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K. Ye. Vydrin https://orcid.org/0009-0008-3056-3783
V. O. Poliakov https://orcid.org/0009-0008-8065-9775
F. I. Kostev https://orcid.org/0000-0003-0256-9279
Yu. M. Dekhtiar https://orcid.org/0009-0004-9953-1422
M. V. Shostak https://orcid.org/0000-0003-0942-6393

CLINICAL MONITORING OF REFRACTORY INTERSTITIAL CYSTITIS DURING PHARMACOTHERAPY IN WOMEN

Odesa National Medical University, Odesa, Ukraine

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K. Ye. Vydrin, V. O. Poliakov, F. I. Kostev, Yu. M. Dekhtiar, M. V. Shostak
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Refractory interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic condition marked by resistance to standard treatments and persistent symptoms such as pelvic pain, urgency, frequency, and reduced bladder capacity.

Objective – to improve treatment outcomes in women with refractory IC/BPS by using a personalized multimodal approach combining intravesical botulinum toxin type A (BTA), gabapentin, and hydroxychloroquine.

Materials and methods. A prospective study included 67 women diagnosed with refractory IC/BPS. Patients were assigned to two groups: the control group (n=32) received intravesical BTA alone, while the main group (n=35) received the combination therapy. Treatment lasted 6 months, with follow-up for 12 months. Efficacy was evaluated using O'Leary-Sant questionnaires, VAS for pain, urinary diaries, and cystoscopy.

Results. Combination therapy showed superior efficacy over BTA monotherapy. In 6 months, 80% of patients in the main group reported good/satisfactory outcomes vs. 53.1% in the control group. At 12 months, Hunner's ulcers were observed in 22.85% of the main group vs. 59.37% of the control group ($p < 0.001$); glomerulations occurred in 40% vs. 87.5% ($p < 0.001$). Functional bladder capacity improved by 99.05%. Pain (VAS) decreased by 68.3%, urinary frequency by 54.6%, urgency by 76.1%, nocturia by 69.7%, and ICSI/ICPI scores by 70% and 65.9%, respectively ($p < 0.05$).

Conclusion. The combination therapy offers better symptom control, improved urothelial healing, and sustained results compared to BTA monotherapy.

Keywords: interstitial cystitis, bladder pain syndrome, botulinum toxin, gabapentin, hydroxychloroquine.

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К. Є. Видрін, В. О. Поляков, Ф. І. Костєв, Ю. М. Дехтяр, М. В. Шостак
КЛІНІЧНИЙ МОНІТОРИНГ ПЕРЕБІГУ РЕФРАКТЕРНОГО ІНТЕРСТИЦІАЛЬНОГО ЦИСТИТУ НА ТЛІ ФАРМАКОЛОГІЧНОЇ ТЕРАПІЇ У ЖІНОК
Одеський національний медичний університет, Одеса, Україна

Рефрактерний інтерстиціальний цистит/больовий синдром сечового міхура (РІЦ/БССМ) – це хронічне захворювання, стійке до стандартної терапії. Мета дослідження – підвищити ефективність лікування жінок з РІЦ/БССМ шляхом застосування персоналізованої комбінованої терапії: внутрішньоміхурового введення ботулінічного токсину типу А (БТА), габапентину та гідроксихлорохіну. Комбіноване лікування показало переваги над монотерапією БТА: після 6 місяців покращення відзначалося у 80% пацієнток проти 53,12%, зниження частоти виразок Гуннера та гломеруляцій – до 22,85% і 40% відповідно. Комбінація препаратів забезпечує кращий контроль симптомів та тривале поліпшення.

Ключові слова: рефрактерний інтерстиціальний цистит, больовий синдром сечового міхура, ботулінічний токсин типу А, габапентин, гідроксихлорохін.

Introduction

Interstitial cystitis (IC), or bladder pain syndrome (BPS), is a chronic inflammatory disease of the urinary bladder, that is accompanied by persistent pelvic/urethral pain, frequent urination, and urgency in the absence of infection or other urological pathology [1]. The international urological community suggests using the term "bladder pain syndrome", but due to the prevalence of the term "interstitial cystitis", the recommended abbreviation is IC/BPS (interstitial cystitis/bladder pain syndrome) [2].

The prevalence of IC/BPS is 100–500 cases per 100.000 people, with women being affected 8–10 times more often (0.045–0.3%) than men (0.03%) [1–3]. The disease significantly reduces the quality of life, affects the ability to work, and requires long-term medical monitoring, which makes its socioeconomic significance high.

The etiology and pathophysiology of IC/BPS remain poorly understood. Current studies indicate a multifactorial nature of the disease, including autoimmune disorders, defects in the glycosaminoglycan (GAG) layer of the urothelium, neurogenic inflammation, and increased permeability of the bladder wall [4–6]. GAGs, which provide the

protective properties of the bladder mucosa, when damaged, make the urothelium sensitive to toxic urinary components [4; 5]. This leads to local inflammation, mast cell activation, and the release of mediators such as histamine, which stimulates sensory nerve fibers [6–8].

Without timely therapy, a vicious pathological cycle is formed, which can lead to irreversible structural changes in the bladder. The persistence of neurogenic inflammation contributes to the development of chronicity of the pathological process with phenotyping of central sensitization and the formation of persistent pain syndrome [9; 10].

IC/BPS encompasses various clinical phenotypes with different causes. To date, the only clinically confirmed phenotype is Hunner's lesions. IC is divided into two subtypes depending on the presence or absence of Hunner's ulcers (HIC) [11]. Studies show that IC is a chronic inflammatory disease histologically characterized by lymphoplasmacytic infiltration, epithelial denudation, stromal edema, and hyperemia, while BPS is a non-inflammatory disease with few signs of bladder pathology and is potentially associated with systemic neurophysiological dysregulation [12; 13]. There is a growing body of evidence that HIC is immune-mediated, possibly autoimmune [11; 14–16]. Patients with HIC often have high titers of autoantibodies in serum and CSF, as well as a high incidence of comorbid autoimmune diseases such as Sjogren's syndrome and systemic lupus erythematosus (SLE), which are accompanied by symptoms similar to HIC [17]. In addition, the female predominance and association with previous microbiome infections, which are typical of systemic autoimmune diseases, are also typical features of HIC, emphasizing its immune nature.

The clinical and nosological profile of IC/BPS is characterized by a variety of symptoms, including chronic pain associated with bladder (with a frequent correlation of pain intensity with the degree of bladder filling), in combination with urinary tract symptoms, and includes a wide range of clinical phenotypes with different etiologies. Typical clinical markers are urgency pollakiuria and nocturia, which causes significant somatic and psychoemotional maladjustment of patients [1–3].

A particularly pressing medical and social problem is refractory interstitial cystitis (RIC), a specific form of IC characterized by resistance to standard treatment and prolonged persistence of the main symptoms, such as chronic pelvic pain, pollakiuria, urinary urgency, and decreased bladder capacity for at least 6 months. This condition requires differential diagnosis with other pathologies of the urinary system and the use of new, individualized approaches to treatment [1–3].

The high level of social maladjustment of patients with IC/BPS emphasizes the need for a comprehensive multidisciplinary approach to studying the pathogenesis of the disease. Modern research is aimed at introducing innovative methods and strategies to understand mechanisms that were previously considered irreversible.

Despite significant progress in understanding the pathophysiology of the disease, the treatment of IC/BPS remains challenging, requiring a multimodal approach and a comprehensive therapeutic strategy. Existing therapies include both conservative measures and invasive interventions, but their effectiveness varies from patient to patient, necessitating further research to develop more effective and personalized therapeutic solutions aimed at improving the quality of life of patients with this complex disease [16].

Objective – to evaluate the effectiveness of combined therapy (botulinum toxin type A, gabapentin, and hydroxychloroquine) in women with RIC by assessing clinical, functional, and endoscopic outcomes in comparison with botulinum toxin type A monotherapy.

Materials and methods

A comprehensive analysis of diagnostic and therapeutic outcomes was performed in 67 women with a verified diagnosis of interstitial cystitis/bladder pain syndrome (IC/BPS) according to the criteria of the European Society for the Study of Interstitial Cystitis (ESSIC). In all patients, previous standard therapy administered for 6 months failed to produce a statistically significant improvement in symptoms, indicating a refractory form of the disease.

Women aged 18–65 years with a verified diagnosis of IC/BPS confirmed by medical documentation in accordance with the ESSIC diagnostic criteria were eligible for inclusion. A mandatory inclusion criterion was persistence of clinical symptoms for at least six months with a severity exceeding 12 points on the O'Leary–Sant Symptom Index. All patients were fully informed about the study and provided written informed consent prior to participation. Additional safety criteria were applied for women of reproductive age: participation was excluded during pregnancy and breastfeeding, and reliable contraception was required throughout the study period. Patients with other urological conditions that could affect diagnostic accuracy or treatment outcomes of IC/BPS, as well as those with malignant neoplasms, severe somatic diseases, psychiatric disorders, or concomitant use of medications interacting with the study drugs, were excluded. Concurrent participation in other clinical trials was not permitted.

Patients were allocated into two groups: a control group (n = 32) and a main group (n = 35). In the control group, intravesical administration of botulinum toxin type A (BTA) was performed in accordance with the recommendations of the European Association of Urology (EAU) for the treatment of RIC. In the main group, patients received combined therapy consisting of BTA, oral gabapentin, and hydroxychloroquine.

The diagnostic protocol included collection of medical history data, urine sediment analysis, ultrasound examination of the lower urinary tract to assess postvoid residual volume, and a three-day voiding diary. All patients underwent diagnostic cystoscopy with bladder hydrodistension under general anesthesia, with simultaneous biopsy sampling for morphological confirmation of the diagnosis. Based on cystoscopic findings, IC/BPS phenotypes were classified as absence of glomerulations, presence of glomerulations, or Hunner's ulcers. When Hunner's ulcers were identified, endoscopic fulguration was performed.

Therapy was initiated 30 days after diagnostic cystoscopy. Both groups underwent intravesical administration of BTA under cystoscopic guidance: a total dose of 200 units was evenly distributed through 20 injection sites into the submucosal layer of the bladder

(apex, lateral walls, and posterior wall) at a depth of 2 mm, with an inter-injection distance of 1–1.5 cm.

In addition, patients in the main group received combined oral therapy consisting of gabapentin with dose titration (300 mg/day on day 1, 600 mg/day on day 2, followed by 900 mg/day divided into three doses) and hydroxychloroquine at a dose of 200 mg twice daily. The total duration of therapy was 6 months.

Outcome monitoring was performed at 1, 3, 6, 9, and 12 months after initiation of therapy. Follow-up cystoscopy was conducted at 3, 6, 9, and 12 months to assess the condition of the bladder mucosa, determine anatomical bladder capacity, evaluate changes in pain threshold, and monitor healing of ulcerative lesions.

Efficacy assessment criteria included:

– O'Leary–Sant indices (ICSI – Symptom Index and ICPI – Problem Index), with a ≥ 30% reduction in the total score considered clinically significant;

– visual analog scale (VAS) for pain intensity (0 cm indicating no pain and 10 cm indicating unbearable pain);

– data from three-day voiding diaries, including urinary frequency, nocturia, urgency episodes, and functional bladder capacity;

– postvoid residual urine volume measured by ultrasound;

– cystoscopic findings and anatomical bladder capacity.

The final two follow-up visits (at 9 and 12 months) were specifically designed to evaluate long-term treatment efficacy and durability of the achieved clinical outcomes.

The study was conducted in accordance with the principles of the Declaration of Helsinki and in full compliance with ethical standards applicable to clinical research. Written informed consent was obtained from all participants for study participation and processing of personal data. The study protocol was approved by the Bioethics Committee of Odesa National Medical University (Protocol No. 18, dated December 6, 2023).

Research results and their discussion

The age range of patients varied from 23 to 72 years (the mean age (50.43 ± 2.88) years). The duration of clinical manifestations of IC/BPS ranged from 8 months to 7 years (mean (31.4 ± 25.4) months). The majority of patients (49.25%, 33 women) had a disease duration of more than 3 years, compared to 37.31% (25 women) with a disease duration of 1 to 3 years and 13.43% (9 women) with a disease duration of up to 1 year.

A comparative analysis of urine diary indicators in patients with RIC revealed significant differences between the groups. At the beginning of the study, the scores in both groups were statistically comparable. According to the VAS scale, the average score in the control group was 7.8 ± 0.6, in the main group – (7.9 ± 0.7) points, which corresponded to severe pain. According to the O'Leary–Sant scale, the ICSI in the control group was (15.62 ± 0.34) points, the ICPI was (12.7 ± 0.35) points, in the main group – ICSI 16.03 ± 0.41 and ICPI (12.9 ± 0.37) points, respectively. Evaluation of the urinary diaries showed that the baseline data also had no statistical differences between the groups. In the control group, the frequency of urination was 60.72 ± 1.23, nighttime urination – 22.19 ± 0.82, urgency episodes – 21.12 ± 1.67 in three days, the mean functional bladder capacity – (72.47 ± 2.74) ml. In the main group, respectively: (62.34 ± 1.47); (23.44 ± 0.56); (20.42 ± 1.22)

Table 1

Monitoring of the intensity of pollakiuria, nocturia, urgency episodes, functional bladder capacity and total O'Leary-Sant score in patients with IC/BPS of the main group (n = 35) and the control group (n = 32), before and after treatment

Indicators	Research groups	Before treatment	In 1 month	In 3 months	In 6 months	Change from the original, %
In 3 days	Control	60.72 ± 1.23	50.47 ± 1.13*	37.15 ± 1.07*	42.13 ± 1.14*	-30.62%
	Main	62.34 ± 1.47	46.63 ± 1.15*	35.57 ± 0.89*	26.73 ± 1.19*	-57.12%
Number of nighttime urinations in 3 days	Control	22.19 ± 0.82	18.37 ± 1.33*	13.23 ± 1.45*	15.25 ± 1.62*	-31.28%
	Main	23.44 ± 0.56	10.12 ± 0.32*	7.88 ± 0.31*	6.73 ± 0.15*	-71.29%
A mean effective bladder volume, ml	Control	72.47 ± 2.74	96.35 ± 3.45*	128.37 ± 4.46*	116.37 ± 4.45*	+ 30.11%
	Main	69.92 ± 2.68	109.34 ± 3.47	141.21 ± 4.48*	151.49 ± 4.33*	+ 116.66%
Number of episodes in 3 days	Control	21.12 ± 1.67	13.48 ± 1.57*	9.85 ± 1.05*	12.18 ± 1.62*	-42.33%
	Main	20.42 ± 1.22	9.31 ± 0.33*	6.72 ± 0.25*	5.75 ± 0.31*	-71.84%
Intensity of urgency by the IUSS scale	Control	3.62 ± 0.09	2.28 ± 0.21*	1.69 ± 0.13*	1.75 ± 0.15*	-51.66%
	Main	3.68 ± 0.11	1.87 ± 0.10*	0.97 ± 0.10*	0.88 ± 0.09*	-76.09%
Total score ICSI	Control	15.62 ± 0.34	11.63 ± 0.28*	9.87 ± 0.21*	7.35 ± 0.42*	-52.95%
	Main	16.03 ± 0.41	7.65 ± 0.34*	5.73 ± 0.37	4.81 ± 0.32	-70.0%
Total score ICPI	Control	12.7 ± 0.35	10.51 ± 0.37	8.48 ± 0.22	6.47 ± 0.11*	-49.06%
	Main	12.9 ± 0.37	6.84 ± 1.83*	4.94 ± 0.14	4.27 ± 0.12*	-65.90%

* a statistically significant change in the parameter from baseline ($p < 0.05$).

and (69.92 ± 2.68) ml. According to the IUSS scale, the intensity of urgency was (3.62 ± 0.09) points in the control group and (3.68 ± 0.11) points in the main group (Table 1).

In 3 months after the start of treatment, both groups showed a significant improvement in all indicators. In the control group, VAS pain decreased to (3.2 ± 0.4) points, in the main group – to (2.7 ± 0.3) points (Fig. 1).

The incidence of pollakiuria in the control group decreased by 38.82% (to 37.15 ± 1.07), the mean functional bladder capacity increased by 77.13% (to 128.37 ± 4.46 ml). The IUSS score decreased to (1.69 ± 0.13) points in the control group and to (0.97 ± 0.10) points in the main group.

At the 6th month of treatment, the differences between the groups became more obvious. In the main group, a stable remission was observed: the frequency of urination decreased to 26.73 ± 1.19, nighttime urination – to 6.73 ± 0.15, urgency episodes – to 5.75 ± 0.31. Formally, the mean effective volume of the bladder increased by 116.66% (up to 151.49 ± 4.33 ml), and judging by the daily urination profile, therapy in patients with IC/BPS is accompanied by a significant restructuring of the reservoir function of the bladder. Both before and after treatment, patients urinated different amounts of urine from urination to urination. However, the number of urinations with a volume of up to 100 ml decreased from 65% to 25%, with a simultaneous increase in micturitions in the ranges of 100–200 ml and 200–300 ml by 25%.

According to the O'Leary-Sant scale, in the main group, ICSI decreased to (4.81 ± 0.32) points (-70.0%), ICPI – to (4.27 ± 0.12) points (-65.90%). In the control group, the indicators also improved, but less pronounced: VAS pain – (4.1 ± 0.5) points, urinary frequency – (42.13 ± 1.14), ICSI – (7.35 ± 0.42) points (-52.95%), ICPI – (6.47 ± 0.11) points (-49.06%). It is important to note that according to the results of 6 months of combined therapy in the main group, a good treatment result (reduction in VAS score by 75% or more) was noted in 11 (31.42%) patients, and a satisfactory result (reduction by 50% or more) – in 17 (48.57%) patients. In the remaining 7 (20%) patients, the improvement in pain intensity was less than 50%. In the control group, the effectiveness of treatment was lower. Only in 6 (18.75%) patients, in 6 months of treatment, the intensity of pain decreased by more than 75%, and a satisfactory result was recorded in 11 (34.37%) patients. In almost half of the patients (15 women; 46.87%), pain reduction was insignificant, not exceeding 50%. At follow-up in 9 and 12 months, the control group showed a gradual deterioration in all indicators, which approached the baseline values. In the main group, despite some deterioration, the values remained significantly better than at baseline. At 12 months in the main group, the frequency of urination was 33.34 ± 1.47, nighttime urination – 7.22 ± 0.66, urgency episodes – 6.09 ± 0.72, bladder volume – (142.32 ± 7.89) ml, ICSI – (5.76 ± 1.91) points, ICPI – (5.42 ± 1.75) points, VAS pain – (3.8 ± 0.4) points.

Thus, the results of the study demonstrate that combination therapy provides not only a faster reduction in the intensity of IC/BPS symptoms, but also a long-term improvement in the functional state of the lower urinary tract. It promotes sustained remission, reduces the frequency of exacerbations and improves the quality of life of patients. Despite the positive results, some patients in the main group experienced recurrence of ulcerative lesions in 12 months, indicating the need for further long-term follow-up and development of individualized approaches to maintenance therapy. The data obtained confirm the need for a comprehensive approach to the treatment of patients with refractory IC/BPS, including not only drug therapy but also dynamic monitoring of the state of the bladder mucosa and correction of therapeutic tactics depending on the results obtained.

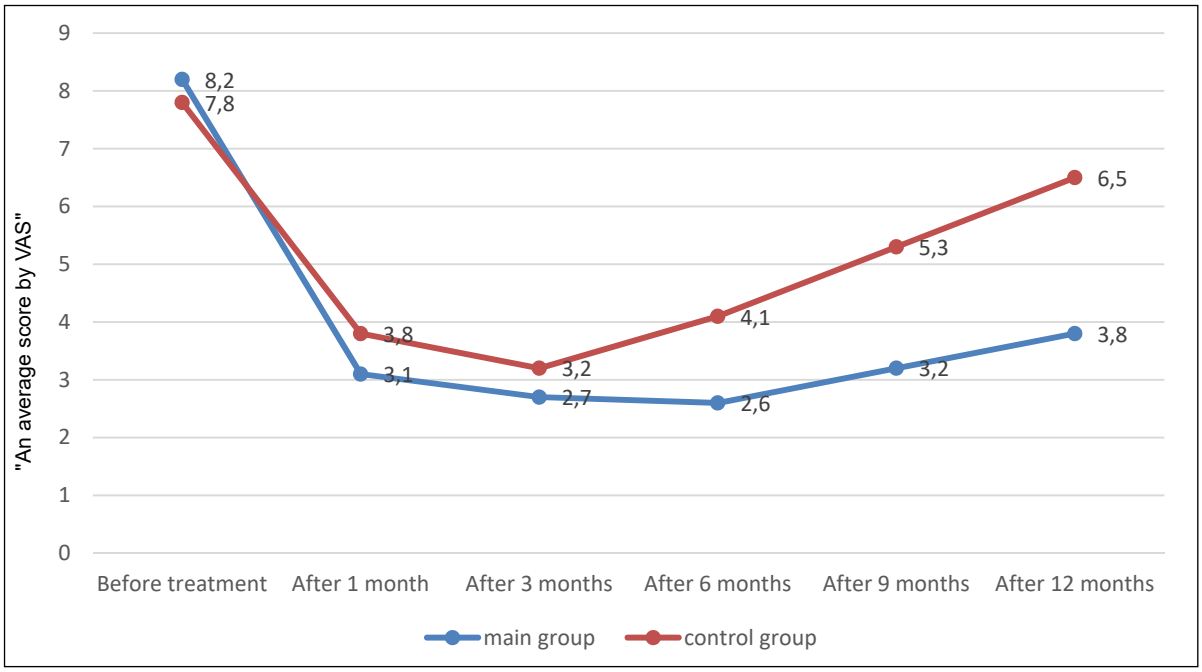

Fig. 1. Dynamics of pain intensity according to the VAS scale in patients with IC/BPS in the main (n = 35) and control (n = 32) groups, before and after treatment

Results of endoscopic monitoring. At the stage of cystoscopic evaluation of the urothelium, special attention was paid to the nature and dynamics of pathological changes in the bladder mucosa, since violation of its integrity is a key pathogenetic factor in the development of pain syndrome and dysuric disorders, which lead to a further decrease in the functional capacity of the bladder. In this regard, dynamic endoscopic monitoring of the condition of Hunner's ulcerative lesions after coagulation was performed.

In the control group, the cystoscopic picture demonstrates pronounced changes, reflecting both the progression of the pathological process and the response to the treatment. At the initial examination using hydrodistension, patients showed characteristic changes in the bladder mucosa: Hunner's ulcers were detected in 22 (68.75%) women, glomerulations – in all 32 (100%) patients. In addition, there was diffuse hyperemia of the mucous membrane and a decrease in the anatomical capacity of the bladder. Three months after the intravesical injection of BTA, 7 (15.4%) patients still had Hunner's ulcerative defects without complete epithelialization, but no new ulcerative lesions were formed. Mucosal glomerulations remained in 14 (43.75%) women, and the severity of inflammatory changes decreased slightly. By the sixth month, an increase in the inflammatory process was noted, accompanied by a recurrence of Hunner's ulcers in 13 (40.62%) patients and an increase in the frequency of glomerulations to 19 (59.37%). Nine months later, the number of patients with ulcerative lesions of the bladder mucosa increased to 16 (50.0%), and glomerulations were recorded in 25 (78.12%) cases. By the twelfth month, further progression of inflammatory changes was observed, with the cystoscopic picture returning to baseline in most patients: ulcerative lesions were detected in 19 (59.37%) women, and glomerulations in 28 (87.5%) patients.

The dynamics of the cystoscopic picture in patients of the main group indicates positive changes reflecting an improvement in the condition of the bladder mucosa. At the initial stage, during the primary cystoscopy with hydrodistension, 26 (74.28%) patients had Hunner's ulcers, and glomerulation of the mucous membrane was observed in all 35 (100%) women. There was also a marked hyperemia of the mucous membrane and a decrease in the anatomical capacity of the bladder. Three months after the start of therapy, there was a decrease in inflammatory changes in the mucosa and an increase in the capacity of the bladder: all patients had complete epithelialization of ulcerative defects, and the number of glomerulations significantly decreased to 12 (34.28%). In 6 months, the condition of the mucosa remained stable, the functional capacity of the bladder remained at the achieved level, no recurrence of ulcerative lesions was observed, and glomerulations were noted in only 7 (20%) patients. By the ninth month, inflammatory changes in the mucous membrane remained moderate, 4 (11.42%) patients had a recurrence of Hunner's ulcers, and the number of patients with glomerulations moderately increased to 10 (28.52%). At the twelfth month, inflammatory changes remained moderate, while bladder capacity remained stable, indicating the persistence of the positive effect of therapy. Ulcerative lesions were observed in 8 (22.85%) patients, and glomerulations – in 14 (40.0%).

Thus, compared with the control group, in patients of the main group, complex therapy promotes a significant improvement in the condition of the bladder tissues, including epithelialization of Hunner's ulcers, reduction in glomerulations and inflammatory changes, as well as stabilization of bladder capacity. However, relapses of ulcerative mucosal lesions were observed in 22.85% of patients, which emphasizes the need for long-term follow-up and an individualized approach to treatment.

These dynamics indicate that the combined therapy of patients with refractory IC/BPS not only effectively controls the inflammatory process, but also promotes long-term urothelial recovery and stabilization of bladder functional capacity. The analysis of the cystoscopic picture showed that in the main group there was a more pronounced decrease in inflammatory changes in the bladder mucosa, which was manifested in the complete epithelialization of Hunner's ulcerative lesions and a decrease in the frequency of glomerulations. In the control group, despite the initial improvement, a gradual return of pathological changes was observed in 6–9 months, indicating a less stable effect of monotherapy. However, the presence of recurrence of ulcerative lesions in 22.85% of patients in the main group emphasizes the need for an individual approach to treatment and long-term dynamic follow up to achieve maximum therapy effectiveness.

Conclusions

Combination therapy (BTA, gabapentin and hydroxychloroquine) demonstrated significantly higher efficacy compared to botulinum toxin A monotherapy in patients with RIC, providing a positive result in 80% of patients in 6 months of treatment (31.42% – good and 48.57% – satisfactory) vs. 53.12% in the control group and long-term maintenance of the achieved results during 12 months of follow-up.

Combined therapy demonstrated a statistically significant improvement in the morphofunctional state of the urothelium and the reservoir function of the bladder. According to the results of 12-month follow-up, the incidence of Hunner's ulcers in the main group decreased to 22.85% versus 59.37% in the control group ($p < 0.001$). A similar trend was noted for glomerulations: 40% in the main group versus 87.5% in the control group, respectively ($p < 0.001$), indicating more effective control of inflammation and urothelial recovery. The average functional bladder volume increased by 99.05%, accompanied by normalization of urodynamic parameters and restoration of the physiological pattern of urination.

Evaluation of the dynamics of clinical manifestations using O'Leary-Sant questionnaires and the VAS scale confirmed a significant improvement in the quality of life of patients in the main group. During 6 months of follow-up, the mean pain intensity score on the VAS scale decreased by 68.30% ($p < 0.05$), which was accompanied by a significant decrease in the severity of dysuric symptoms reduction in urinary frequency by 54.62%, and urgency intensity by 76.09%, reduction of nocturia episodes by 69.69%, which was reflected in a significant decrease in the IC/BPS symptom and problem indices (ICSI and ICPI) according to the O'Leary–Sant scale by 70% and 65.9%, respectively ($p < 0.05$).

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Електронна адреса для листування kirill.vydrin@onmeduedu.ua