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Bladder Instillation of 2% Adelmidrol + 0.1% Sodium Hyaluronate for the Treatment of Bladder Pain Syndrome/Interstitial Cystitis-Related Pelvic Pain

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Abstract: Introduction: Bladder pain syndrome (BPS)/interstitial cystitis (IC) is a chronic inflammatory condition characterized by bothersome symptoms as pain, urgency, urinary incontinence and in some cases urinary retention, impacting a patient's quality of life. However, also recurrent cystitis could cause a chronic bladder inflammation which can explain discomfort of the bladder and similar symptoms, often referred by younger patients during clinical evaluation. The aetiology of IC/BPS is still unknown, and it may be multifactorial. Although a definitive treatment is not available, the challenge is finding new therapeutic strategies. Different intravesical treatments such as heparin, hyaluronic acid, chondroitin sulfate, pentosan polysulfate, dimethylsulfoxide, liposomes, and botulinum onabotulinumtoxinA (BoNT-A) are commonly proposed for BPS/IC. The aim of study was to evaluate the anti-inflammatory effects of intravesical Vessilen® (a new formulation of 2% adelmidrol (the diethanolamide derivative of azelaic acid) + 0.1% sodium hyaluronate) administration in patients affected by IC/BPS or other bladder disorders. **Methods:** This was a prospective observational study. At baseline and after the treatment, validated questionnaires were administered to the patients: the Visual Analogue Scale (VAS) and International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms Modules (ICIQ-FLUTS Long Form). The subjective perception of the severity of symptoms was investigated by the Patient global impression scale (PGIs). **Results:** Based on 25 patients who completed the cycle of weekly instillation for six weeks, we observed a significant decrease in the severity of bladder symptoms according to both ICIQ-FLUTS scale (89.3 vs 61.3; p=0.021) and VAS score (4.4 vs 2.6; p<0.001). Moreover, according to PGI-I, 80% of patients observed an improvement in symptoms (PGI-I score ≤ 3). **Conclusion:** Intravesical administration of adelmidrol combined with sodium hyaluronate (Vessilen®) could be an innovative therapeutic approach for patient complaining interstitial cystitis/bladder pain syndrome (IC/BPS) or other chronic inflammatory bladder disorders, due to its well-known anti-inflammatory and antinociceptive properties.

Keywords: IC/BPS; adelmidrol; intravesical treatment; Vessilen®

1. Introduction

Bladder pain syndrome (BPS)/ interstitial cystitis (IC) is a clinical inflammatory condition based on chronic pain perceived by the patient to derive from the bladder and/or pelvis associated with urinary urgency or frequency in the absence of other causes of the symptoms. The International Continence Society (ICS) prefers the term "painful bladder syndrome", defined as "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and nighttime frequency, in the absence of proven urinary infection or other obvious pathology" [1]. The first definition promulgated by The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in 1987 and revised in 1988, required the presence of either glomerulations or "Hunner ulcers" on cystoscopic examination, and pain associated with either

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filling of the urinary bladder or urinary urgency with symptoms presents at least for 9 months [2]. However, nowadays, most of urological society (American Urological Association, European Society for the Study of Interstitial Cystitis; ICS, International Continence Society) moved away from requiring cystoscopy with hydrodistention as a necessary criterion for the diagnosis [3,4].

On the contrary, recurrent cystitis is characterized by the repeated occurrence of urinary tract infections (UTIs). Clinically, it is defined as two or more UTIs within six months or three or more UTIs within one year [5]. Symptoms typically include dysuria, increased urinary frequency, and urgency. Differentiation of IC/BPS from chronic UTI is especially difficult, given a possible common mechanism as well as the possibility of coexistence of the conditions [6].

Estimates of the prevalence of interstitial cystitis/bladder pain syndrome (IC/BPS) have increased as definitions have evolved. Earlier reports suggested a range of 10 to 510 cases per 100,000 individuals. In a population-based cross-sectional study conducted in Boston, Clemens et al. found that the prevalence of IC/BPS varies based on the definition used—0.83% in women with a more restrictive definition versus 2.71% with a more inclusive one [7]. However, evidence indicates that the prevalence may be underreported, with fewer than 10% of individuals with the condition receiving a formal diagnosis [8].

In terms of economic impact, medical costs and lost productivity related to IC/BPS in the United States were estimated at $428 million in 1987, which amounts to approximately $1.226 billion when adjusted for inflation to 2014, according to the U.S. Department of Labor, Bureau of Labor Statistics [3].

The exact pathogenesis of PBS still remains unclear and a multifactorial origin involving interactions between the bladder epithelium, immune system, neural pathways, and the microbiome could be the most accredited hypothesis. For this reason, this condition is often difficult to manage, and treatment protocols are variable and not yet fully established.

BPS/IC may be thought to occur in two phases: the first one may include processes that lead to epithelial cell pathology, corresponding in permeability increase, and generation of an inflammatory or immune response, while the second one may be characterized by progressive changes in the tissue and nerves of the bladder that result in the chronic pain and characteristic storage symptoms.

The morphological integrity of the urothelium is essential for the normal function of the bladder. In the course of BPS, the protective function of the urothelial coating is progressively compromised by the phenomenon of transepithelial mast cell superficialization, which induces local neuroinflammation and the release of depolymerizing enzymes (proteases, hyaluronidase) that target the fundamental components of the urothelial coating (Glycosaminoglycans, GAGs) [9,10].The increased mast cell density near the urothelial epithelium and the consequent impairment of the apical barrier (coating) represent a common denominator of the fragility of the bladder mucosa and chronic pelvic pain, observable in various pathologies included in Bladder Pain Syndrome [11]. Actually, a major inappropriate mast cell activation has been found especially in areas of weakened urothelium or in the presence of the typical Hunner's lesions [12].

Damage to urothelial cell function, along with subsequent increased infiltration of urine and solutes (potassium) into the bladder interstitium, leads to a loss of normal tissue distensibility, self-maintenance, and amplification of the neuroinflammatory process, the intensity of which is directly proportional to the rate of degradation/depolymerization of the basic components of the urothelial coating (Glycosaminoglycans, GAGs)

In fact, different pattern of biomarkers and GAGs in the urine of patients suggest poor urothelial differentiation in patients with IC/BPS compared to healthy controls [13].

Infection could potentially trigger the morphological alterations seen in IC/BPS, since evidences link decreased antibacterial glycoproteins and an hyperactivation of immune cells to the condition. Differentiating IC/BPS from chronic urinary tract infections (UTIs) is challenging due to overlapping mechanisms and possible coexistence.

As a pain state, IC/BPS exhibits neural pathophysiological mechanisms commonly seen in chronic overlapping pain conditions, such as enhanced neuronal excitability and central nervous system remodelling [14]. Neurogenic inflammation may play a key role in symptom persistence, with

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changes in pain perception and sensitivity linked to both peripheral and central nervous system mechanisms. Together with histamine, other mast cell-derived mediators (such as 5-HT, renin, adenosine, heparin, tryptase, chymase, elastase, carboxypeptidase A and B, cathepsin, β-galactosidase, β-glucoronidase, MMP, chemotatactic factors for eosinophils and neutrophils, platelet-derived factor, PGD2, LT B4, C4 and D4, TXA2 and B2, NO, TNF-α and other cytokines and neuropeptides) contribute to the functional picture of neurogenic inflammation [15].

There is ongoing debate regarding the importance of cystoscopic findings, such as Hunner's lesions (seen in 4-10% of IC/BPS patients) and glomerulations (mucosal bleeding after bladder overdistension), in relation to symptoms. The significant improvement observed after the resection of Hunner's lesions, along with the documented association with pain and urgency, and the finding that patients without Hunner's lesions have a statistically higher prevalence of chronic disorders, have led some to suggest two distinct categories of interstitial cystitis/bladder pain syndrome (IC/BPS): ulcerative IC/BPS and nonulcerative IC/BPS [16]. Clinically, compared with IC/BPS without Hunner lesions, IC/BPS with Hunner lesions is characterized by an older age of onset, more severe bladder-centric symptoms, diminished bladder capacity, fewer comorbid non-bladder syndromes, and more favorable outcomes upon endoscopic treatment.

Although Simon et al.'s preliminary findings from the Interstitial Cystitis Data Base (ICDB) indicated that approximately 90% of the patients had glomerulations, an analysis examining the correlation between symptoms and cystoscopic findings with hydrodistention revealed that "the presence, density, or diffuseness of glomerulations was not associated with urinary pain or urgency on the analog scales" [17]. Additionally, a systematic review by Wennevik and colleagues concluded that there is no convincing evidence to suggest that glomerulations observed during cystoscopy with hydrodistention are specifically linked to IC/BPS [18]. However, the discordant results in literature about the correlations between findings on cystoscopy and symptoms, make interpretation of the overall association difficult.

Definitely, IC/BPS appears to involve a multifaceted interplay of urothelial dysfunction, inflammation, mast cell activity, hormonal influences, and neural sensitivity, complicating diagnosis and treatment.

Treatment for interstitial cystitis/bladder pain syndrome (IC/BPS) should begin with conservative therapies, moving to more aggressive options if symptom control is insufficient or if the patient's quality of life (QoL) remains poor. Manual physical therapy techniques are recommended for patients experiencing pelvic floor tenderness.

Oral medications such as amitriptyline, cimetidine, hydroxyzine, and pentosan polysulfate (Elmiron) have been utilized to alleviate IC/BPS symptoms, primarily serving as supplements to other treatments.

The proposed pathogenesis of IC/BPS involves damage to the uroepithelium, leading to inflammation and sensory symptoms. Therefore, delivering medication directly to the bladder seems logical. Intravesical instillation has become a standard treatment for IC/BPS due to several benefits: (i) higher concentrations of the drug in the bladder, (ii) fewer systemic side effects, (iii) reduced risk of drug interactions that can occur with oral medications, and (iv) direct repair of urothelial defects [19].

On the other side, intravesical drug delivery has its limitations. The impermeability of urothelial cells, characterized by tight junctions and umbrella cells, can hinder effective treatment. Additionally, the short duration of action and the need for frequent administrations can be painful, costly, and may increase the risk of infection. Given the multifactorial nature of the disease, a multimodal approach using various intravesical methods may enhance therapeutic outcomes.

Several drugs and compounds have been suggested as effective intravesical treatments for IC/BPS, including heparin, heparinoids such as hyaluronic acid and chondroitin sulfate, pentosan polysulfate (Elmiron), dimethylsulfoxide (DMSO), and botulinum toxin A (BoNT-A) [19].

In this context, Aldemidrol, an analogue of palmitoylethanolamide (PEA), has been proven to be a valid intravesical alternative for PBS symptoms. It is a well-known anti-inflammatory and anti-oxidant compound, which has been used for the management of acute and chronic inflammation. In

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detail, Aldemidrol is an innovative active ingredient, able to control the mast cell component through the ALIA (Autacoid Local Injury Antagonism) mechanism. It makes this possible both by directly modulating mast cell activity through the activation of the nuclear receptor PPAR-γ and by increasing local endogenous levels of palmitoylethanolamide [20].

In dermatological field, Aldemidrol, resulted to be a potent topical treatment in a canine model of allergic dermatitis: the skin biopsy specimens revealed that it acts maintaining mast cells (MC) normal reactivity, reducing MC granule density and their degranulation [21]. Similarly, the combination of Aldemidrol with hyaluronic acid has been demonstrated to have beneficial effects on pain severity and modulation of the inflammatory response in a rat model of osteoarthritis induced by monosodium iodoacetate (MIA): the degeneration of articular cartilage, the mast cell infiltration, and the pro-inflammatory cytokine (TNF-α, IL-1β, and NGF) and chemokine plasma levels were significantly downregulated by intraarticular application of delmidrol 2% + sodium hyaluronate 1.0% [22].

The aim of study was to evaluate the anti-inflammatory effects of intravesical Vessilen® ((a new formulation of 2% adelmidrol (the diethanolamide derivative of azelaic acid) + 0.1% sodium hyaluronate) administration in patients affected by IC/BPS or with condition associated to local inflammation, urothelial lesions, voiding dysfunctions and pain in pelvis/perineal area

2. Materials and Methods

A prospective observational study was carried out in a tertiary-level Urogynaecology department. The study was conducted in San Gerardo Hospital, Monza, (Italy) in the period between November 2023 and July 2024. All patients considered eligible for the study complained of a chronic pelvic pain associated with symptoms of the lower urinary tract including increased urinary frequency, urgency and unpleasant pressure and discomfort. Recruitment was limited to patients with symptoms lasting for at least 3-6 months. 26 women referred to our urogynecological clinics fulfilled the criteria and were enrolled. They underwent to a cycle of 6 intravesical instillations of Vessilen® (a new formulation of 2% adelmidrol (the diethanolamide derivative of azelaic acid) + 0.1% sodium hyaluronate), once weekly.

Prior to the onset of treatment and after the 6th (final) bladder instillation, validated questionnaires were administered to the patients: the Visual Analogue Scale (VAS) and International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms Modules (ICIQ-FLUTS Long Form). VAS is a tool for assessing intensity of symptoms perceived by the patient and is represented by a line, usually 10 cm long, where one end (0) indicates absence of the symptom, and the other end (10 cm) represents the worst imaginable symptom intensity. The ICIQ-FLUTS allows to evaluate female lower urinary tract symptoms and impact on quality of life (QoL) in research and clinical practice across the world. Additionally, the personal satisfaction was investigated by the Patient global impression scale (PGIs), filled in by patients after the final instillation.

All patients were monitored during the treatment period to control for the occurrence of any adverse effects.

3. Results

In total 26 patients were analyzed. Population characteristics are shown in Table 1.

Table 1. Population baseline characteristics. Continuous data are reported as mean (SD). Non-continuous data are reported as absolute (relative) frequency.

Age (years)	58.4 (16.4)
Parity (n)	0.8 (0.4)

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Smoking	1 (3.8%)
Previous pelvic surgery	11 (42.3%)

All patients underwent 6 intravesical instillation of Vessilen® - once per week - except one patient who did not bear urethral catheterization and decided to interrupt the procedure at the first instillation. Consequently, complete baseline and after treatment data were available for 25 patients. Baseline and after treatment comparison is shown in Table 2. We observed a significant decrease in the severity of bladder symptoms according to both ICIQ-FLUTS scale (89.3 vs 61.3; p=0.021) and VAS score (4.4 vs 2.6; p<0.001). Moreover, according to PGI-I, 80% of patients observed an improvement in symptoms (PGI-I score ≤ 3).

Table 2. Baseline vs after-treatment comparison. Continuous data are reported as mean (SD). Non-continuous data are reported as absolute (relative) frequency.

	Baseline	After treatment	p-value
ICIQ-FLUTS	89.3 (41.1)	61.3 (42.5)	0.021
VAS	4.4 (1.5)	2.6 (1.8)	<0.001
PGI-I	n/A	2.8	n/A

4. Discussion

IC/BPS is a chronic condition characterized by recurrent pelvic pain or pressure and increased urinary frequency. Similarly, the same symptoms could be also experienced by women with recurrent cystitis, despite long pharmacological treatments and supplements. Additionally, these medical issues result in significant deterioration of both mental and physical quality of life, often associated with depression, anxiety, and reduced social interactions [23]. Historically, diagnostic criteria set by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) included objective indicators like cystoscopic confirmation of diffuse glomerulations or Hunner's lesions (HLs), along with specific cystometric measurements, such as a bladder capacity of less than 350 ml while awake [24]. However, there has been a shift toward diagnosing based on the presence of the aforementioned symptom constellation.

The exact cause of IC/BPS remains unclear, with several potential factors proposed, including inflammation, mast cell activation, genetic predisposition, autoimmune mechanisms, and neurogenic factors [25]. These complexities make IC/BPS particularly difficult to study and highlight the pressing need for new therapeutic strategies.

Clinical experience and limited literature indicate that modifying certain behaviors can alleviate symptoms in some patients with IC/BPS. Behavioral modification strategies may include adjusting urine concentration and volume through fluid restriction or increased hydration, avoiding foods that are common bladder irritants, following an elimination diet to identify foods or fluids that may trigger symptoms, and using over-the-counter products such as nutraceuticals, calcium glycerophosphates, and phenazopyridine. Appropriate manual physical therapy techniques (eg, maneuvers that resolve pelvic, abdominal and/or hip muscular trigger points, lengthen muscle contractures, and release painful scars and other connective tissue restrictions), if appropriately trained clinicians are available, should be offered to patients who present with pelvic floor tenderness [26].

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Oral pharmacotherapy becomes the primary option when conservative approaches have failed: amitriptyline, cimetidine, hydroxyzine, or pentosan polysulfate are the main oral medications recommended to better control the symptoms [26].

As a second step, several instillation therapies are available globally, including chondroitin sulfate (CS), hyaluronic acid (HA), heparin, lidocaine, pentosan polysulfate sodium (PPS), and dimethyl sulfoxide (DMSO). Most of these strategies aim to replenish and restore the structure of the glycosaminoglycan (GAG) layer and the natural protection it provides [27]. In Europe, chondroitin sulfate (CS) and hyaluronic acid (HA) are two of the most commonly used agents. A typical regime is once weekly for six weeks and monthly thereafter as required. Gülpinar et al. randomized 42 patients to receive one of these two agents. At the six-month follow-up, both agents significantly reduced pain ($P < 0.001$). However, chondroitin sulfate (CS) demonstrated superiority in decreasing 24-hour frequency ($P < 0.001$) and was the only agent to significantly improve nocturia ($P < 0.001$) [28]. A subsequent study investigated the outcomes associated with a combined HS/CS instillation. Özkıdık et al. randomized 72 patients to receive either hyaluronic acid (HA), chondroitin sulfate (CS), or a combination of HA and CS, following them over a 24-month treatment period. The greatest reduction in pain was observed in the HA/CS group, though this outcome was not statistically significant compared to the other treatment arms ($P = 0.15$). On the other hand, improvements in both urgency and Health-Related Quality of Life (HRQoL) scores were significantly better in the HA/CS group ($P = 0.04$ and $P = 0.02$, respectively) [29]. The most frequently reported adverse events (AEs) are pain, irritation, and urinary tract infections (UTIs). There is no strong evidence to suggest that any particular instillation therapy is superior [27]. However, pentosan polysulfate sodium (PPS) and dimethyl sulfoxide (DMSO) have worse side effect profiles, which may include headaches and dizziness, and necessitate ophthalmologic monitoring due to the risk of lens opacification.

Beside these agents, an emerging molecule investigated for bladder instillation is Adelmidrol. Adelmidrol is a synthetic derivative of azelaic acid which works as a palmitoylethanolamide (PEA) enhancer increasing endogenous PEA levels which lead to anti-inflammatory and immunomodulatory effects [30]. As with PEA, Adelmidrol belongs to the family of Autacoid Local Injury Antagonist Amides (ALIAmides) and its amphiphilic and amphipathic properties make Adelmidrol particularly soluble and suitable for topical and intra-articular administration [21,31]. In this sense, its efficacy has been demonstrated in numerous experimental studies on inflammatory systemic disorder: Di Paola et al. observed that mechanical allodynia and motor functioning along with the degeneration of articular cartilage were reduced by the combination of hyaluronic acid and Adelmidrol [22]. Furthermore, Cordaro et al. proposed Aldemidrol as a new pharmacological approach for inflammatory bowel disease. In this study, Adelmidrol (10 mg/kg daily, orally) was evaluated in a murine model of colitis induced by intracolonic administration of dinitrobenzene sulfonic acid. Following this administration, there was a significant increase in nuclear factor-κB translocation, cyclooxygenase-2, phospho-extracellular signal-regulated kinase, tumor necrosis factor-α, and interleukin-1β in colon inflamed tissues. Treatment with adelmidrol led to a reduction in diarrhea, body weight loss, and myeloperoxidase activity. Simultaneously, adelmidrol treatment diminished nuclear factor-κB translocation, cyclooxygenase-2, and phospho-extracellular signal-regulated kinase expression; proinflammatory cytokine release; and the occurrence of nitrotyrosine and poly(ADP)ribose in the colon [32].

The present study was designed to investigate the anti-inflammatory effects of intravesical Vessilen® (a new formulation of 2% adelmidrol (the diethanolamide derivative of azelaic acid) + 0.1% sodium hyaluronate) administration in patients affected by IC/BPS or with conditions associated to local inflammation, urothelial lesions, voiding dysfunctions and pain in pelvis/perineal area. We observed a significant mitigation of pain, urgency and frequency intensity after a weekly treatment for 6 weeks as demonstrated by the score of ICIQ-FLUTS (89.3 vs 61.3; $p=0.021$) and VAS score (4.4 vs 2.6; $p<0.001$). The improvement was also confirmed by the personal satisfaction of most of the patients: the mean PGI-I score resulted < 3. No significant adverse reactions were noted during the treatment cycle and only one patient interrupted the procedure because of the catheter discomfort. Our evidence is in agreement with a previous observational study in which intravesical Vessilen was

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tested in a rodent model of IC/BPS, induced by cyclophosphamide (CYP). CYP instillation caused macroscopic and histological changes in the bladder, including inflammatory infiltrates, increased mast cell counts, bladder pain, elevated nitrotyrosine expression, and decreased expression of the endothelial tight junction protein zonula occludens-1. Intravesical treatment with Vessilen® effectively reduced CYP-induced inflammation and pain by inhibiting the nuclear factor-κB pathway and lowering levels of inflammatory mediators, as well as alleviating mechanical allodynia and reducing nerve growth factor levels [33]. In a second phase, Ostardo et al. preclinical murine data were confirmed on a population of 128 men and women suffering from chronic pelvic pain associated with symptoms of the lower urinary tract. In accordance with our findings, an improvement of symptoms (pain, frequency, voiding dysfunction, urgency) was recorded after a weekly treatment for 8 weeks. In a more recent study, the combination of Adelmidrol + hyaluronic acid was administered in a population of patients affected by non-muscle invasive bladder cancer (NMIBC), after transurethral surgical resection (TUR). Aldemidrol (AD) and hyaluronic acid (HA) intravesical instillation as a supplementary treatment to intravesical anticancer therapy allowed to keep under control pain intensity, urgency and frequent micturition-related discomfort, enabling all patients to complete the entire course of anticancer treatment such as immunotherapy with Bacillus Calmette-Guérin (BCG) and intravesical chemotherapy with mitomycin C (MMC) or epirubicin (EPI). Moreover, the continuation of AD + HA treatment after the end of anticancer cycle, led to a further improvement of symptomatology (reduction of VAS score and percentage of patients with side effects) [34].

The proven benefits in symptom intensity and tolerability associated with Vessilen® treatment supports the need for additional clinical studies to assess its long-term effects in patients with IC/BPS or other bladder conditions.

5. Conclusion

In conclusion, we demonstrate the anti-inflammatory action of intravesical administration of adelmidrol combined with sodium hyaluronate (Vessilen®) in patients suffering from interstitial cystitis/bladder pain syndrome (IC/BPS) or other chronic bladder disorders, especially in term of pain relief and lower urinary tract symptoms mitigation. For that reason, intravesical instillation of Vessilen® could be considered a valid alternative for patients who do not completely benefit from traditional pharmacological therapies. Further studies, including a larger patient population, are needed to determine the optimal number of treatment sessions and cycles required to maintain the effect over the time.

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