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REVIEW

Glycosaminoglycan Replacement Therapy with Intravesical Instillations of Combined Hyaluronic Acid and Chondroitin Sulfate in Patients with Recurrent Cystitis, Post-radiation Cystitis and Bladder Pain Syndrome: A Narrative Review

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ABSTRACT

Defects in the glycosaminoglycan layer (GAG) of the bladder mucosa have been identified as a significant contributor to the pathogenesis and clinical progression of chronic inflammatory diseases of the bladder, such as post-radiation cystitis, bladder pain syndrome and recurrent urinary tract infections. This narrative review aims to explore the contemporary evidence on the role of GAG reconstitution with intravesical installations of hyaluronic acid and chondroitin sulfate in the management of those patients, with a goal to provide valuable insights for clinical practice. The reviewed studies consistently demonstrate that GAG reconstitution can result in varying degrees of clinical improvement in patients with post-radiation cystitis, bladder pain syndrome and recurrent urinary tract infections, and is associated with a very favorable safety profile. While the available evidence is growing, its level is still limited, mainly by relatively low number of randomized controlled trials, with small sample sizes. Further research with larger, well-designed trials is needed to solidify the findings and optimize the clinical application of GAG reconstitution.

Keywords: Bladder pain syndrome; Cystitis; Glycosaminoglycans; Intravesical instillation; Interstitial cystitis; Urinary tract infections

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Key Summary Points

Why carry out this study?

Chronic forms of cystitis, including recurrent urinary tract infections, post-radiation cystitis and bladder pain syndrome / interstitial cystitis, are prevalent and morbid diseases with limited options of effective treatment.

What was learned from this study?

Intravesical instillations of hyaluronic acid and chondroitin sulfate solution are a promising treatment for patients with chronic forms of cystits, especially when first-line treatment has failed.

Increasing evidence shows clinical efficacy of this treatment, defined as a reduction in disease symptoms and improvement in urodynamic parameters.

Intravesical therapy is safe and well-tolerated by patients.

INTRODUCTION

Damage to the protective glycosaminoglycan (GAG) layer covering urothelial epithelial cells in the bladder has been indicated as an important step in the pathogenesis of chronic inflammatory diseases of the bladder, as well as a trigger for clinical manifestation of those conditions [1, 2]. Intravesical GAG restoration is an effective therapy is effective for bladder pain syndrome/interstitial cystitis (BPS/IC) and post-radiation cystitis, as well as it may prevent recurrent urinary tract infections (rUTIs). The goal of this article was to non-systematically review and discuss the contemporary evidence regarding clinical outcomes of intravesical therapy with hyaluronic acid and chondroitin sulfate in patients with various diseases of the bladder. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

STRUCTURE AND IMPORTANCE OF THE GLYCOSAMINOGLYCAN LAYER IN THE BLADDER

The urothelium lining the bladder is composed of a complex of highly specialized epithelial cells with numerous and multidirectional functions [3]. In addition to participating in the effective collection of urine, the two basic physiological tasks of the urothelial epithelium are:

- Afferent function, based on the transmission of local impulses to the central nervous system [4];
- Efferent or paracrine function associated with the secretion of mediators of physiological and pathological bladder function (including P substance, bradykinin, endothelin, and others) [5].

Damage to, and dysfunction of, the urothelial epithelium can lead to several bladder disorders and diseases, including frequent urination, urgency, urinary incontinence, and chronic pain. One of the defense mechanisms ensuring proper functioning of the urothelial epithelium is the presence of a protective GAG layer. The GAG layer is a thin, waterproof polysaccharide coating that plays an isolating role. It separates sensitive urothelial cells from urinary irritants (especially urea, potassium ions, and drug metabolites) and potential infectious agents (especially bacteria). It consists of multiple polysaccharides, including hyaluronic acid, chondroitin sulfate, heparan sulfate, dermatan sulfate, keratan sulfate, and heparin [3]. These polysaccharides combine with urothelial proteins to form proteoglycans [6].

Damage to, and loss of, the GAG layer are considered triggers for chronic inflammatory diseases of the bladder, including BPS/IC, post-radiation cystitis, and rUTIs. Exposure of urothelial cells to the toxic effects of urine leads to their neurogenic damage and inflammation [7]. Activation of nerve fibers in the submucosal

layer leads to neuronal hypersensitivity. The cascade of adverse events ends with the presence of bothersome symptoms of disease [3].

RECURRENT URINARY TRACT INFECTIONS

One in every two women will experience a UTI during their lifetime [8], and nearly 70% of cases relapse within the following 12 months [9, 10]. The most common definition of rUTIs, adopted, among others, by experts of the European Urological Association, requires two documented episodes of infection within 6 months or three documented episodes within 12 months.

Risk factors for rUTI vary depending on a woman's hormonal status. In women before menopause, sexual activity, use of spermicides, changing sexual partners, maternal history of UTIs, and history of UTIs in childhood are considered the most important. For postmenopausal women, the risk of UTI is higher in women with urinary incontinence, vaginal mucosal atrophy, cystocele, urinary retention after micturition, or urinary catheter, and in those who are under institutional care [11].

Three main pathomechanisms of rUTI have been proposed. The two classic mechanisms include repeated de novo infections caused by ascending bacteria of the anogenital region and activation of persistent infection associated with the presence of a bacterial reservoir [12–14]. A third possible mechanism related to the ability of *Escherichia coli* bacteria to replicate in urothelial cells and form intracellular colonies that periodically cause cystitis is also being considered [15].

Regardless of the pathomechanism of rUTIs, the GAG layer plays an important role in preventing infection. It isolates the urothelial cells from bacteria present in the urine, while also reducing bacterial adhesion [16, 17]. Damage to the GAG layer can lead directly to infection [18]. For this reason, a promising form of UTI prophylaxis is the reconstitution of the GAG layer. As shown in numerous preclinical studies, intravesical GAG infusions lead to reductions in the severity of inflammatory processes, the frequency and amplitude of contractions of the bladder detrusor muscle, urothelial damage, and bacterial growth in urine and cells [19]. In postmenopausal women, intravesical administration of chondroitin sulfate may be particularly important. This polysaccharide has been indicated as extremely defective in rUTI, and is negatively correlated with the development of dysbiosis of the vaginal microbiota [20].

In the prevention of rUTI, a number of interventions, both pharmacological and behavioral, are considered. From a practical point of view, they are often divided into behavioral management, non-antibiotic prophylaxis, and antibiotic prophylaxis (Table 1).

Table 1 Prevention options for women with recurrent urinary tract infections

Behavioral management	Non-antibiotic prophylaxis	Antibiotic prophylaxis
The proper rules of everyday functioning, i.e.:	• Immunoprophylaxis	• Prolonged (several weeks) antibiotic therapy
• Proper diuresis	• Vaginal estrogen therapy	• Postcoital antibiotic therapy
• Regular micturition	• D-mannose	
• Hygiene	• Probiotics	
• Wiping up technique after micturition	• Herbal extracts	
• Micturition after intercourse	• Cranberry preparations	
• Loose underwear	• Oral supplementation of hyaluronic acid and chondroitin sulfate	
	• Intravesical instillations	

In view of the decreasing effectiveness of antibiotics and growing drug resistance, interest in effective non-antibiotic prophylaxis is growing significantly. This is also reflected in clinical management guidelines [21].

Numerous studies have assessed the efficacy and effectiveness of intravesical instillations of hyaluronic acid and chondroitin sulfate in the prevention of rUTIs. They are presented in Table 2. In general, the evidence behind the therapy mainly comes from retrospective observations with consistent outcomes. Intravesical therapy reduces the risk and prolongs time to UTI recurrence, has marginal risk of adverse events and improves the quality of life to a varying extent. The two available randomized trials and two available meta-analyses of studies require separate discussion. Also worth mentioning is a study in which Tasdemir and co-authors showed that, in rats with UTI, intravesical infusions of hyaluronic acid or chondroitin sulfate reduce bacterial multiplication, while infusions of both components also have a positive effect on reducing of pathological morphological lesions of the urothelium [22].

In the study by Damiano and co-authors, 57 women with a history of rUTI were included and randomly assigned to the intervention or control group [23, 24]. The intervention group received prophylaxis based on intravesical instillations of 800 mg of hyaluronic acid and 1 g of chondroitin sulfate, administered every 7 days for 4 weeks and thereafter every 4 weeks for another 5 months. In the control group, placebo was administered. A decrease in the rate of infection episodes by 77% (a decrease of 10% vs 87%) was observed in the group receiving prophylaxis. The mean time to relapse was also prolonged in the intravesical therapy group (53 vs 185 days). In addition, patients from the prophylaxis group rated their quality of life as better on the SF-36 questionnaire and declared less severe disease symptoms in the screening history Pelvic Pain and Urinary Urgency/Frequency (PUF) questionnaire. Three patients in the prophylaxis group had non-infection-related urine collection disorders, one of whom required treatment.

In a study by De Vita and Giordano, 28 women with a history of rUTI were randomly assigned to prophylaxis with intravesical instillations of hyaluronic acid and chondroitin sulfate or prolonged antibiotic prophylaxis with trimethoprim and sulfamethoxazole [25]. In the first group, intravesical instillations containing 800 mg of hyaluronic acid and 1 g of chondroitin sulfate were administered every 7 days for 4 weeks, followed by two infusions at 2 week intervals. In the second group, 200 mg of sulfamethoxazole and 40 mg of trimethoprim were administered every 7 days for 6 weeks. Over 12 months of observation, there were lower numbers of episodes of infection (1.0 vs 2.3), a lower number of micturitions over 3 days (18 vs 24), a greater cystometric capacity of the bladder (380 ml vs 229 ml), lower pain (visual analogue scale scores of 1.6 vs 7.8), lower severity of ailments of overactive bladder syndrome (PUF 11.2 vs 19.6), and better scores for sexual satisfaction and quality of life among those receiving intravesical instillations of hyaluronic acid and chondroitin sulfate.

The first meta-analysis of studies on the effectiveness of intravesical instillations of hyaluronic acid and chondroitin sulfate solution in the prevention of rUTIs was published by De Vita et al. in 2013 [30]. The researchers analyzed four studies, including the two randomized trials discussed above. In total, the meta-analysis included 143 patients. Prophylaxis with intravesical instillations of hyaluronic acid and chondroitin sulfate solution was calculated to avoid, on average, 3.4 episodes of infection per year in each patient. Moreover, the average time to recurrence of infection was prolonged by an average of 187 days in patients receiving prophylaxis. In terms of symptoms reported by patients, prevention led to a reduction in pain, frequency of urination, and urgency as assessed in the PUF questionnaire, but did not significantly affect the average number of micturitions.

A second meta-analysis was published in 2018 by Goddard and Janssen [31]. It included data from eight studies, including the two randomized trials described above. In total, the meta-analysis included 800 patients with rUTI. Prophylaxis with intravesical instillations of

Table 2 Results of studies on the effectiveness of intravesical instillations of hyaluronic acid and chondroitin sulfate solution in the prevention of recurrent urinary tract infections

Author, year	Study type	Number of patients	Intervention	Comparator	Endpoints	Key results
Damiano et al. [23, 24]	Randomized trial	57	HA 800 mg + CS 1 g (Ialuril)	Placebo	– Number of UTI episodes per year – Time to UTI recurrence – Quality of life – Change in frequency and micturition volume – Adverse events	– Reduction in the number of UTI episodes – Prolongation of the time to UTI recurrence – Improvement in quality of life – Improvement in symptom severity – No serious adverse events
De Vita and Giordano [25]	Randomized trial	28	HA 800 mg + CS 1 g (Ialuril)	Cotrimoxazol 240 mg	– Recurrence of UTI – Pain – Frequency of micturition – Frequent urination – Urgency – Sexual function – Quality of life – Cystometric capacity of bladder	– Significant improvement across all endpoints – No adverse events
Torella et al. [26]	Prospective and retrospective observational study	69	HA 800 mg + CS 1 g (Ialuril)	Fosfomycin or Fosfomycin + Ialuril	– Recurrence of UTI within a year – Severity of urinary tract symptoms – Cystoscopic image after a year	– Significantly better outcomes in patients receiving HA + CS – No significant additional impact of addition of fosfomycin to HA + CS – Improvement of the cystoscopic image in all groups

Table 2 continued

Author, year	Study type	Number of patients	Intervention	Comparator	Endpoints	Key results
Cicione et al. [27]	Retrospective, multicenter	157	HA 800 mg + CS 1 g (Ialuril)	None	– Adverse events – Pain/discomfort associated with infusion – Number of UTI episodes within a year – Time to UTI recurrence – Quality of life	– Adverse events in 5% of patients within 6 months – Recurrence of UTI in 44% of patients within 1 year – Prolongation of the time to the first relapse – Improvement in quality of life
Gugliotta et al. [28]	Retrospective	174	HA 800 mg + CS 1 g (Ialuril)	Cotrimoxazole 240 mg	– Recurrence of UTI within a year – Number of UTI episodes per year – Treatment tolerance – Safety profile	– Higher percentage of UTI-free patients throughout the year – Lower proportion of patients with > 1 UTI episode annually – Mild or moderate pain during intravesicular infusions in 78% of women – No serious adverse events

Table 2 continued

Author, year	Study type	Number of patients	Intervention	Comparator	Endpoints	Key results
Ciani et al. [29]	Retrospective, multicenter	276	HA 800 mg + CS 1 g (Ialuril)	Any (prophylaxis antibiotic, immunoprophylaxis, probiotics, preparations of cranberries)	– Recurrence of UTI within a year – Time to UTI recurrence – Number of relapses per year – Quality of life associated with health – Consumption of health-care resources (number of visits, diagnostic tests, etc.)	– Lower risk of UTI recurrence – No difference in time to relapse and overall number relapses during the year – No differences in quality of life according to SF-36 questionnaire – Improvement in quality of life according to the EQ-5D questionnaire – No differences in health-care resource consumption – The greater the number of infusions, the better the effect (optimally at least 5 infusions)

CS chondroitin sulfate, *HA* hyaluronic acid, *SF-36* 36-Item Short Form Health Survey, *UTI* urinary tract infection

hyaluronic acid and chondroitin sulfate was reported to lead to a reduction in the number of infectious episodes in the urinary tract by an average of 2.6 per year and to prolong the time to the next episode by 130 days on average. A beneficial effect of prophylaxis on the PUF questionnaire was also noted. However, no effect was seen on the number of micturitions or quality of life as measured with the SF-36 questionnaire. The authors highlighted that the results of the studies varied from each other, and that the number of studies and number of included patients were small.

Both meta-analyses described above have several limitations. One such limitation is the inclusion of studies in which the intervention involved the administration of a complex formulation of a solution of hyaluronic acid and chondroitin sulfate, as well as studies on hyaluronic acid monotherapy.

The growing role of intravesical therapy with a solution of hyaluronic acid and chondroitin sulfate is illustrated by the presence of this form of treatment in the European Urological Association guidelines. The 2021 guidelines suggested the need for even more studies [32], and in the guidelines from 2022 onwards, the authors additionally refer to the two meta-analyses [33].

BLADDER PAIN SYNDROME/ INTERSTITIAL CYSTITIS

BPS/IC can be defined as the presence of persistent or recurrent pain in the bladder region, which is accompanied by worsening with filling of the bladder and/or frequent daily or nocturnal urination [34]. Diagnosis requires the exclusion of UTI and other recognizable local pathologies. The definition of the disease is not universal, which makes it difficult to determine its scale. While the disease is estimated to affect about 3% of the female population and 2% of the male population, a prevalence of up to 30% of the population has also been reported [35, 36].

The pathogenesis of BPS/IC has not yet been clearly determined, and inconsistent data in this area has led to the theory of a multifactorial and multistage process. Urothelial damage is one of the best known pathogenic mechanisms. Loss of the protective GAG layer and urothelial exposure to toxic urine components, including ions of sodium, potassium, and chlorine, drugs and their metabolites, and other toxins, leads to activation of nerve endings, neurogenic inflammation, and disease symptoms [37–39]. In preclinical studies, reconstitution of the GAG layer in BPS/IC reduces the inflammatory process and increases the viability and migratory capacity of urothelial cells [40–42]. However, regeneration of the urothelium and changes in the severity of symptoms are associated with an improvement in the endoscopic image of the bladder only in some cases [43, 44].

Patients with BPS/IC require complex and holistic care involving doctors of various specialties, a psychologist, and other therapists. A simplified overview of therapeutic options is presented in Table 3. Intravesical treatment has a firmly established position within this indication. The efficacy of intravesical instillations of hyaluronic acid and chondroitin sulfate has been evaluated in eight studies so far (Table 4). To summarize, majority of the studies were prospective and controlled with different comparators, enrolling in total a significant number of individuals. The intravesical instillations of hyaluronic acid and chondroitin sulfate led to a significant subjective and objective improvement as illustrated in dedicated questionnaires (mainly ICSI, ICPI, VAS and PUF) and urodynamic parameters, respectively. When compared to alternative intravesical therapies, hyaluronic acid and chondroitin sulfate combination was at least non-inferior. In addition, five meta-analyses and two randomized controlled trials comparing hyaluronic acid with chondroitin sulfate are discussed below.

Studies on the effectiveness of intravesical therapy in patients with BPS/IC have been the subject of five meta-analyses. A detailed analysis of four of them goes beyond the scope of this study, as they consider all options for pharmacological management in BPS/IC [53] or all possible intravesicular treatment options [54–56]. The main limitation of these meta-analyses is the very limited number of studies directly comparing different management

Table 3 Review of treatment options for patients with bladder pain syndrome/interstitial cystitis

Conservative management	Pharmacological treatment	Surgical treatment
•Pain education	• Painkillers	• Neuromodulation
•Physiotherapy	• Antidepressants	• Hydrodistension
•Acupuncture	• Antihistamines	• Botulinum toxin
•Psychological support	• Amitriptyline	• Resection of Hunner's lesion
• Other	• Immunosuppressants	• Urine drainage
	• Hyperbaric oxygen	• Cystectomy
	• Intravesical insillations of:	
	– Hyaluronic acid + /– chondroitin sulfate	
	– Heparin	
	– Lidocaine	
	– "Cocktails"	

strategies in patients with BPS/IC, which in turn leads to the risk of erroneous inference from the comparison of absolute results of different studies or network meta-analyses. As such, these meta-analyses draw quite differing conclusions. Taking intravesical therapies into account, four different meta-analyses indicated four different preparations as the most effective: hyaluronic acid [56], resiniferatoxin [54], dimethylsulfoxide (DMSO) [53], and botulinum toxin [55]. Given this, a personalized combination of several therapeutic options may be a promising form of management in selected patients [57].

In the context of assessment of the effectiveness of hyaluronic acid with chondroitin sulfate in patients with BPS/IC, the meta-analysis published in 2016 by Pyo and Cho, is probably the most valuable [58]. It included 10 observational studies involving a total of 390 patients. Importantly, the meta-analysis considered together studies on the effectiveness of intravesical treatment with hyaluronic acid alone or in combination with chondroitin sulfate. Treatment led to a reduction in the severity of pain (decrease by 3.7 points on the VAS), the severity of symptoms (decrease in the Interstitial Cystitis Symptom Index [ICSI] questionnaire score by 3.2 points), and health problem scores (decrease in the Interstitial Cystitis Problem Index [ICPI] questionnaire score by 2.9 points), and an increase in bladder capacity (by 60 ml) and micturition volume (by 31 ml). However, in view of the results of this meta-analysis, it is impossible to avoid questions about the differences in the effectiveness of treatment with hyaluronic acid alone and in combination with chondroitin sulfate. While the authors of the meta-analyses found no significant differences on the basis of secondary analyses, two randomized controlled trials published in subsequent years compared the efficacy of hyaluronic acid and chondroitin sulfate alone and in combination in patients with BPS/IC.

In the study by Gulpinar and co-authors, 42 patients with BPS/IC were randomized in a 1:1 ratio to treatment with intravesical hyaluronic acid or chondroitin sulfate [59]. They were given 120 mg of hyaluronic acid or 80 mg of chondroitin sulfate every 7 days for the first 4 weeks, then every 2 weeks in the second month, and every 4 weeks in the third and fourth months. The observation lasted 6 months. Study endpoints were: pain severity on the VAS pain intensity scale, functional parameters from the 3-day micturition diary (micturition number, nocturia, micturition volume), symptom severity assessed with the ICSI questionnaire,

Table 4 Results of studies on the effectiveness of intravesical instillations of hyaluronic acid and chondroitin sulfate solution in the treatment of patients with bladder pain syndrome/interstitial cystitis

Author, year	Study type	Number of patients	Intervention	Comparator	Endpoints	Key results
Porru et al. [45]	Prospective	20	HA 800 mg + CS 1 g (Ialuril)	–	– Severity of pain on the VAS scale – Functional parameters in 3 day micturition diary – Severity of symptoms on the ICSI and PUF questionnaires – Aggravation of the health problem on the ICPI questionnaire	– Significant improvement for all endpoints – Urinary tract infection in 1 patient (5%)
Cervigni et al. [46]	Prospective	12	HA 800 mg + CS 1 g (Ialuril)	–	– Severity of pain on the VAS scale – Functional parameters in the 3 day micturition diary – Severity of symptoms on ICSI and PUF questionnaires – Severity of the health problem on the ICPI questionnaire	– Clinical improvement across all endpoints – Lack of statistical analysis in the study – No adverse events

Table 4 continued

Author, year	Study type	Number of patients	Intervention	Comparator	Endpoints	Key results
Giberti et al. [47]	Prospective	20	HA 800 mg + CS 1 g (Ialuril)	–	– Severity of symptoms on the ICSI and PUF questionnaires – Severity of the health problem on the ICPI questionnaire – Severity of depressive symptoms on the PHQ-9 questionnaire	– Improvement in the severity of disease symptoms and the severity of the health problem – No effect on the severity of depressive symptoms
Gulpinar et al. [48]	Retrospective	53	HA 800 mg + CS 1 g (Ialuril)	HA 120 mg	– Severity of pain on the VAS scale – Severity of symptoms on the ICSI questionnaire – Severity of the health problem on the ICPI questionnaire – Functional parameters in the 3-day micturition diary – Cystometric capacity of the bladder	– Significant reduction in pain severity in both groups – Significant improvement in micturition diary functional parameters, ICPI and ICSI questionnaire scores in both groups – No differences between study groups – No effect of therapy on cystometric capacity of the bladder and micturition volume – Mild adverse events in 15% of patients

Table 4 continued

Author, year	Study type	Number of patients	Intervention	Comparator	Endpoints	Key results
Cervigni et al. [49]	Randomized trial	110	HA 800 mg + CS 1 g (Ialuril)	DMSO 50% (RIMSO)	– Severity of pain on the VAS scale – Severity of symptoms on ICSI and PUF questionnaires – Severity of the health problem on the ICPI questionnaire – Functional parameters in the 3-day micturition diary – Quality of life in the EQ-5D, EQ Index and EQ VAS questionnaires – pharmacoeconomic analysis	– Reduction in pain in both groups, higher response rate and greater effect in the study group – Improvements across all other endpoints with no differences between study groups – No statistically significant differences in the frequency of total adverse reactions (15% vs 31%) – Lower rate of treatment-related adverse reactions - Better cost efficacy in the intervention group
Arslan et al. [50]	Retrospective	51	HA 800 mg + CS 1 g (Ialuril)	CS 80 mg (Gepan Instill)	– Sexual functions on the FSFI questionnaire – Severity of pain on the VAS scale – Severity of symptoms on the ICSI questionnaire – Severity of the health problem on the ICPI questionnaire – Functional parameters in the 3-day micturition diary	- Improvement in both groups across all endpoints excluding micturition volume - A more favorable effect in the intervention group in relation to frequency of urination and ICSI and ICPI scores

Table 4 continued

Author, year	Study type	Number of patients	Intervention	Comparator	Endpoints	Key results
Sherif et al. [51]	Prospective	37	HA 800 mg + CS 1 g (Ialuril)	-	– Severity of pain on the VAS scale - Functional parameters in a 3-day micturition diary and urodynamic examination - Worsening of symptoms on ICSI and PUF questionnaires - Severity of the health problem on the ICPI questionnaire	– Significant improvement for all endpoints excluding maximal flow rate
Keane et al. [52]	Prospective Multicenter	52	HA 800 mg + CS 1 g (Ialuril)	DMSO 50% + bupivacaine 0.25% + hydrocortisone 100 mg + heparin 5000 i.u. (historical cohort)	– Severity of symptoms on the ICSI questionnaire – Aggravation of the health problem on the ICPI questionnaire – Functional parameters in the 3-day micturition diary	– Significant improvement in ICSI and ICPI questionnaire scores, without significant differences between groups – Reduction of nocturia in the study group – Reduction of urgency in the control group – No effect of treatment on frequent urination

CS chondroitin sulfate, *DMSO* dimethylsulfoxide, *FSFI* Female Sexual Function Index, *HA* hyaluronic acid, *ICPI* Interstitial Cystitis Problem Index, *ICSI* Interstitial Cystitis Symptom Index, *i.u.* international units, *PHQ-9* Patient Health Questionnaire-9, *PUF* Pelvic Pain and Urinary Urgency/Frequency questionnaire, *VAS* visual analogue scale

Table 5 Treatment regimen for patients with post-radiation cystitis

First-line treatment	– Behavioral management: lifestyle change (e.g. fluid intake habits, caffeine intake), bladder training
	– Oral pharmacotherapy (cholinolytics)
Second-line treatment	– Intravesical instillations (hyaluronic acid + /– chondroitin sulfate)
	– Bladder detrusor muscle injection with botulinum toxin
Third-line treatment	– Bladder augmentation
	– Urine drainage

and health problems assessed with the ICPI questionnaire. In both treatment groups, significant improvements were observed across all endpoints, excluding mean micturition volume in patients treated with hyaluronic acid. Moreover, chondroitin sulfate resulted in greater improvements than hyaluronic acid in terms of the number of micturitions per day, nycturia, and ICPI score. Finally, the authors suggest that chondroitin sulfate has higher efficacy than hyaluronic acid, but point to the need to confirm their observations in larger studies involving longer follow-up.

Ozkidik and co-authors published the results of a randomized controlled trial that compared the efficacy and tolerability of intravesical treatment with hyaluronic acid alone, chondroitin sulfate alone, or their combination [60]. The study enrolled 72 patients with BPS/IC, including 10 men. They were given intravesical instillations of 120 mg of hyaluronic acid or 80 mg of chondroitin sulfate, or a combination of 60 mg of hyaluronic acid with 40 mg of chondroitin sulfate. Intravesical instillations were repeated every 7 days for the first 6 weeks, then every 2 weeks for 6 months, then monthly until the follow-up period of 24 months was completed. Endpoints of the study were functional parameters from micturition diaries and the results of the Patient Perception of Bladder Condition (PPBC), VAS, PUF, ICSI, ICPI and Health-Related Quality of Life (HRQoL) questionnaires. Significant improvements across all endpoints were noted in all groups. The comparison of the groups revealed higher efficacy of the combination therapy in terms of pain, frequency of urination, and urgency assessed with the PUF questionnaire and quality of life assessed with the HRQoL score. There were no other differences between groups. Five patients were diagnosed with UTI during therapy, three had a transient hematuria after catheterization. No other side-effects were reported.

POST-RADIATION CYSTITIS

Radiation therapy is an effective treatment for pelvic neoplasms. Most often it is used in patients with prostate cancer, rectal cancer, or endometrial cancer. Despite the increasing precision in delivering the dose of radiation to the target organ, therapy involves the risk of radiation damage to neighboring organs. Possible complications of pelvic radiotherapy include a few affecting the urinary tract, including post-radiation cystitis, lower urinary tract dysfunctions, ureteral stenosis, urethral stricture stenosis, and urinary fistulas. The risk of bladder complications is related to its variable volume, and thus the position in the pelvis changes depending on the degree of urine filling.

Post-radiation cystitis can be divided into early/acute and late/chronic disease [61]. Although the nature of both is similar, they differ in incidence and prognosis [62]. Typically, patients complain of frequent urination, nocturia, and urgency. Additionally, pelvic pain and hematuria may occur. Early inflammation is found in more than half of patients, resulting from inflammatory lesions and urothelial edema after treatment. In urodynamic examination, reduced functional capacity of the bladder can be found, as well as reduced capacity at the first feeling of urgency and reduction in the urine volume backflow after micturition [63]. Late symptoms affect 5–10% of patients [61], at an average of 35 months after radiotherapy, and may occur even 20 years after treatment [64]. Their cause is irreversible bladder fibrosis. Decreased compliance of the

bladder and detrusor overactivity are noted on urodynamic examination [65–67].

Underlying the development of symptoms of post-radiation cystitis are urothelial edema and chronic inflammation. They result from direct damage to the urothelial epithelium, which occurs as a result of loss of the GAG layer [68]. For this reason, reconstitution of the GAG layer is one of the therapeutic options available to patients with post-radiation cystitis. The scheme of typical treatment is presented in Table 5. Intravesical treatment is considered a second-line treatment. In the case of hemorrhagic inflammation, alum salts, silver nitrate, or formalin can also be considered in addition to hyaluronic acid and chondroitin sulfate. However, their use is burdened with limited availability of efficacy data, and, in the case of formalin, with a high risk of adverse reactions.

It should be emphasized that treatment of patients with post-radiation cystitis should be preceded by a thorough diagnosis, aimed in particular at excluding bladder cancer and upper urinary tract damage. Typical diagnostic tools include: laboratory tests (general examination and urine culture), functional tests (uroflowmetry, micturition diary), imaging (ultrasonography), endoscopic examination (cystoscopy), and questionnaires (International Prostate Symptom Score [IPSS], International Consultation on Incontinence Questionnaire–Urinary Incontinence Short Form [ICIQSF]).

The efficacy of intravesical instillations of hyaluronic acid and chondroitin sulfate solution was confirmed in four prospective observational studies. They are presented in Table 6. In addition, studies confirming the effectiveness of individual components of this combination are available [69–73]. To summarize findings from these studies, intravesical instillations of hyaluronic acid and chondroitin sulfate significantly improve symptoms, quality of life and urodynamic parameters. They also reduce the risk of hematuria and hemorrhagic complications.

Therapeutic efficacy prompted two research groups to evaluate the effectiveness of intravesical instillations in the prevention of post-radiation bladder symptoms. Hazewinkel and co-authors conducted a prospective observational study on a group of 20 women treated with radiotherapy for uterine/endometrial cancer [78]. The intervention included prophylactic instillations of chondroitin sulfate every 7 days for 8 weeks of radiotherapy in 10 women. In this study, good tolerability of treatment (one patient discontinued therapy due to urethral pain) and high efficacy (reduction of symptoms of overactive bladder syndrome, urinary incontinence, micturition disorders, and pain) were noted.

Palou and co-authors conducted a randomized controlled trial that included 49 men treated with radiotherapy for prostate cancer [79]. Patients were randomly assigned to the intervention group or control group. In the intervention group, prophylactic intravesical instillations for post-radiation cystitis were applied. Intravesical chondroitin sulfate and hyaluronic acid were given every 7 days for 6 weeks of radiotherapy and Ialuril oral capsules with chondroitin sulfate, hyaluronic acid, quercetin, and curcumin were administered every 12 h for 12 weeks. In the control group, no additional intervention was implemented. Prophylactic therapy was well tolerated, and no patients discontinued treatment. The endpoints in the study were the severity of symptoms and the quality of life, as measured by the Expanded Prostate Cancer Index Composite (EPIC), International Consultation on Incontinence Questionnaire—Male Lower Urinary Tract Symptoms (ICIQ-MLUTS), and EQ-5D-5L questionnaires. All of these endpoints showed a significant benefit of prevention in annual follow-up. It is worth noting that adverse reactions were reported in 12% of patients; these were mild and self-limiting in nature in all cases (hematuria, nausea, urticaria).

FUTURE CONSIDERATIONS

The confirmed efficacy of GAG replacement therapy in patients with chronic forms of cystitis has led to research into expanded indications and new formulations.

Intravesical instillations of hyaluronic acid and chondroitin sulfate solution are becoming

Table 6 Results of studies on the effectiveness of intravesical instillations of hyaluronic acid and chondroitin sulfate solution in the treatment of patients with post-radiation cystitis

Author, year	Study type	Number of patients	Malignancy	Key results
Gacci et al. [74]	Prospective observational	23	Prostate cancer 100%	– Reduction in the severity of nocturia in 56% of cases, – Reduction in symptom severity (decrease from 9.7 to 6.8 points on the ICSI questionnaire) and severity of the health problem (decrease from 7.9 to 5.9 points on the ICPI questionnaire)
Gacci et al. [75]	Prospective observational	30	Prostate cancer 100%	– Reduction in symptom and health problem severity (assessed by ICSI and ICPI) – Regression of urgency, frequency, nocturia, and pain
Sommriva et al. [76]	Prospective observational	32	Prostate cancer 81% Colorectal cancer 16% Endometrial cancer (3%)	– Reduction in frequency of urination (from 15 to 9 micturitions per day) – Increase in bladder capacity (from 67 to 174 ml) – Reduction in hematuria – Reduction in the severity of disease – Improvement in quality of life (increase in EQ-5D score by more than 60%), – UTI in 6% of patients after treatment
Sanguedolce et al. [77]	Prospective observational	51	Prostate cancer 88% Gynecological malignancies 10% Colorectal cancer 2%	– More than 70% of patients did not require repeated emergency care for bleeding in the subsequent 59 months of follow-up

an attractive method for prevention of UTI in patients with neurogenic bladder. Current studies have indicated the high efficacy of this form of management in patients with spinal cord injury [80] and in children with spina bifida using pure intermittent catheterization [81]. The efficacy of this form of prophylaxis for recurrent infections with an etiology of multidrug-resistant bacteria has also been reported, which is of significant clinical importance, especially for patients with neurogenic lower urinary tract dysfunction [82].

Reconstitution of the GAG layer appears to be a valuable form of prevention and treatment of cystitis symptoms after Bacillus Calmette-Guerin (BCG) intravesicular immunotherapy in patients treated for bladder cancer. Two studies on this issue have been published so far. A study by Topazio et al. showed that prophylactic intravesical instillations of hyaluronic acid solution in patients treated with BCG reduces the severity of pain, the severity of lower urinary tract symptoms, and the number of micturitions [83]. A study by Imperatore et al. documented the efficacy of intravesical

instillations of hyaluronic acid and chondroitin sulfate solution in the treatment of post-BCG cystitis symptoms refractory to first-line treatment. Treatment led to a reduction in the severity of pain and improvement in basic urodynamic parameters [84].

For the prophylaxis of rUTI, an oral combined preparation containing hyaluronic acid, chondroitin sulfate, quercetin, and curcumin is also available. Two prospective studies published so far have confirmed its effectiveness in both women of reproductive age and in postmenopausal women [85, 86]. In postmenopausal women, the combination of the above-described oral prophylaxis with intravaginal estrogen therapy proved to be particularly effective. Oral use of a combination of hyaluronic acid, chondroitin sulfate, quercetin, and curcumin has also been shown to significantly reduce the severity of chemo-induced cystitis symptoms in patients treated with intravesicular chemotherapy for bladder cancer [87].

CONCLUSIONS

Intravesical instillations of hyaluronic acid and chondroitin sulfate solution are a promising treatment for patients with rUTIs and PBS/IC, as well as in patients with post-radiation cystitis in whom first-line treatment has failed. Numerous studies conducted to date have shown the clinical efficacy of this treatment, defined as a reduction in disease symptoms and improvement in urodynamic parameters. At the same time, intravesical therapy is safe and well-tolerated by patients. The biggest limitation remains the small number of randomized trials and the small population of patients included in these studies.

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Declarations

Conflict of interest. Sławomir Poletajew is consultant to IBSA. Magdalena M. Brzózka is employee of IBSA Poland. Wojciech Krajewski has nothing to disclose. Hubert Kamecki has nothing to disclose. Łukasz Nyk has nothing to disclose. Piotr Kryst has nothing to disclose.

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