

# Efficacy of intravesical cocktail therapy with or without dimethyl sulphoxide in interstitial cystitis

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**Introduction** Interstitial cystitis (IC) is a chronic bladder inflammation with unknown etiologies that impairs the quality of life of patients. We aimed to investigate the efficacy of dimethyl sulphoxide (DMSO) use in the cocktail therapy in IC patients.

**Material and methods** Patients treated with intravesical cocktail therapy which contained a mixture of 10 mL of bupivacaine, 1 mL of heparin, and 9 mL of sodium bicarbonate, was introduced to Group 1, and, 25 mL of DMSO was added to this cocktail and introduced to Group 2. Statistical analyses between groups were assessed by Turkish validated O'Leary Sant score composed of IC Symptom Index (ICSI) and IC Problem Index (ICPI), visual analog scale (VAS) score, and short form-36 (SF-36) questionnaire in the baseline versus post-instillation week 6, month 6, and month 12, comparatively.

**Results** A total of 62 patients (58 women and 4 men) with a median age of 52 (28–76) years were included. Baseline versus post-instillation 6<sup>th</sup> week of ICSI and ICPI scores were  $15 \pm 3.4$  vs  $7.4 \pm 2.9$  and  $12.6 \pm 2.8$  vs  $6.1 \pm 2.7$ , respectively ( $p < 0.001$  and  $< 0.001$ , respectively). VAS scores of Group 2 were statistically significantly lower than that of Group 1 in the post-instillation month 6 ( $p = 0.03$ ) whereas, the baseline of VAS scores were similar.

**Conclusions** Intravesical cocktail therapy is an effective and reliable treatment method and can be safely applied with or without DMSO. Adding DMSO to cocktail therapy provides a further decrease in VAS score in the post-instillation month 6.

**Key Words:** bladder pain syndrom ◊ interstitial cystitis ◊ interstitial cystitis symptom index ◊ interstitial cystitis problem index ◊ short form-36 ◊ visual analog scale

## INTRODUCTION

Interstitial cystitis (IC) or bladder pain syndrome is defined as a symptom complex with unpleasant sensations like pain, pressure, discomfort, or lower urinary tract symptoms without infection or other identified etiologies [1]. Most of the affected people are middle-age (40–60 years old) women. Although the occurrence of IC is thought to be underreported due to the complexity of the disease and unstandardized diagnostic criteria, its prevalence is about 300 per 100,000 population [2]. IC is a bothersome disease that is at high-risk for impairment of quality of life and sexual life of pa-

tients in addition to psychological stress and bowel disorders [2, 3].

The glycosaminoglycan (GAG) layer of bladder epithelium has a primary role in the selective permeability of urinary toxins. Although the underlying etiology of IC is not well defined, possible etiologies of IC are dysfunction of uroepithelium and deficiency of the thick mucus GAG layer leading to an inflammatory reaction due to urine penetration [4].

It is known that acidic urine is more prone to disrupt the GAG layer. Heparin is a member of the sulfated polysaccharide family and its use is to promote the restoration of the GAG layer but it has a limited effect on acute pain relief. Local anesthetics have been

introduced to the bladder for pain relief and oral or intravesical steroid use has a beneficial effect on decreasing local inflammation [5].

Common treatment modalities of IC are a spectrum changing from conventional therapies like lifestyle modification, oral pharmacotherapy, and intravesical cocktail therapy to major surgical treatments like cystoplasty or cystectomy that can be offered depending on the severity of the disease [6]. Preclinical and clinical evidence of GAG layer replenishment showed that it can decrease local inflammation and reduce symptoms like pain and discomfort [7]. In this manner, most intravesical therapeutics such as steroids, heparin, local anesthetics, and dimethyl sulfoxide (DMSO) were previously introduced into the bladder to restore the GAG layer [6]. In this study, we aimed to analyze the benefits of adding DMSO to intravesical cocktail therapy, which helps to replenish the GAG layer of the bladder epithelium, on symptoms and quality of life of patients with IC.

## MATERIAL AND METHODS

### Methodology

This study was approved by the research ethics review committee by providing the decision/protocol number of 2022/68 in March, 2022.

A total of 62 patients (58 women and 4 men) who were diagnosed with IC with clearly defined criteria [8] and admitted to outpatient clinics between January 2015 to January 2021 were included in the study. Patients taking concurrent oral pharmacotherapy for IC or with a history of recurrent urinary tract infection or bladder cancer were excluded from this study. Patients had available data and were accepted to be a part of this study. The intravesical cocktail contained a mixture of 10 mL of bupivacaine (Marcaine, AstraZeneca, UK), 1 mL of heparin (Nevparin, Mustafa Nevzat, Turkey), and 9 mL of sodium bicarbonate (Galen, Turkey), was introduced to Group 1 (n = 42 patients), whereas, 25 mL of DMSO (Botafarma, Turkey) was added to this cocktail and introduced to Group 2 (n = 20 patients) patients via transurethral route with a single-use 8 Fr catheter. Patients were encouraged to keep this cocktail in their bladder for 2 hours.

Demographic data of patients such as gender, age, body mass index (BMI), comorbidities, and pre-instillation cystoscopy and biopsy results were recorded. Patients were entered into a schedule of intravesical cocktail instillation for 6 times weekly, then monthly for a year. The medicine cocktail was prepared by an expertise specialist in sterile conditions just before instillation. All adverse events were monitored and

patients were encouraged to be admitted to the hospital in case of any side effects.

The questionnaires of O'Leary Sant, visual analog scale (VAS), and short form-36 (SF-36) were used to analyze the scores of patients. The Turkish validated O'Leary Sant score is mainly composed of 2 indexes [9]. The first Interstitial Cystitis Symptom Index (ICSI) focuses on four symptoms (urgency, frequency, nocturia, and pain) and is scored as 0–5 for each question (20 points total) and the second Interstitial Cystitis Problem Index (ICPI) in which these problems arising from previous four symptoms and is scored as 0–4 for each (16 points total). VAS score is a validated subjective measurement of pain and is scored as from 0 (no pain) to 10 (the worst pain) [10]. SF-36 questionnaire is used to assess mainly physical, mental health and score on general health-related quality of life [11]. In this study, we assessed the patients by using VAS and SF-36 scores in the pre-instillation versus post-instillation month 6, and validated O'Leary Sant scores in the pre-instillation versus post-instillation week 6, month 6, and month 12.

### Statistical analysis

All statistical analyses were performed using the SPSS 22.0 (IBM Corp, Chicago, USA) software. Kolmogorov-Smirnov test was used to test the normality of variables distribution. Descriptive statistics were presented as mean ± standard deviation for para-

**Table 1.** Demographics of patients treated with intravesical cocktail therapy

Demographics	Values
Gender (M/F), n (%)	58 (93.5)/4 (6.5)
Age, years, median (range)	52 (28–76)
BMI, kg/m <sup>2</sup> , mean ±SD	26.3 ±1.7
Duration of symptoms, years, mean ±SD	3.1 ±1.2
Comorbidities, n (%)	
Hypertension	12 (19.3)
Diabetes	4 (6.4)
Fibromyalgia and depression	10 (16.1)
Previous treatment history, n (%)	
Intravesical other agents	14 (22.5)
Oral pharmacotherapy	11 (17.7)
Major symptoms, n (%)	
Dysuria	30 (48.3)
Hematuria	5 (8.1)
Urgency	25 (40.3)
Dyspareunia	2 (3.2)
Ulcer in cystoscopy, n (%)	3 (4.8)

M – male; F – Female; BMI – body mass index; SD – standard deviation; n – number

metric variables and median (minimum-maximum) for nonparametric variables while, qualitative variables were expressed as counts and percentages. Independent samples T-test for 2 variables and repeated measurements ANOVA test were used for more than 2 parametric variables and Wilcoxon test were used to analyze non-parametric variables. P-value lower than 0.05 was considered statistically significant.

This study was performed in accordance with the ethical standards of the Declaration of Helsinki.

## RESULTS

A total of 62 patients (58 women and 4 men) with a median age of 52 (range 28–76) years were included in this study. The mean body mass index (BMI) of patients and the duration of symptoms were  $26.3 \pm 1.7 \text{ kg/m}^2$  and  $3.1 \pm 1.2$  years, respectively. Of the patients, 12 (19.3%) presented with hypertension, 4 (6.4%) with diabetes mellitus, and 10 (16.1%) with depression and fibromyalgia. A total of 25 (40.3%) patients had a past history

of previous intravesical or oral pharmacotherapy. Most of the major symptoms upon admission were dysuria in 30 (48.3%) patients, followed by urgency in 25 (40.3%) patients. There was ulceration in cystoscopic examination in 2 patients in Group 1 and 1 patient in Group 2. Demographics of patients are summarized in Table 1.

Baseline versus post-instillation 6<sup>th</sup> week of ICSI and ICPI scores were  $15 \pm 3.4$  vs  $7.4 \pm 2.9$  and  $12.6 \pm 2.8$  vs  $6.1 \pm 2.7$ , respectively ( $p < 0.001$  and  $< 0.001$ , respectively). The ICSI and ICPI scores of patients visited in the post-instillation on month 6 and month 12 were kept almost steady state ( $p > 0.05$ ). The median VAS score of patients from baseline was 5 (3–10), whereas 3 (1–5) in the post-instillation month 6 ( $p = 0.001$ ). The scores of patients in role limitations due to physical health, social functioning, bodily pain, and general health were statistically significantly improved in the SF-36 questionnaire from baseline to post-instillation month 6 and were shown in Table 2 ( $p < 0.001$  for all).

The baseline of ICSI, ICPI, and VAS scores of Group 1 were  $14.9 \pm 4.1$ ,  $12.8 \pm 2.7$ , and 5 (3–10) whereas,

**Table 2.** Baseline versus post-instillation scores of patients

	Baseline	PI- week 6	PI- month 6	PI- month 12	P value
ICSI (n = 62)	15 $\pm$ 3.4	7.4 $\pm$ 2.9	6.9 $\pm$ 3.2	7.1 $\pm$ 3.4	<0.001 <sup>§</sup>
ICPI (n = 62)	12.6 $\pm$ 2.8	6.1 $\pm$ 2.7	6.3 $\pm$ 2.9	6.3 $\pm$ 3.0	<0.001 <sup>§</sup>
VAS, median (range) (n = 41)	5 (3–10)		3 (1–5)		0.001+
SF-36, median (range) (n = 22)					
PF	90 (60–95)		95 (60–100)		0.76
RF	5 (0–40)		40 (30–100)		<0.001 <sup>+</sup>
RE	45 (0–80)		55 (18–100)		0.12
GH	36 (0–70)		75 (0–100)		<0.001 <sup>+</sup>
E/F	50 (40–70)		60 (40–80)		0.07
SF	42 (25–82)		90 (90–100)		<0.001 <sup>+</sup>
BP	26 (10–50)		88 (50–100)		<0.001 <sup>+</sup>
MH	60 (40–100)		70 (50–100)		0.07

PI – post-instillation; n – number; min-max – minimum-maximum; ICSI – interstitial cystitis symptom index; ICPI – interstitial cystitis problem index; VAS – visual analog scale; SF-36 – short form-36; PF – physical functioning; RF – role physical; RE – role emotional; GH – general health; E/F – energy/fatigue; SF – social functioning; BP – bodily pain; MH – mental health

<sup>§</sup> represents the statistically significant difference between baseline to PI-week 6 in repeated measures ANOVA

<sup>+</sup> represents the statistically significant difference between baseline to PI-month 6 in the Wilcoxon test

**Table 3.** Comparative analysis of ICSI, ICPI, and VAS scores between groups

	Baseline			PI- week 6			PI- month 6			PI- month 12		
	Group 1 (n = 42)	Group 2 (n = 20)	P value	Group 1 (n = 42)	Group 2 (n = 20)	P value	Group 1 (n = 42)	Group 2 (n = 20)	P value	Group 1 (n = 42)	Group 2 (n = 20)	P value
ICSI, mean $\pm$ SD	14.9 $\pm$ 4.1	15.2 $\pm$ 3.1	0.85	7.3 $\pm$ 2.8	7.5 $\pm$ 2.9	0.62	6.7 $\pm$ 3.0	7.0 $\pm$ 3.2	0.76	7.2 $\pm$ 3.2	7.0 $\pm$ 3.3	0.59
ICPI, mean $\pm$ SD	12.8 $\pm$ 2.7	13.1 $\pm$ 2.8	0.72	5.9 $\pm$ 2.7	6.3 $\pm$ 2.1	0.56	6.2 $\pm$ 2.8	6.3 $\pm$ 3.0	0.92	6.4 $\pm$ 3.1	6.0 $\pm$ 3.3	0.65
VAS, median (range) (n = 41)	5 (3–10)	5 (3–9)	0.95				3 (1–5)	2 (1–5)	0.03 <sup>*</sup>			

PI – post-instillation; n – number; min-max – minimum-maximum; ICSI – Interstitial Cystitis Symptom Index; SD – standard deviation; ICPI – Interstitial Cystitis Problem Index; VAS – Visual Analog Scale

<sup>\*</sup> bold value denotes statistical significance in the Wilcoxon test

these scores of Group 2 were  $15.2 \pm 3.1$ ,  $13.1 \pm 2.8$ , and 5 (3–9), respectively ( $p > 0.05$ ). The scores in the following periods of post-instillation week 6, month 6, and month 12 were decreased ( $p < 0.001$  for baseline vs PI-week 6,  $p > 0.05$  for PI week 6 vs PI – month 6 and PI – month 12). There was no statistically significant difference on ICSI and ICPI scores between groups. However, VAS scores of patients treated with DMSO were statistically significantly lower than those treated without DMSO in the comparative analysis which can be seen in Table 3 ( $p = 0.03$ ).

## DISCUSSION

IC is a complex disease and its definitive treatment has still not been clearly demonstrated. Some palliative therapies include oral, intravesical, or rehabilitation physiotherapy to much more complex surgical therapies can be chosen due to the aggressiveness of the disease [12]. Intravesical therapies such as local anesthetics, DMSO and GAG which include heparin, hyaluronic acid, and chondroitin sulphate is the pillar to maintain the GAG of bladder epithelium and reduce the troublesome pain symptoms [13]. Most of the previous studies reported that exogenous GAG biopolymers decrease urothelial permeability and proinflammatory markers like  $\text{TNF}\alpha$ , IL8 and IL6. Therefore, symptomatic relief of patients can be obviously seen for more than 2 decades with increasing the GAG replenishment [6]. This is the first study, to the best of our knowledge, that compares patients with and without DMSO administration by validated O'Leary Sant and VAS score together with the SF-36 score during a one-year follow-up period.

The exact cure for IC has not been developed currently. The main purpose in the management of this disease is to increase the quality of life since it affects people worse than patients under hemodialysis, having Crohn's disease, or other rheumatological diseases [14]. Current literature has shown that intravesical cocktail therapy is effective on bladder discomfort and quality of life of patients [15]. The addition of alkalinizing agents like sodium bicarbonate to the combination of lidocaine and heparin may increase the efficacy via the improvement of urothelial penetration. It has been shown that alkalinized lidocaine and heparin combination statistically significantly reduced pain, global assessment response and urgency symptoms in a prospective, multicenter and randomized placebo-controlled trial [16]. However, it should be kept in mind that not all patients can benefit from cocktail therapy equally and the use of such therapy cannot be lifelong. In a retrospective clinical study,

61.3% of patients treated with cocktail therapy with DMSO needed to be retreated after a median of 36 weeks [17]. So, in addition to the intravesical treatment patients should be encouraged to modify lifestyle changes to decrease the recurrence. In this current study, we offered to continue intravesical therapy to all patients as long as they wanted after a year.

Demographics, clinical, and urodynamic factors were determined to predict the response of therapy. Erol et al. showed that cystoscopic findings such as glomerulation, hypervascularization, and Hunner's lesions can affect the response to treatment [18]. Stav et al. demonstrated that responders to intravesical therapy were younger (43 vs 58 years) and treatment failure was associated with small bladder capacity (less than 225 mL), diabetes mellitus, menopause, and higher BMI (over  $27 \text{ kg/m}^2$ ) but the only predictive factor for treatment failure in the multivariate analysis of the study was small bladder capacity under general anesthetic (less than 657 ml) [19]. Urodynamic detrusor overactivity and frequency, urgency, and nocturia which are the clinical presentations of this overactivity also decrease the treatment efficacy [20].

The addition of oral pharmacotherapy or physiotherapy to the intravesical cocktail increases the functional well-being and quality of life by increasing the efficacy of treatment [21]. There are some studies that investigated the efficacy of DMSO with cocktail therapy and found up to 70% response rate on quality of life and VAS [22]. The cocktail with DMSO markedly decreases the VAS score and significantly improves the voiding and cystometric parameters [19, 23, 24]. Our study obviously shows that cocktail therapies even without DMSO decrease the ICSI, ICPI, and VAS scores in the follow-up. Furthermore, the addition of DMSO to the cocktail facilitates the decrease of VAS score in Group 2.

Another entity of this chronic disease is sexual dysfunction. A systematic review showed that a limited number of publications assessed the sexual health outcomes of intravesical therapy and reported that some publications claimed that improved sexual health outcomes while some publications did not [25]. Two (3.2%) patients in our study suffered from dyspareunia at the beginning of treatment and both responded to treatment in the following periods.

This study does have some limitations. First, this non-randomized retrospective clinical study has a limited number of patients with a short-term follow-up. Second, we did not investigate treatment efficacy in responders with objective parameters like urodynamic results.

## CONCLUSIONS

In conclusion, since there is no curative treatment method for IC, the main aim of treatment for this disease is to relieve the symptoms and to increase the health-related quality of life. Intravesical cocktail therapy has been accepted as an effective and reliable treatment method and can be safely applied with or without DMSO in IC patients. It was observed that adding DMSO to cocktail therapy provides a further decrease in VAS score in the short-term follow-up.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## ETHICS APPROVAL STATEMENT

This retrospective cohort study was approved by the Bolu Abant İzzet Baysal University research ethics review committee by providing the decision/protocol number of 2022/68 in March, 2022. This study was performed in accordance with the ethical standards of the Declaration of Helsinki.

## INFORMED CONSENT

An information leaflet was given, and informed consent was obtained from all patients.

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