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REVIEW

The Efficacy and Safety of Dimethyl Sulfoxide Into the Bladder for the Treatment of Interstitial Cystitis/Bladder Pain Syndrome: A Systematic Review and Meta-Analysis

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Keywords: DMSO | interstitial cystitis | meta-analysis

ABSTRACT

Objective: To investigate the efficacy and safety of intravesical DMSO instillation for the treatment of interstitial cystitis/bladder pain syndrome.

Method: The following databases were searched for relevant studies: PubMed, EMBASE, MEDLINE, Cochrane Library, and Web of Science (updated August 10, 2024). All studies on intravesical DMSO met the inclusion criteria and were evaluated using various quality assessment methods based on the type of study. Data were then analyzed using Review Manager 5.4 (Cochrane Collaboration software). The primary outcomes and indicators included the Interstitial Cystitis Symptom Index, the Interstitial Cystitis Problem Index, and Pain Scores. The secondary outcomes were bladder diary metrics and Pelvic Pain and Urgency/Frequency Symptom Scale (PUF).

Results: This systematic review and meta-analysis included 5 randomized controlled trials and 9 single-arm or cohort studies, involving 554 patients. The combined statistics indicated an average pretreatment Interstitial Cystitis Symptom Index score was 14.27, an average Interstitial Cystitis Problem Index Score was 12.72, and an average Pain Score was 7.06. Compared to pretreatment values, the results indicated that the Interstitial Cystitis Symptom Index score decreased by 5.59 (95% CI: −6.68 to −4.50, $p < 0.00001$), the Interstitial Cystitis Problem Index score decreased by 5.14 (95% CI: −6.45 to −3.83, $p < 0.00001$), and the Pain Score decreased by 3.27 (95% CI: −3.95 to −2.60, $p < 0.00001$). Additionally, the overall incidence rate of adverse events in patients was 37.6%. Although 37% of cases had adverse events, the majority were considered mild and acceptable.

Conclusion: Evidence-based statistical analysis of the literature on intravesical DMSO treatment for interstitial cystitis/bladder pain syndrome indicates that this therapy is both effective and safe. Therefore, intravesical DMSO instillation can be considered a standard treatment method for interstitial cystitis/bladder pain syndrome.

Abbreviations: AVV, average voided volume; BPS, bladder pain syndrome; DMSO, dimethyl sulfoxide; IC, interstitial cystitis; ICPI, Interstitial Cystitis Problem Index; ICSI, Interstitial Cystitis Symptom Index; IC/BPS, interstitial cystitis/bladder pain syndrome; MD, mean difference; MINORS, Methodological Index for Non-Randomized Studies; MVV, maximum voided volume; M, mean; NRS, Numeric Rating Scale; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRP, platelet rich plasma; PS, Pain Scores; PUF, Pelvic Pain and Urgency/Frequency Symptom Scale; SD, standard deviation; VAS, Visual Analogue Scale.

Hai-rui Li and Si-hong Shen contributed equally to this study.

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1 | Introduction

Interstitial cystitis (IC) is a chronic condition predominantly observed in females, with a female-to-male ratio of 10:1 [1]. The disease was first described in the early 20th century by Hunner, who characterized its features and typical lesions as Hunner's ulcers [2]. As understanding of this condition has evolved, most experts have recognized that IC exhibits considerable variability in symptoms and severity, leading to the view that it is not a single disease but rather a spectrum of disorders. Consequently, the term bladder pain syndrome (BPS) has been increasingly employed to describe cases involving painful urinary tract disorders [3]. BPS is characterized by chronic pelvic pain, pressure, or discomfort related to the bladder, accompanied by at least one urinary symptom, such as urgency or increased frequency. The European Society for the Study of Interstitial Cystitis (ESSIC) has designated this condition as "interstitial cystitis/bladder pain syndrome (IC/BPS)" [4]. Despite decades of fundamental and clinical research, the etiology of IC/BPS remains unclear. Current mechanistic theories include infection, autoimmunity, neurogenic inflammation, or defects in the bladder urothelium [5]. Consequently, effective treatment options for IC/BPS are still lacking.

DMSO is a nonproton solvent, and its proton self-transfer reaction is extremely weak or has no self-transfer tendency, making it difficult to form hydrophobic substances with membranes. Therefore, DMSO can dissolve polar and nonpolar compounds, and is miscible with water, lipids, and organic reagents. Its mechanisms of action are thought to involve anti-inflammatory effects, nerve blockade, smooth muscle relaxation, and collagen inhibition [6]. Consequently, DMSO has been explored for the treatment of IC/BPS, leading to its FDA approval for this indication in 1978. Although a small, short-term, single-center trial reported efficacy [7], further validation through additional studies is lacking. As highlighted in the updated EAU guidelines for chronic pelvic pain in April 2014, there is insufficient evidence to recommend the use of DMSO [8]. Therefore, this review aims to incorporate more relevant studies and investigate the efficacy of intravesical DMSO instillation for the treatment of IC/BPS, providing the latest evidence for clinical practice.

2 | Methods

This study was registered in the PROSPERO database (ID:CRD42024591077) and was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9].

2.1 | Study Search

We performed the results according to the PRISMA guidelines. Records published up to August 2024 were searched from PubMed, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials. The search terms utilized in the database queries encompass, but are not confined to, "interstitial cystitis," "dimethyl sulfoxide," and "DMSO." Additionally, the references from all eligible studies were manually reviewed to identify any other relevant studies.

2.2 | Eligibility Criteria

The inclusion criteria used to select studies in this meta-analysis were: (1) the study population consisted of patients with IC; (2) the intervention involved intravesical DMSO instillation; (3) outcome measures included, but were not limited to, symptom scores (e.g., IC Symptom Index [ICSI], IC Pain Index [ICPI]), metrics from bladder diaries (e.g., frequency of urination, nocturia); and (4) the study was published in English.

The exclusion criteria were listed below: (1) involved patients with other lower urinary tract dysfunctions or infections; (2) a type of reviews, meta-analyses, letters, case reports, or studies based on animal or pediatric subjects; and (3) lacked the necessary outcome measures for analysis. To include more evidence, the analysis is not limited to RCTs.

2.3 | Data Extraction

Two experienced investigators independently screened the records based on the established inclusion and exclusion criteria. Any discrepancies during data extraction were resolved either through consensus between the two reviewers or with the assistance of a third reviewer. Subsequently, another researcher extracted relevant information from the included studies, primarily through direct examination of the original texts. The following items were extracted from all enrolled studies: study title, authors, publication year, sample size, study type, patient demographics, outcome data, and adverse events.

Additionally, intravesical DMSO may cause adverse events such as bladder pain, bladder irritation, hematuria, garlic odor, etc. For better statistical analysis, the researchers performed a basic classification of adverse reactions into major and minor categories. The definition of major adverse event is based on patient-reported experiences. Adverse events are considered major if patients find them intolerable. For objective symptoms, such as hematuria, the presence of visible blood in the urine was classified as a primary adverse reaction.

2.4 | Bias Assessment

This analysis includes randomized controlled trials, single-arm trials, and cohort studies. To ensure the integrity of the data, we will implement distinct quality assessment methods specific to each study design. Two researchers independently evaluated the quality of randomized controlled trials using the Cochrane Collaboration tool, including random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting [10]. They evaluated the risk of bias in the cohort studies included in the analysis using the Newcastle Ottawa Scale, which includes three categories: "study group selection," "group comparability," and "outcome evaluation." This scale uses a star system for semi-quantitative evaluation, with a maximum score of 9 stars [11].

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For the single-arm studies included in the analysis, they used the Non Randomized Study Methodology Index (MINORS) to assess quality. The MINORS criteria include: "clear objectives," "continuous inclusion of patients," "prospective data collection," "appropriate outcome measures for research objectives," "objective evaluation of outcomes," "appropriate follow-up period for research objectives," "dropout rate below 5%," and "prospective calculation of sample size" [12]. MINORS uses a scoring system to assess research quality, with each project rated on a scale of 0–2: 0 indicates no report; 1 point represents partial report; a score of 2 indicates that the report is complete and sufficient. Resolve any differences in quality assessment by consulting with a third researcher.

2.5 | Outcomes

The primary outcome of interest in this meta-analysis was Interstitial Cystitis Symptom Scores (ICSS), which included ICSI, ICPI, and Pain Scores (PS). It is worth noting that this PS includes the Visual Analogue Scale (VAS) and the Numeric Rating Scale (NRS). As we know, IC primarily manifests as bladder pain accompanied by urinary urgency. Therefore, we take the indicators that evaluate patients' subjective feelings as the main indicators, including the ICSI, ICPI, and PS. Key parameters included in both the ICSI and ICPI questionnaires are urgency, daytime frequency, nighttime frequency, and bladder pain, with each consisting of four questions. The ICSI employs a 6-point scoring system (0–5), while the ICPI uses a 5-point scale (0–4). Although both questionnaires mentioned pain or discomfort, they did not provide a clear quantification of it. Thus, PS are included as a primary measure. Most studies utilize the VAS for pain assessment, where patients rate their pain from 0 to 10 (0 = *no pain*; 10 = *worst pain ever*), while some use the NRS with a similar range. Both scales have consistent definitions and ranges for pain, allowing for unified analysis in our meta-analysis.

To comprehensively evaluate the efficacy of intravesical DMSO instillation for the treatment of IC/BPS, we selected several indicators as secondary outcomes. These secondary outcomes primarily include bladder diary and PUF. The bladder diary specifically includes urinary frequency, nocturia, AVV, and MVV, all of which objectively reflect bladder function. The scoring system for PUF was designed by Pearson in 2002 to quantify the severity of IC symptoms and the extent to which patients are troubled by each symptom. This questionnaire consists of a total of eight items, covering pelvic pain, urinary frequency, and urgency. However, only a limited number of studies have utilized the PUF questionnaire to assess the effects of intravesical DMSO treatment for IC/BPS, thus we have included this questionnaire as a secondary outcome.

Additionally, IC/BPS can be categorized into classical and nonulcer types based on distinct pathological manifestations observed under cystoscopy. Consequently, we also conducted a subgroup analysis based on these different subtypes.

2.6 | Statistical Analysis

Data were analyzed using Review Manager 5.4 (Cochrane Collaboration, Oxford, UK) [13]. All measures were either extracted directly from the articles or calculated. Since all outcome measures are continuous variables, we mainly use mean (M), standard deviation (SD), and mean difference (MD) to combine statistical data. The heterogeneity was assessed using I^2 statistics with $I^2 > 50\%$ being considered to be significant. A fixed-effects model was used when $I^2 < 50\%$, while a random-effects model was applied when I^2 exceeded 50% [14, 15]. If there is heterogeneity in these results, sensitivity analyses were performed to determine the source of heterogeneity. Additionally, subgroup analysis was conducted based on follow-up time and subtypes. For all of these analyses, $p < 0.05$ indicated statistical significance.

3 | Results

After conducting an electronic search, a total of 999 articles were identified. After excluding 421 duplicate references and performing a review of titles and abstracts, 520 articles were initially excluded. The full texts of 58 articles were then reviewed, resulting in the inclusion of 14 studies involving 554 patients [16–29]. This meta-analysis comprised 5 randomized controlled trials, 7 single-arm studies, and 2 cohort studies. Among them, there are 4 articles focused on pure DMSO, which are fewer in number compared to DMSO cocktails. However, the DMSO content of the solutions used in each study was 50%. The search and selection process is illustrated in Figure 1.

The baseline characteristics of the study are shown in Table 1. According to the baseline characteristic table, there are 525 female patients among all patients, resulting in a female-to-male ratio of ~18:1. The average age range is 38.8–68.3 years, and the follow-up duration for all studies was within 6 months. No significant statistical differences were observed among the included studies. It has to be said that we also consider covariates, such as race, economic level, education level, etc., in the baseline data. When extracting data from the included studies, we found that almost all baseline features of the studies did not include these covariates. Therefore, in order to ensure the accuracy of the data, we have decided not to consider these covariates in the baseline features.

All quality assessments of the research were conducted using the aforementioned tools. Additionally, we analyzed the research design of the randomized controlled trials. Most of the studies employed software-based randomization to generate a random number table, which was then used for allocation via a website. As for blinding, only one study implemented an open-label approach, which did not involve the blinding of either patients or researchers. The quality assessment of all studies is shown in Tables S1–S3. The risk of bias in randomized controlled trials is shown in Figures S1 and S2.

3.1 | Primary Outcome

3.1.1 | ICSI

The follow-up data of the included studies were collected primarily at 1, 2, 3, and 6 months. Analysis indicated that

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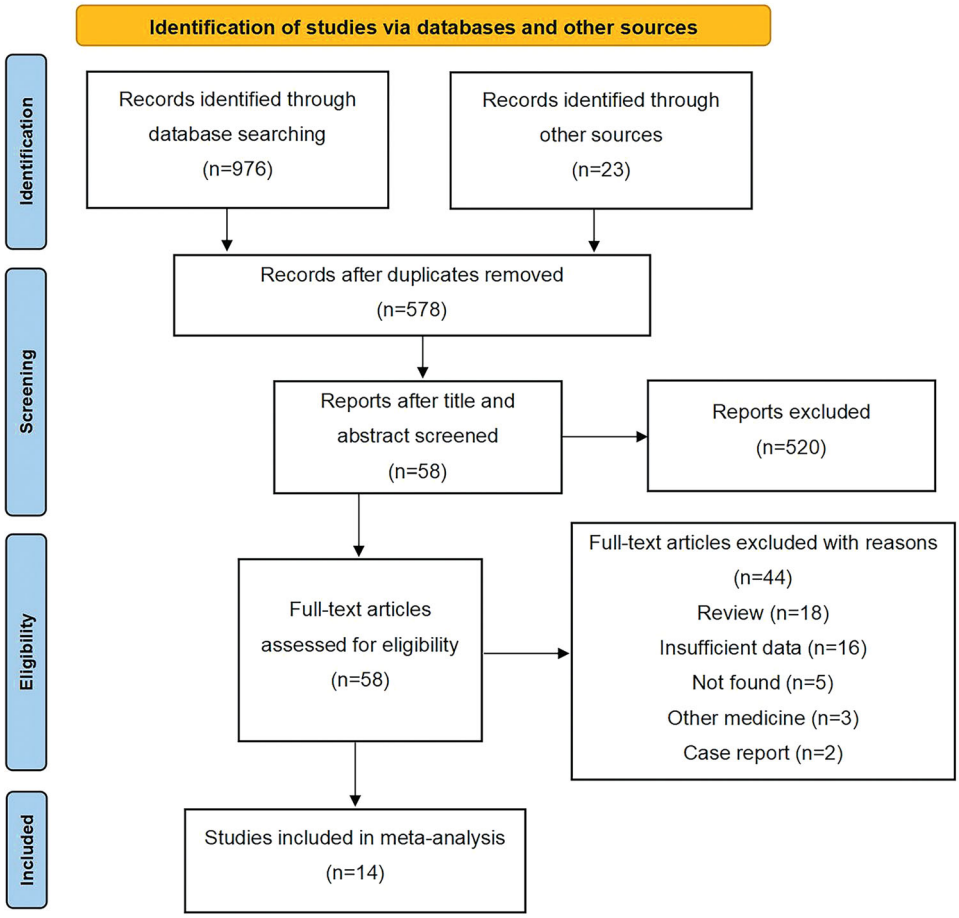

FIGURE 1 | PRISMA flow diagram for study selection.

TABLE 1 | Characteristics of included studies.

References	Year	Study design	Sample size	Female	Age	Follow-up	Outcome
[17]	2012	SAT	84	84	38.8 ± 9.3	1mo	ICSS
[18]	2012	SAT	51	41	48.9 ± 16.6	1mo	ICSS, VD
[21]	2016	SAT	55	55	44.8 ± 15.5	2mo	ICSS
[26]	2008	SAT	41	41	44.0 ± 13.5	1mo, 2mo	PUF
[27]	2022	SAT	7	7	68.3 ± 8.5	1mo	ICSS, VD
[28]	2024	SAT	30	18	68.3 ± 12.2	1mo, 2mo, 3mo	ICSS, VD
[29]	2010	SAT	80	80	—	1mo	ICSS
[16]	2000	RCT	21	20	51.4 ± 14.0	1mo	VD
[19]	2013	RCT	20	20	47.6 ± 18.4	1mo	ICSS, VD
[20]	2016	RCT	36	36	48.8 ± 17.0	3mo, 6mo	ICSS, VD, PUF
[24]	2023	RCT	42	42	46.4 ± 17.8	2mo	ICSS, VD
[25]	2021	RCT	49	43	63.6 ± 14.2	1mo, 2mo, 3mo	ICSS, VD
[22]	2021	CS	18	18	57.1 ± 15.8	3mo	ICSS
[23]	2022	CS	20	20	52.0 ± 12.0	2mo, 6mo	ICSS

Abbreviations: CS, Cohort study; ICSS, Interstitial Cystitis Symptom Scores; PUF, Pelvic Pain and Urgency/Frequency Symptom Scale; RCT, randomized controlled trial; SAT, single-arm trial; 1mo, after 1 month follow-up; 2mo, after 2 months follow-up; 3mo, after 3 months follow-up; 6mo, after 6 months follow-up;VD, voiding diaries.

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there were significant statistical differences between the ICSI scores at each follow-up month and the baseline data (1 month: MD = −5.54, 95% CI −8.17 to −2.91, $p < 0.0001$; 2 months: MD = −5.46, 95% CI −6.60 to −4.33, $p < 0.00001$; 3 months: MD = −5.31, 95% CI −6.33 to −4.30, $p < 0.00001$; 6 months: MD = −6.95, 95% CI −9.66 to −4.24, $p < 0.00001$). The results are shown in Figure 2.

3.1.2 | ICPI

Similar to the ICSI, the ICPI follow-up data at each time point also exhibited significant statistical differences when compared to the baseline data (1 month: MD = −4.90, 95% CI −7.73 to −2.07, $p = 0.0007$; 2 months: MD = −5.06, 95% CI −6.29 to −3.83, $p < 0.00001$; 3 months: MD = −5.03, 95% CI −6.06 to −4.00, $p < 0.00001$; 6 months: MD = −6.48, 95% CI −7.93 to −5.02, $p < 0.00001$). The results are shown in Figure 3.

3.1.3 | PS

In contrast to the ICSI and ICPI, the PS data were available only for the 1-, 2-, and 3-month follow-ups. However, the MD for each month was numerically similar, averaging around −3. Moreover, all follow-up data demonstrated statistical significance when compared to the baseline data (1 month: MD = −3.48, 95% CI −4.78 to −2.19, $p < 0.00001$; 2 months: MD = −2.96, 95% CI −3.56 to −2.36, $p < 0.00001$; 3 months: MD = −3.07, 95% CI −3.57 to −2.56, $p < 0.00001$). The results are shown in Figure 4.

3.2 | Secondary Outcome

3.2.1 | Frequency

Compared to baseline data, there is a statistically significant improvement in urinary frequency following DMSO instillation therapy (1 month: MD = −2.26, 95% CI −3.27 to −1.26, $p < 0.00001$; 2 months: MD = −3.50, 95% CI −5.41 to −1.59, $p = 0.0003$; 3 months: MD = −3.06, 95% CI −4.51 to −1.61, $p < 0.0001$). The results are shown in Figure S3.

3.2.2 | Nocturia

The International Continence Society (ICS) defines nocturia as "the complaint of having to wake up at night one or more times to void" [30]. Research has shown that nocturia adversely affects quality of life and worsens health outcomes by disrupting sleep, and it is associated with various complications, including diabetes, coronary artery disease, obstructive sleep apnea, obesity, metabolic syndrome, and depression [31]. Our analysis found that DMSO bladder instillation effectively alleviates nocturia symptoms, with statistically significant improvements observed (1 month: MD = −1.91, 95% CI −3.04 to −0.78, $p = 0.001$; 2 months: MD = −1.44, 95% CI −2.13 to −0.74, $p < 0.0001$). The results are shown in Figure S4.

3.2.3 | Voided Volume

Our analysis revealed that both the AVV and MVV showed statistically significant increases compared to baseline data (AVV: 1 month: MD = 22.85, 95% CI 4.24–41.46, $p = 0.02$; 2 months: MD = 31.17, 95% CI 11.04–51.31, $p = 0.002$; 3 months: MD = 32.12, 95% CI 11.41–52.82, $p = 0.002$; MVV: 1 month: MD = 20.86, 95% CI 4.21–37.52, $p = 0.01$; 2 months: MD = 45.36, 95% CI 13.93–76.78, $p = 0.005$; 3 months: MD = 40.88, 95% CI 9.51–72.26, $p = 0.01$). The results are shown in Figures S5 and S6.

3.2.4 | PUF

Due to the limited number of studies utilizing this questionnaire, only two studies included in our analysis addressed this metric. The results indicated a statistically significant decrease in PUF scores compared to baseline data (MD = −9.48, 95% CI −11.16 to −7.81, $p < 0.00001$). The results are shown in Figure S7.

3.3 | Subgroup Analysis

As is widely recognized, IC/BPS is classified into classic and nonulcer subtypes. Accordingly, a subgroup analysis was performed. However, due to the limited original literature differentiating these subtypes, only two studies were included in the analysis. We thoroughly reviewed the included studies and identified three common indicators: Frequency, PS, and MVV. Finally, we conducted a subgroup analysis based on these factors. Overall, DMSO seems to have a better effect on the classic subtypes of IC (Frequency: classic: MD = −5.05, 95% CI −7.53 to −2.57, $p < 0.0001$; nonulcer: MD = −4.00, 95% CI −9.00 to 1.00, $p = 0.12$; PS: classic: MD = −3.29, 95% CI −4.31 to −2.28, $p < 0.0001$; nonulcer: MD = −2.00, 95% CI −3.43 to −0.57, $p = 0.006$; MVV: classic: MD = 49.25, 95% CI 5.79 to 92.71, $p = 0.03$; nonulcer: MD = 75.70, 95% CI −18.02 to 169.42, $p = 0.11$). The results are shown in Figure S8.

4 | Safety

DMSO is primarily metabolized by the kidneys, with a small portion metabolized by the lungs and liver [32]. When excreted through the lungs, it can produce a characteristic garlic or oyster-like odor [33]. Studies have indicated that DMSO may induce histamine release, potentially leading to adverse reactions such as flushing, dyspnea, abdominal cramps, and cardiovascular responses [34]. When DMSO is used for bladder instillation, the adverse reactions are mainly related to urogenital symptoms, including pelvic discomfort and urinary difficulties. Among the 14 studies included in our analysis, 11 reported relevant adverse reactions. Data showed that out of 378 patients, 142 experienced adverse reactions, resulting in an overall adverse reaction rate of 37.6%. A detailed analysis of the adverse events revealed that the five most common adverse reactions were hematuria ($n = 28$), bladder irritability ($n = 25$), bladder pain ($n = 24$), urethral pain ($n = 10$), and urinary difficulties ($n = 9$). However, it is important to note that all

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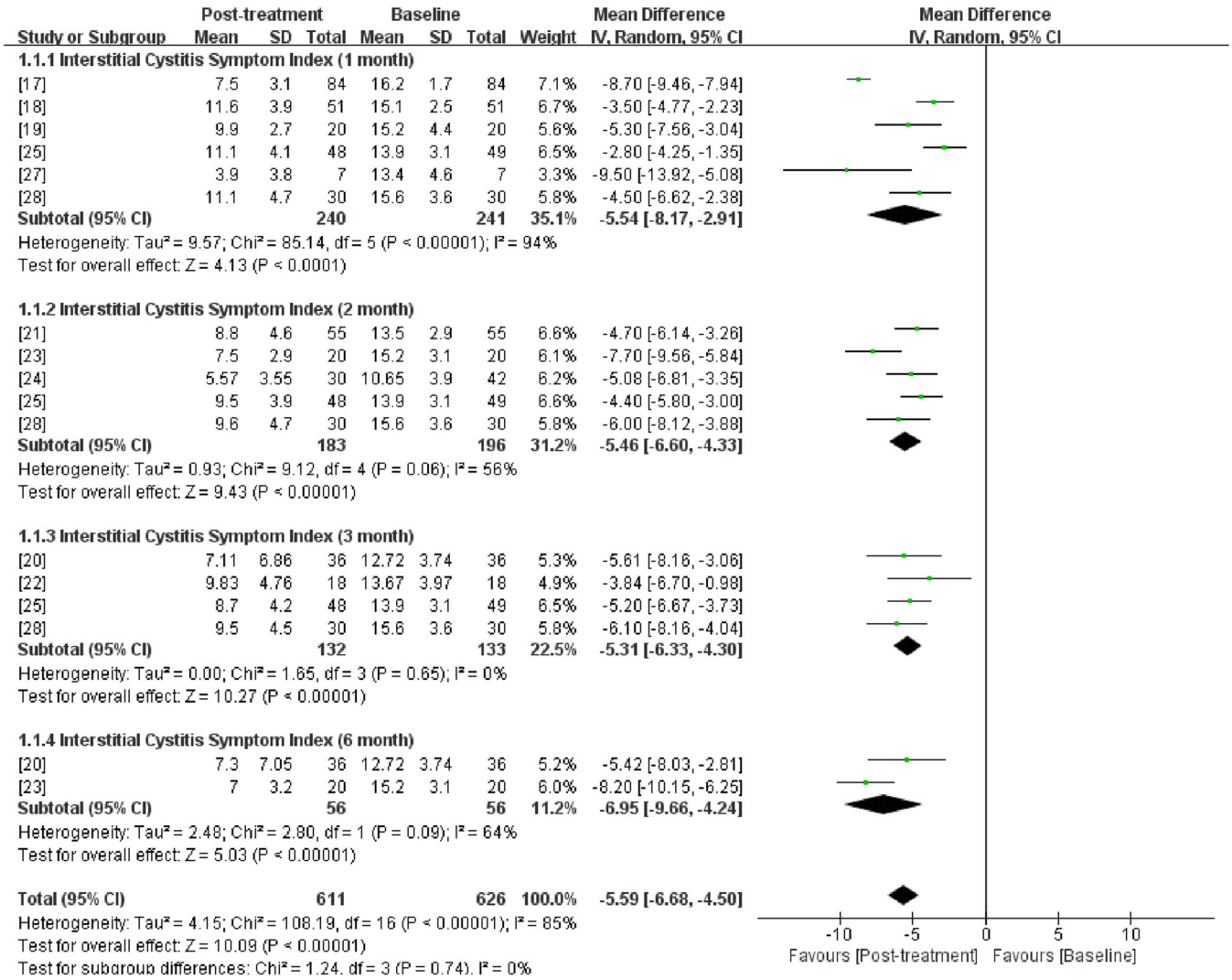

FIGURE 2 | Forest plots showing the MD of the ICSI in DMSO instillation.

instances of hematuria observed were microscopic. Additionally, upon reviewing the original research text, it was found that other adverse events resulted from patients withdrawing from the study midway. This suggests that the patients were able to tolerate these adverse events. Therefore, we consider these adverse reactions to be minor. Specific data are presented in Table 2.

5 | Discussion

Currently, the pathophysiological mechanisms underlying IC/BPS remain unclear, with various hypotheses proposed in the literature, including chronic inflammation, dysfunction of the urothelium, oxidative stress, viral infections, bladder microbiota, and so on [35]. This uncertainty has led to a multitude of treatment approaches for IC/BPS. Recent studies have shown that hyaluronic acid can provide supplemental protection for the glycosaminoglycan layer in the urothelium [36], and it is now widely used as an initial treatment for IC/BPS. However, the high cost of hyaluronic acid and the transient nature of its therapeutic effects are significant drawbacks. On the other hand, botulinum toxin type A (BoNT-A) has demonstrated characteristics that inhibit the sensation of urgency and detrusor contraction, playing a vital role in alleviating bladder pain symptoms in patients with IC/BPS [37]. Platelet-rich plasma (PRP) is rich in various growth factors and cytokines that modulate inflammation and promote tissue regeneration. Intravesical treatment with PRP can regulate HIF-1α expression and the HIF-1α mediated endogenous apoptotic pathway, thereby protecting the urothelial cells of IC/BPS patients from apoptosis while increasing the expression of urothelial barrier proteins and cytoskeletal proteins involved in cell proliferation [38, 39]. Consequently, there are ongoing attempts to utilize intrabladder injections of PRP for the treatment of IC/BPS.

Regarding DMSO, its mechanism of action remains poorly understood despite its decades-long use in treating IC/BPS. Experimental models suggest that DMSO exerts a direct analgesic effect on the afferent nerves of the lower urinary tract by desensitizing pain pathways [40]. Additionally, research indicates that DMSO can relax the detrusor muscle by reducing the

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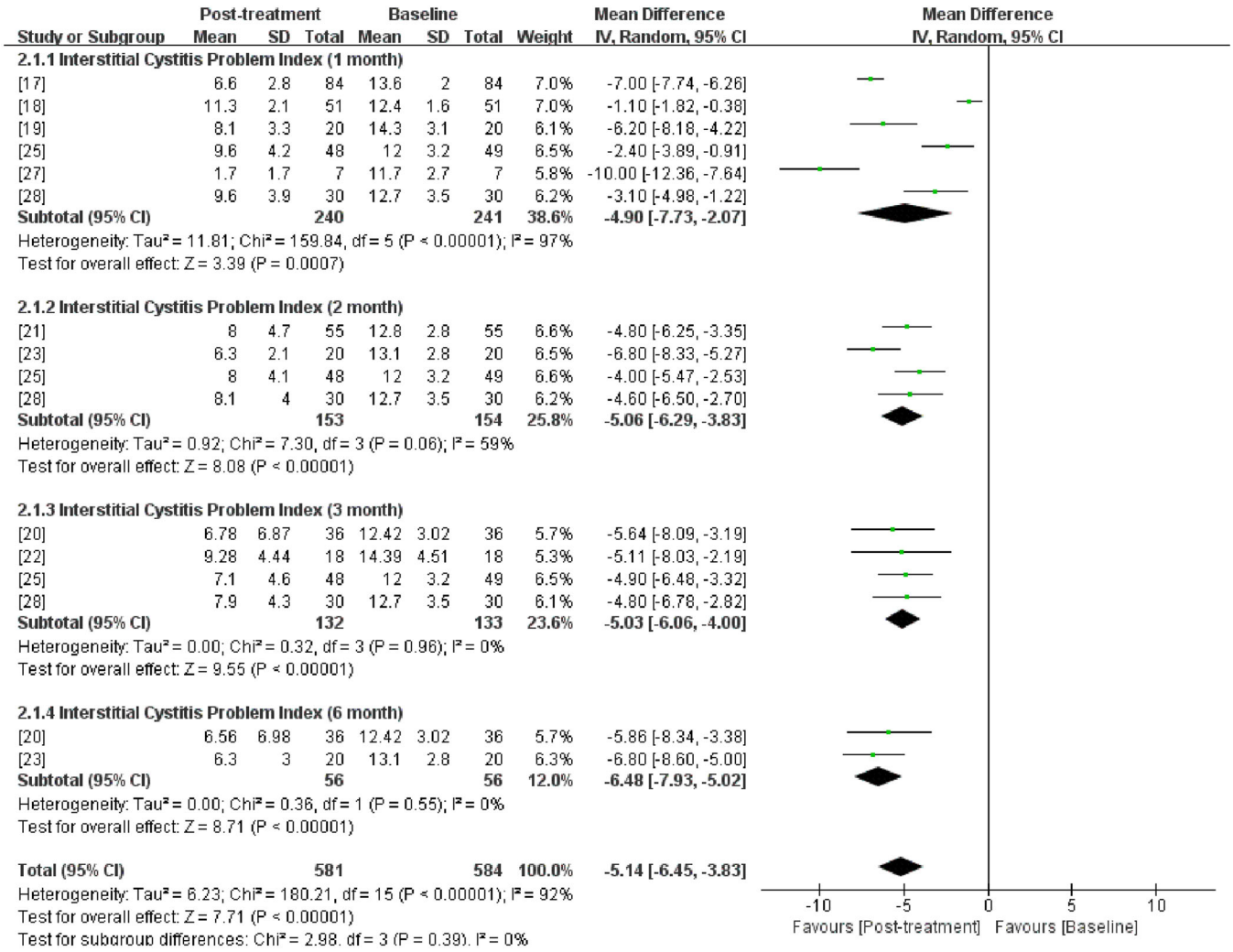

FIGURE 3 | Forest plots showing the MD of the ICPI in DMSO instillation.

calcium (Ca^{2+}) sensitivity of myofilaments, leading to decreased bladder tension and urgency in patients with IC/BPS [41]. However, the unclear mechanisms have resulted in varied treatment outcomes, leading several urological associations to present differing management guidelines and recommendations for IC treatment [42–44].

Thus, we aim to employ evidence-based medicine by utilizing systematic reviews and meta-analysis strategies to evaluate clinical research data involving the use of DMSO in IC/BPS patients, thereby further assessing the value of DMSO treatment for these patients and providing reference for clinical decision-making.

From our comprehensive analysis, we found that DMSO bladder instillation benefits for 3 months. Bladder instillation of DMSO effectively alleviates symptoms such as frequency, nocturia, and pain, as evidenced by improvements in the ICSI, ICPI, and PS. This finding aligns with the results of a pioneering randomized, double-blind, placebo-controlled clinical trial conducted in Japan, which indicated that DMSO can improve bladder symptoms, bladder capacity, and overall relief assessments in IC/BPS patients.

Moreover, 11 of the 14 studies included in this review reported adverse events related to DMSO. Out of these 11 studies, 2 reports showed no adverse reactions at all. Despite a calculated adverse event rate of 37.6% based on data analysis, a thorough examination of the adverse events revealed that most reported side effects from DMSO treatment were mild, including hematuria, bladder irritation, and bladder pain, all of which were deemed acceptable.

Interestingly, when analyzing the baseline data, we found that the age range of participants was quite broad. Female patients, particularly during perimenopause, may experience hormonal changes that could alter the structure and function of the urinary tract. Estrogen, in particular, plays a crucial role in the function of the lower urinary tract in adult women [45]. Estrogen receptors are present in the squamous epithelium of the bladder trigone, the proximal and distal urethra, the vagina, and the pelvic floor pubococcygeal muscles [46, 47]. Estrogen exerts a broad range of effects on these receptors, including raising the sensory threshold of the bladder [48], stimulating cell cycle activity, and improving the “maturation index” of the urethral epithelium [49], and so on. Some epidemiological studies suggest that estrogen deficiency may contribute to various urinary

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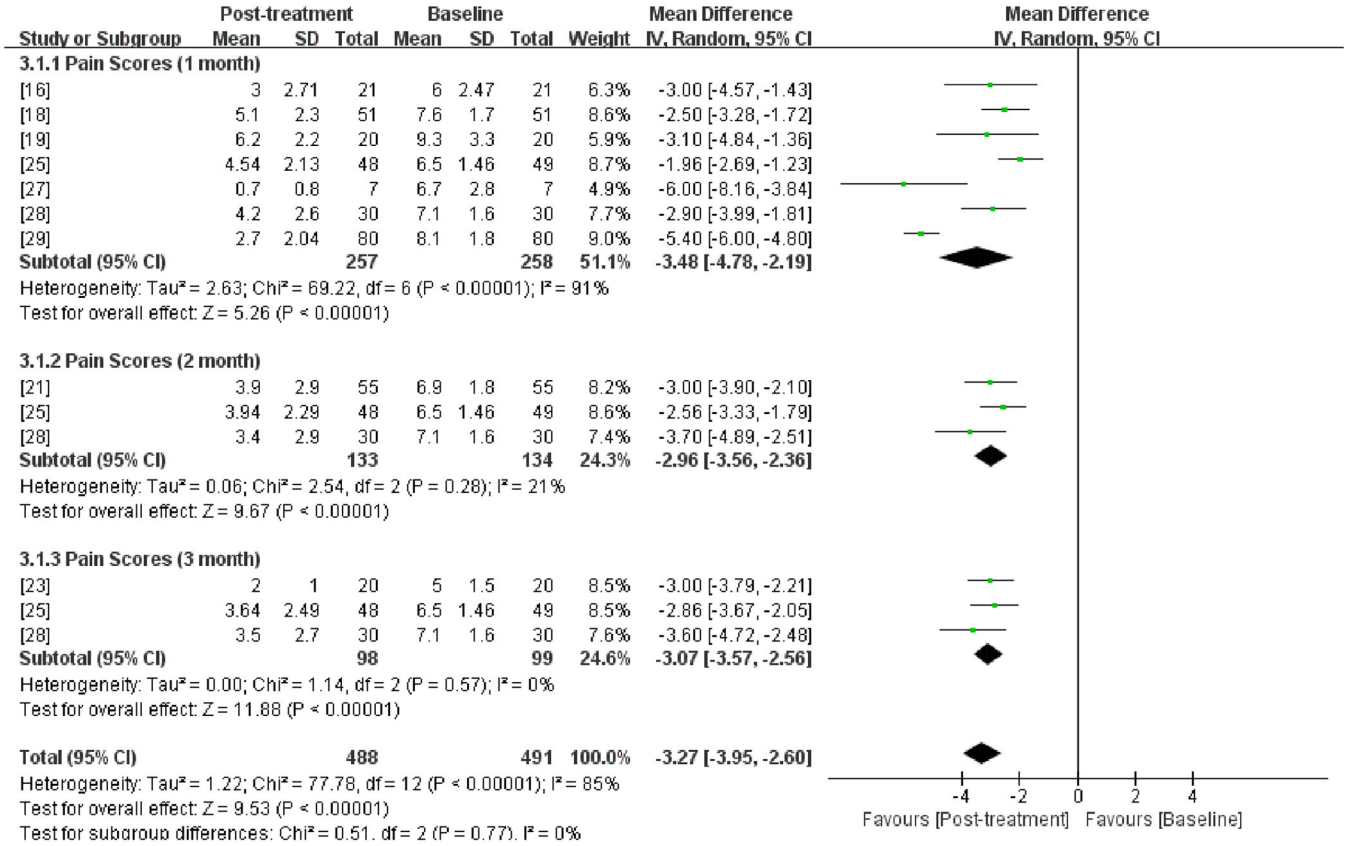

FIGURE 4 | Forest plots showing the MD of the PS in DMSO instillation.

system complaints [50]. However, the underlying mechanisms remain unclear and require further investigation.

During the data extraction process, we also encountered several issues. First, three of the included studies did not report adverse reactions, and these missing data somewhat limit our safety assessment of DMSO for IC/BPS patients. We hope that future research will provide more comprehensive reporting in this regard. Second, some studies did not adequately report outcomes related to DMSO treatment. For instance, the study by Gafni-Kane only utilized PS as an outcome measure and did not incorporate ICSI or ICPI into the final outcome metrics [29]. This absence of data may hinder our efficacy assessment of DMSO for IC/BPS patients, and we encourage future researchers to improve data reporting for better evaluation. Lastly, this analysis focused on short-term outcomes (≤ 3 months) and did not assess the long-term efficacy and safety of DMSO instillation for IC/BPS patients. This is primarily because most studies reported results only within a 3-month period. Although some studies had follow-up periods exceeding 6 months, the follow-up times were not consistent, and there was insufficient data for analysis. Future studies should consider the long-term outcomes associated with DMSO treatment.

This study also had certain limitations. First, the number of high-quality randomized controlled trials included was limited ($n = 5$), necessitating more high-quality, multicenter studies to strengthen the evidence base. Second, there was significant heterogeneity in outcome data among the included studies, which may arise from differences in the ethnic composition of the study populations. Nevertheless, we obtained significant differences when combining the data using a random-effects model, providing reason to believe that DMSO is effective for IC/BPS patients. Additionally, some outcome measures in this study were lacking, such as overall relief assessment scores, primarily because the studies considered did not account for these measures. Future research should evaluate these indicators for a more comprehensive assessment of efficacy and safety. Finally, the data collection method in these studies involved posttreatment follow-ups, which may introduce recall bias regarding symptoms, potentially affecting the study results.

Finally, it is important to note that although the classical and nonulcer subtypes of IC/BPS share similar symptoms and a chronic course, they exhibit significant differences in various aspects. This underscores the importance of differentiating between subtypes during treatment. While our study conducted a subgroup analysis of IC/BPS subtypes, further high-quality research is needed to support these findings. Currently, there is a limited number of studies distinguishing between the subtypes, and some studies are hindered by short follow-up periods and relatively narrow outcome measures. It is hoped that future research will better differentiate these subtypes, extend follow-up durations appropriately, and comprehensively address a broader range of outcome indicators, including both efficacy and safety measures.

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TABLE 2 | Adverse event reports of intravesical DMSO instillation.

References	Author	Sample size	Number of adverse events										
			BP	BI	BD	Dysuria	Cystitis	Frequency	GBO	UP	Urgency	Hematuria	Others
[16]	Peeker	21	0	0	0	3	0	0	0	0	2	0	0
[17]	Hung	84	0	0	0	0	0	0	0	0	0	28	0
[18]	Stav	51	0	0	0	0	3	0	2	3	0	0	0
[19]	Gallego-Vilar	20	0	0	0	0	0	0	0	0	0	0	0
[20]	Cervigni	36	1	1	0	4	4	0	1	0	0	0	1
[21]	Lim	55	Not mention										
[22]	Keane	18	0	0	0	0	0	0	0	0	0	0	0
[23]	Sogutdelen	20	0	0	0	0	0	0	0	0	0	0	2
[24]	Moss	42	0	0	2	0	0	0	0	0	0	0	1
[25]	Yoshimura	49	15	5	4	2	0	4	0	7	0	0	3
[26]	Shalom	41	Not mention										
[27]	Nanri	7	7	0	0	0	0	0	0	0	0	0	0
[28]	Akiyama	30	1	19	1	0	0	2	0	0	6	0	8
[29]	Selo-Ojeme	80	Not mention										

Abbreviations: BD, bladder discomfort; BI, bladder irritation; BP, bladder pain; GBO, garlic-like breath odor; UP, urethral pain.

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6 | Conclusion

In conclusion, we conducted a statistical analysis of the literature regarding the use of DMSO for the treatment of IC/BPS using evidence-based medicine. The results indicated that DMSO instillation had a favorable short-term efficacy, with adverse events occurring within an acceptable range. Our data indicated that DMSO provided statistically significant benefit in the treatment of IC/BPS. Although 37.6% of patients experienced adverse events, these were all minor.

Author Contributions

Hai-rui Li: conceptualization, methodology, data curation and writing – original draft preparation. **Si-hong Shen:** data analysis and curation, investigation. **Liao Peng:** supervision, manuscript editing. **Xiao-shuai Gao:** supervision, manuscript editing. **De-yi Luo:** supervision, manuscript editing.

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Ethics Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The trial was conducted in accordance with the Declaration of Helsinki.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data generated or analyzed during this study are obtained from published articles from known databases.

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