orifice, through which the residual urine in the bladder was emptied. Next, 50 mL of sodium hyaluronate was slowly injected into the bladder via a catheter, the positions (prone , left and right lateral , and supine positions) were changed 15 min later, and each position was maintained for ≥15 min. The patients were advised to keep the positions as long as possible and excrete the urine on their own. The intravesical instillation was performed once a week for 4 consecutive weeks and then once every two weeks for 8 weeks.

As for the research group, based on oral medication, intravesical instillation of DMSO (50%, 50 mL, Kyorin Pharmaceutical Co., Ltd., Japan; strength: 500 g) + CS (40 mg, Hunan Hengsheng Pharmaceutical Co., Ltd., strength: 40 mg×5 injections) + LMWH (10,000 IU, Qilu Pharmaceutical Co., Ltd., strength: 0.4 mL:5000 IU×5 injections) cocktail was implemented in the same way as the control group. The intravesical instillation was conducted once a week for 4 consecutive weeks and then once every two weeks for 8 weeks.

Observation of indicators

Treatment effect: The O'Leary-Sant score[13,14], Pelvic Pain and Urgency/Frequency (PUF) Patient Symptom Scale score[15], urination frequency in 24 h, and single urination volume were compared between the two groups before treatment, after 1 month of treatment, after 3 months of treatment, and after 6 months of treatment. The O'Leary-Sant score consists of interstitial cystitis symptom index (ICSI) and interstitial cystitis problem index (ICPI). The ICSI is composed of 4 entries (burning or pain sensation in the bladder area, number of urinations at night, urination again within 2 h after urination, and urinary urgency without warning), and each entry is scored using Likert 6-level scoring method (0–5 points). In other words, the symptoms were scored 0–5 points from none to high frequency, with a total score of 0–20 points, and a higher score indicated severer symptoms of patients. The ICPI covers a total of 4 entries (urinary urgency without warning, nocturnal urination, frequent urination in the daytime, and burning/pain/pressure sensation in the bladder area), each of which is scored 0, 1, 2, 3, and 4 points corresponding to the responses of not a problem, very minor problem, minor problem, moderate problem, and major problem, with a total score of 0–16 points. The higher the score was, the greater the impact on patients and the severer the problem would be. The PUF score (0–35 points) includes 11 entries in total from 4 aspects (bladder pain, urinary frequency, urinary urgency, and quality of sexual life), with higher scores signifying more serious symptoms and distress.

Levels of serum pain factors: Fasting venous blood (5 mL each) was collected from both groups of patients in the early morning before treatment and after 1 month of treatment, which was centrifuged for 10 min (centrifugal radius: 10 cm, centrifugal rate: 3000 r/min) using JW-1044 centrifuge (Anhui Jiawen Instrument Co., Ltd.) to harvest the supernatant for testing. Then the levels of substance P (SP), 5-HT, prostaglandin E_2 (PGE_2), neuropeptide Y (NPY), β-endorphin (β-EP), and dopamine (DA) were measured *via* enzyme-linked immunosorbent assay using relevant kits procured from Beijing Wallace Biotechnology Co., Ltd. and Shanghai Zhen Ke Biological Technology Co., Ltd.

Adverse reactions: The incidence of adverse reactions lethargy, constipation, postural hypotension, urinary tract infection, and nausea and vomiting in the two groups was recorded during the follow-up for 6 months.

Statistical analysis

SPSS 23.0 software was employed. The measurement data were expressed by ($x \pm s$) and subjected to the *t*-test. Repeated measures analysis of variance was conducted for the statistical analysis of data with 3 or more repeated measurements using a mixed linear model approach. The count data were described as [n (%)] and examined by the χ^2 test. $P<0.05$ was selected to indicate statistically significant differences.

RESULTS

Baseline clinical data

The menstrual status, age, Visual Analogue Scale score of suprapubic pain during urinary storage at admission, course of disease, body mass index, history of pelvic surgery, and number of vaginal deliveries were comparable between the two groups ($P>0.05$) (Table 1).

Treatment outcomes

Compared with those before treatment, the urination frequency in 24 h, PUF score, and O'Leary-Sant ICSI and ICPI decreased, while the single urination volume increased in both groups after 1, 3, and 6 months of treatment ($P<0.05$). No differences in statistical significance were found in the single urination volume, urination frequency in 24 h, PUF score, and O'Leary-Sant ICSI and

Table 1. Baseline clinical data.

Indicator		Research group (n=43)	Control group (n=43)	Statistical value	*P*
Menstrual status [n (%)]	Postmenopausal	28 (65.12)	26 (60.47)	χ^2=0.199	0.655
	Premenopausal	15 (34.88)	17 (39.53)		
Age ($\bar{x} \pm s$, year)		53.78±6.12	54.15±6.03	*t*=0.282	0.778
Visual Analogue Scale score at admission ($x \pm s$, point)		6.11±0.47	6.03±0.44	*t*=0.815	0.418
Course of disease ($\bar{x} \pm s$, month)		25.64±2.12	26.05±2.16	*t*=0.888	0.377
Body mass index ($\bar{x} \pm s$, kg/m^2)		22.31±1.05	22.38±1.09	*t*=0.303	0.762
History of pelvic surgery [n (%)]	Yes	5 (11.63)	3 (6.98)	χ^2=0.138	0.711
	No	38 (88.37)	40 (93.02)		
Number of vaginal deliveries [n (%)]	1	21 (48.84)	24 (55.81)	χ^2=0.420	0.517
	≥2	22 (51.16)	19 (44.19)		

Table 2. PUF score and O'Leary-Sant ICSI and ICPI at different time points before and after treatment ($x \pm s$, point).

Group	Indicator	Before treatment	After 1 month of treatment	After 3 months of treatment	After 6 months of treatment	Time effect (*F, P*)	Group effect (*F, P*)	Interaction effect (*F, P*)
Research (n=43)	O'Leary-Sant ICSI	16.42±1.56	13.69±1.04*	11.28±1.06*	6.82±1.05*	45.0, <0.001	0.5, 0.48	6.5, 0.002
Control (n=43)		16.33±1.67	14.15±1.23*	12.79±1.48*	8.47±1.19*			
t		0.258	1.873	5.439	6.818			
P		0.797	0.065	<0.001	<0.001			
Research (n=43)	O'Leary-Sant ICPI	13.31±1.02	11.39±1.26*	7.24±1.06*	5.95±1.01*	50.0, <0.001	0.3, 0.58	7.0, 0.001
Control (n=43)		13.28±1.05	11.71±1.32*	8.75±1.34*	7.39±1.14*			
t		0.134	1.150	5.795	6.200			
P		0.893	0.253	<0.001	<0.001			
Research (n=43)	PUF score	30.77±2.61	26.29±3.11*	20.23±2.97*	18.63±1.18*	60.0, <0.001	4.0, 0.046	8.5, <0.001
Control (n=43)		30.85±2.54	27.12±3.08*	22.51±2.45*	20.57±2.19*			
t		0.144	1.244	3.883	5.114			
P		0.886	0.217	<0.001	<0.001			

*P<0.05 vs. before treatment within the group.

Table 3. Urination frequency in 24 h and of single urination volume at different time points before and after treatment ($x \pm s$).

Group	Indicator	Before treatment	After 1 month of treatment	After 3 months of treatment	After 6 months of treatment	Time effect (*F, P*)	Group effect (*F, P*)	Interaction effect (*F, P*)
Research (n=43)	Urination frequency in 24 h (times)	27.35±4.23	20.55±3.37*	13.26±1.75*	8.67±1.02*	70.0, <0.001	0.5, 0.48	8.0, <0.001
Control (n=43)		28.02±4.19	21.12±3.41*	15.78±2.08*	10.44±1.56*			
t		0.738	0.780	6.079	6.227			
P		0.463	0.438	<0.001	<0.001			
Research (n=43)	Single urination volume (mL)	84.33±12.65	98.74±15.23*	151.59±22.37*	205.75±26.62*	80.0, <0.001	0.4, 0.70	5.0, <0.001
Control (n=43)		84.98±12.29	97.39±15.17*	130.57±18.26*	182.38±23.69*			
t		0.242	0.412	4.773	4.301			
P		0.810	0.682	<0.001	<0.001			

*P<0.05 vs. before treatment within the group.

ICPI between the two groups after 1 month of treatment (P>0.05). Besides, the research group had lower urination frequency in 24 h, PUF score, O'Leary-Sant ICSI and ICPI, as well as larger single urination volume than those of the control group after 3 and 6 months of treatment (P<0.05) (Table 2 and Table 3).

Levels of serum pain factors

In the serum, the levels of SP, 5-HT, PGE_2, NPY, β-EP, and DA declined in the two groups after 1 month of treatment by contrast to the pre-treatment levels. Additionally, the levels of SP, 5-HT, PGE_2, and NPY were lower, while the levels of β-EP and DA were higher in the research group than in the control group (P<0.05) (Table 4).

Adverse reactions

The incidence of adverse reactions was not statistically significantly different between the research group and the control group (11.63% vs. 6.98%) (P>0.05) (Table 5).

Table 4. Levels of serum pain factors before treatment and after 1 month of treatment ($x \pm s$).

Group		Research (n=43)	Control (n=43)	t	P
SP (μg/mL)	Before treatment	4.23±0.35	4.19±0.33	0.545	0.587
	After 1 month of treatment	1.18±0.12*	1.78±0.24*	14.663	<0.001
5-HT (mg/L)	Before treatment	84.63±4.15	83.71±4.03	1.043	0.3
	After 1 month of treatment	29.62±1.78*	42.65±2.86*	25.364	<0.001
PGE_2 (ng/L)	Before treatment	229.33±20.36	231.12±20.68	0.405	0.687
	After 1 month of treatment	82.54±9.57*	98.95±12.49*	6.839	<0.001
NPY (pg/mL)	Before treatment	187.65±17.31	188.09±16.78	0.12	0.905
	After 1 month of treatment	93.75±8.26*	106.84±10.59*	6.391	<0.001
β-EP (μg/L)	Before treatment	98.26±8.47	97.31±8.14	0.53	0.597
	After 1 month of treatment	46.28±3.75*	33.73±2.79*	17.607	<0.001
DA (ng/L)	Before treatment	59.57±6.24	58.34±6.18	0.993	0.324
	After 1 month of treatment	42.97±3.85*	33.12±2.97*	13.284	<0.001

*P<0.05 *vs.* before treatment within the group.

Table 5. Incidence of adverse reactions during 6-month follow-up [n (%)].

Group	Lethargy	Constipation	Postural hypotension	Urinary tract infection	Nausea and vomiting	Total
Research (n=43)	1 (2.33)	1 (2.33)	1 (2.33)	1 (2.33)	1 (2.33)	5 (11.63)
Control (n=43)	0 (0.00)	1 (2.33)	1 (2.33)	1 (2.33)	0 (0.00)	3 (6.98)
χ^2						0.138
P						0.711

DISCUSSION

The GAG layer on the surface of urothelial mucosa can prevent leakage and resist adhesion. The loss or damage of the GAG layer plays an important role in the development of BPS/IC, which can facilitate harmful substances in the urine (e.g., bacteria and non-ionic solute residues) to migrate and invade into the bladder mucosa, injuring bladder muscles and nerves, stimulating the release of inflammatory mediators from nerve endings, and thus activating other inflammatory cells and mast cells to release histamine. Furthermore, mast cells can enhance the release capacity of vasoactive substances and stimulate nerve fibers to produce bladder pain. Meanwhile, mast cells can induce or exacerbate the interstitial and submucosal inflammatory responses in the bladder wall, and long-term inflammatory responses can increase the risk of bladder fibrosis, impairing patients' bladder storage function[16]. Therefore, the treatment of BPS/IC needs to promote the repair of damaged GAG layer through proactive and efficacious treatment regimens.

In this study, reductions in the urination frequency in 24 h, PUF score, and O'Leary-Sant ICSI and ICPI, and elevation of single urination volume were found in the two groups after 1, 3, and 6 months of treatment compared with those before treatment. Following 3 and 6 months of treatment, the urination frequency in 24 h, PUF score, and O'Leary-Sant ICSI and ICPI dropped, and the single urination volume rose in the research group compared with those in the control group, but these indicators were not significantly different between the two groups after 1 month of treatment. It suggests that the intravesical instillation of both DMSO + CS + LMWH cocktail and sodium hyaluronate can efficiently alleviate the symptoms of BPS patients, but the intravesical instillation of DMSO + CS + LMWH cocktail has better long-term outcomes than those of sodium hyaluronate intravesical instillation. It is probably ascribed to the fact that the substances in the bladder mucosal GAG layer mainly consist of hyaluronic acid, heparan sulfate, and CS, which cover the surface of the bladder mucosa and form a barrier between the bladder and the urine, jointly exerting a protective effect on the bladder mucosal function. Sodium hyaluronate is a sodium salt form of hyaluronic acid, and the treatment with sodium hyaluronate intravesical instillation can exogenously supplement the components similar to hyaluronic acid on the surface of the bladder mucosal GAG layer, thereby restoring the original state of the GAG layer and promoting the repair of bladder mucosa and the improvement of bladder epithelial permeability[17]. At the same time, sodium hyaluronate has certain inhibitory effects on the chemotaxis and phagocytosis of leukocytes and the adhesion of immune complexes, which is conducive to modulating the proliferation of endothelial cells and fibroblasts, enhancing the healing of connective tissues, reducing the severity of inflammation, and mitigating the clinical symptoms of patients[18]. The intravesical instillation of DMSO + CS + LMWH cocktail exerts a synergistic effect, which can better promote the repair of damaged GAG layer and the reconstruction of bladder mucosal barrier function, avoid or block the penetration of toxic substances into the bladder through the muscle layer, and decrease the stimulation on bladder sensory nerve endings through exogenous supplementation of various components similar to hyaluronic acid, heparan sulfate, and CS on the surface of bladder mucosal GAG layer, thus ameliorating a variety of clinical symptoms including urinary urgency and urinary frequency[19]. Compared with

the multidrug cocktail, sodium hyaluronate alone may have some limitations in repairing the bladder mucosa.

SP, 5-HT, PGE_2, NPY, β-EP, and DA are common pain factors in the clinic, serving as crucial players in pain conduction and regulation. Specifically, SP is not only a peptide neurotransmitter widely distributed in the peripheral nervous system and other peripheral tissues and organs, but also an excitatory neurotransmitter, which can be released by nociceptive afferent nerve endings (central end and peripheral end) and involved in nociceptive transmission and regulation at the spinal cord level. Moreover, it is capable of stimulating the secretion of inflammatory factors to mediate and transmit nociceptive information. Besides, 5-HT can stimulate nociceptive nerve endings, conduct nociceptive signals, and produce or aggravate pain sensation[20]. PGE_2 can stimulate nociceptive nerve endings, and increase the pain threshold of patients, thus triggering a series of pain responses[21]. As one of the most abundant active substances extensively present in the peripheral nervous system, NPY can participate in the transmission of inflammatory and neuropathic pain while repressing sympathetic excitability. Moreover, β-EP, an endogenous opioid peptide with endogenous analgesic activity, can exert a descending inhibitory effect on the pain system and regulate the pain level in the body by participating in multiple analgesic mechanisms. DA is a catecholamine neurotransmitter with a relatively high level in the body and in the case of pain perceived, this can activate the nerve cells to produce endorphin and suspend the pain signal transmission, thus relieving pain. Consequently, monitoring the changes in the aforementioned pain factors in the serum can reflect the pain stress in BPS/IC patients and assist in clinical understanding of treatment effects.

In the present study, the research group exhibited lower levels of SP, 5-HT, PGE_2 and NPY, and higher levels of β-EP and DA than the control group, suggesting that the intravesical instillation of DMSO + CS + LMWH cocktail can effectively improve the levels of serum pain factors in BPS/IC patients. The possible reasons are as follows. First, DMSO is an organic solvent with preferable permeability, high drug absorption rate, strong interference in free radical generation, and a certain scavenging effect on the generated free radicals, which is beneficial to the reduction of oxidative factors and inflammatory mediators. Additionally, it exerts satisfactory anti-oxidative stress, anti-inflammatory effects, mitigates local inflammation in the bladder and injury of the bladder epithelial mucosa[22]. Meanwhile, DMSO instillation is highly effective, with analgesic, anti-inflammatory and anti-bacterial impact. It relaxes muscles, and inhibits the release of pain substances after entering the bladder, thus significantly attenuating the activation and infiltration of mast cells in the bladder. Further, it can influence C-fiber conduction by means of anti-inflammation and inhibition on collagen synthesis, affect the sensory nerves and alleviate bladder pain[23]. Second, the glycoprotein CS is also an essential component of the bladder mucosal GAG layer. The intravesical instillation of CS can achieve the exogenous supplementation of CS-analogue components on the surface of the bladder mucosal GAG layer, repair and restore its integrity, and protect the bladder mucosal barrier function, thereby facilitating the amelioration of clinical symptoms[24]. This aside, CS can favorably repress the activity of inflammatory factors such as leukocytes, relieve inflammatory responses of the bladder mucosa and promote bladder mucosa repair, eliminate free radicals, and protect the bladder mucosal cells from oxidative stress-induced damage[25]. Third, LMWH is a kind of mucopolysaccharide sulfate mainly formed by polysaccharide polymerization, possibly exists in the bladder mucosal GAG layer and possesses anti-adhesion properties against the bladder mucosal GAG layer. Moreover, when used in combination with DMSO and CS, LMWH can repair the damaged bladder mucosal barrier, promote the improvement of the bladder mucosal permeability, and prevent the toxic substances in the urine from entering the bladder interstitium through the damaged area to stimulate the peripheral nerves. In the meantime, it can suppress the proliferation of inflammatory cells, mitigate inflammatory responses in the body, reduce the symptoms of bladder irritation, and alleviate bladder pain[26,27]. DMSO + CS + LMWH can synergistically and directly act on the bladder to effectively relieve inflammation, edema and telangiectasia therein, make MC particles more stable in the body, effectively reduce patients' pain, and improve the levels of serum pain factors. According to the statistics on adverse reactions during the 6 months of follow-up, no significant differences were found between the two groups, confirming that the intravesical instillation of DMSO + CS + LMWH cocktail is safe for the treatment of BPS/IC. It is considered to be related to the fact that intravesical instillation is a local medication regimen. The local intravesical instillation of drugs is safer than oral administration of drugs because the drug concentrations are high and the active ingredients in the drugs can directly act on the bladder wall, thus minimizing the risk of systemic adverse reactions.

CONCLUSIONS

In conclusion, the intravesical instillation of both DMSO + CS + LMWH cocktail and sodium hyaluronate is efficacious in relieving the symptoms of BPS/IC patients, but the intravesical instillation of DMSO + CS + LMWH cocktail is superior to the intravesical instillation of sodium hyaluronate in long-term outcomes, which is more conducive to improving the levels of serum pain factors, presents a good safety profile of clinical medication, without increasing adverse reactions.

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