UROLOGY

Intravesical hyaluronic acid — An effective option in the treatment of hemorrhagic radiocystitis

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Hemorrhagic cystitis – an inflammatory disease of the bladder with a complex etiology. The frequency of this pathology has increased substantially due to the increase in the number of patients undergoing radiation therapy for malignant neoplasms of pelvic organs. The development of a rational treatment for hemorrhagic cystitis is a difficult problem. Given the pathogenetic basis of this disease, it is assumed that, the optimal method of treatment should be aimed at the regeneration of the glycosaminoglycan mucosal layer of the bladder.

This article presents the results of a study of the effectiveness of intravesical instillations of hyaluronic acid in the treatment of hemorrhagic cystitis.

Keywords: hemorrhagic cystitis, hyaluronic acid, radiotherapy.

Hemorrhagic cystitis (HC) is a diffuse inflammatory disease of the bladder of infectious and non-infectious etiology, which is characterized by mucosal bleeding. This pathology is often a serious complication of the use of cytostatics or radiation therapy concerning malignant neoplasms of the pelvic organs, especially in combination with the transplantation of hematopoietic stem cells. A characteristic symptom that distinguishes HC from other forms of bladder inflammations is the present of blood in urine. Moreover, hematuria varies from microscopic to pronounced, with the formation of clots, blocking the urinary tract. Obstruction of the urinary tract can lead to the development of hydronephrosis and acute renal failure in both chronic and recurrent course of the process. In addition, the clinical picture of HC is characterized by frequent urination, usually of imperative (urgent) character, and lower abdominal pain, extending to the whole pelvic area. The act of urination is also accompanied by painful sensations, including burning and cutting in the urethra. Over time, the capacity of the bladder decreases in many patients due to fibrous changes in its wall. Chronic blood loss leads to an anaemic state in patients, which is manifested by weakness, increased fatigue, pallor and at a severe degree - the appearance of shortness of breath, tachycardia, syncope.

Currently, it has been proven that the main link in the pathogenesis of chronic inflammation of the urinary bladder (hemorrhagic, interstitial cystitis/painful bladder syndrome, recurrent infections) is due to damage of the glycosaminoglycan layer. As a result of this disorder, epithelial cells are exposed to toxic components of urine, which exacerbate the destructive process in the mucosa.

In the search for effective remedies for the treatment of chronic inflammation of the bladder, most specialists have come to the conclusion that the intravesical instillations of medications contributing to the restoration of the inner layer of the mucous membrane are the optimal method. Based on the analysis of information on the effectiveness of various methods for the prevention and treatment of interstitial cystitis or HC, many scientists concluded that intravesical administration of hyaluronic acid is the most reasonable method at the standpoint of evidence-based medicine [1-3].

Hyaluronic acid is the most important component of the intercellular matrix, an essential component of

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the glycosaminoglycan layer, which as a protective barrier of the urothelium, helps prevent inflammatory processes of the bladder. Intravesical instillations of hyaluronic acid are recommended by the European Association of Urologists for the treatment of painful bladder syndrome (grade B recommendation). Herewith, it has been noted that the effectiveness of such an administration persists for a long period (level of evidence 2b) [4].

The effect of hyaluronic acid in HC therapy has been demonstrated in a number of studies. Thus, M. Miodosky et al. (2007) demonstrated that hyaluronic acid has a rapid positive effect in eliminating hematuria, pain syndrome and decreasing the frequency of urinations [5]. M. Sommariva et al. (2010) showed that intravesical administration of the drug causes a significant reduction of the symptoms of cystitis induced by chemo- and radiotherapy [2]. Based on the results of these and other studies, experts of the British Association of Urological Surgeons (BAUS) recommend the intravesical administration of hyaluronic acid for the prevention and treatment of HC in cancer patients [6].

The purpose of our study was to evaluate the effectiveness of intravesical administration of hyaluronic acid to relief symptoms of HC induced by radiotherapy.

Materials and methods of the study

The study included 18 patients (14 men and 4 women) whose HC developed after radiation therapy related to prostate cancer (n = 10) and rectal cancer (n = 8). HC was determined by the presence of hematuria after excluding other causes of bleeding (e.g. nephrolithiasis, microtraumas and/or bacterial infections of the lower urinary tract). The average age of the patients was 59 years (from 46 to 74 years).

All patients were administered 80 mg of sodium hyaluronate in the form of 50 ml of 0.16% solution of Instylan (YURiA-PHARM, Ukraine) in a previously emptied bladder via a Foley catheter. The clamp was placed on the catheter for 30-45 minutes before patients were urged to urinate, then the catheter was removed and the patients emptied the bladder on their own. The instillations were performed weekly during the first month of treatment and monthly for the next two months – i.e. only six procedures in total.

The presence of hematuria, frequency of urination and intensity of pain (according to the visual analogue scale, VAS) was determined before and after the course of therapy. The duration of the effect of treatment was studied after 6 and 12 months.

The response to the therapy was evaluated as follows: the initial effect was defined as a decrease in clinical manifestations; complete remission – e.g. the disappearance of all symptoms; cessation of blood clot discharges with the preservation of hematuria was considered to be a partial response to the therapy.

Results

All 18 patients completed the study. No cases of side effects from the intravesical administration of hyaluronic acid were detected. The results of this study are represented in the table below.

Improvement was generally observed in all patients during intravesical instillations. 15 (87.5%) patients had complete remission in 6 months after completion of the procedures. Analysis of the effectiveness of treatment after 12 months showed that complete remission persisted in 14 (77%) patients, and 4 (23.3%) patients had a partial response to the therapy.

Gradual decrease of dysuric phenomena, which was defined as a decrease in the frequency of urgent urinations, and a decrease in pelvic pain was noted during the course of the therapy. In this case, the positive effect was maintained throughout the observation period. Reduction of the frequency of urinations (once per day) in 6 and 12 months after therapy, compared with the initial data, was -2.9 ± 1.7 and -1.5 ± 1.4 respectively was observed. The number of points for the intensity of pain according to the VAS scale decreased by 0.88 ± 1.41 after 6 months and by 1.31 ± 1.3 after 12 months. Adverse reactions were not detected in the patients throughout the course of treatment.

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Table.

Dynamics of HC manifestations after the course of intravesical therapy with hyaluronic acid

Clinical sign	Initial data	Period after the course of	
		6 months	12 months
Relief of symptoms (n) - partial response - complete remission		 3 15	 4 14
frequency of urination (times per day)	10.4 ± 1.8	7.5 ± 0.9	8.9 ± 1.4
Pain intensity (points according to the VAS scale)	2.75±2.24	1.88 ± 1.41	1.44 ± 1.36

Discussion

Currently, the treatment of HC arising due to radiation therapy related to oncological pathologies of pelvic organs is a great challenge. Due to the lack of well-organized controlled trials comparing current therapeutic options, evidence-based recommendations cannot be developed. According to available publications, after applying the majority of modern methods of treating this disease, recurrences and complications are often observed [7]. According to the results of a systematic review, the authors of which compared the effectiveness of several methods of treatment of HC (administration of mesna, pentosan polysulfate sodium, bladder irrigation), the most reasonable is intravesical administration of hyaluronic acid as a preventative and therapeutic measure [1].

Hyaluronic acid is a glycosaminoglycan, which is part of the connective, epithelial and nerve tissues as well as one of the main components of the extracellular matrix, which significantly affects the proliferation and migration of cells.

Hyaluronic acid has a number of positive effects:

- suppression of the formation of immune complexes;
- suppression of the migration of leukocytes;
- regulation of the proliferation of fibroblasts and endothelial cells;
- increase in the healing of connective tissue, etc.

These properties determine its preventive effect.

Many studies have demonstrated the effectiveness of the use of hyaluronic acid in the treatment of patients with interstitial cystitis/painful bladder syndrome [2, 3, 5, 8]. At the same time, the problem of rational effective therapy of HA has not been studied adequately. M. L. Sommariva et al. [2] conducted a prospective study involving 69 patients with cystitis, which developed after chemo- and radiotherapy related to prostate cancer. All patients received intravascular instillations of sodium hyaluronate at a dose of 40 mg weekly for 8-24 weeks, depending on the rate at which the symptoms were resolved. The disappearance of pain, urgency and increase in the capacity of the bladder were noted after 4 weeks. Nevertheless, taking into account the likelihood of the development of recurrences with early discontinuation of the treatment, the course of therapy was continued for another 4 weeks, even in patients with complete remission. Overall, 67 (97%) patients had complete relief of dysuria and pain. In two cases of ineffective therapy, this was due to low compliance. An increase in the average bladder capacity in groups of patients with cystitis was observed both after chemotherapy and after radiation therapy. Adverse reactions of sodium hyaluronate in both groups were not observed.

In the study by M. Miodosky et al. [5] intravesical instillations of hyaluronic acid were used in seven patients with HC associated with the transplantation of hematopoietic stem cells. The procedures were performed once a day for 3 days on average (from 2 to 7). Four patients showed a response to the therapy during this period, for the rest patients the treatment was extended for another 7 days. Relief of cystitis related symptoms was achieved in six patients after 3.5 days on average. Five patients had a complete remission within 12 days, one had a partial response, and one patient had no effect while on hyaluronic acid treatment. There were no local and systemic side effects of the drug. The authors of the study concluded that hyaluronic acid has a quick positive effect in eliminating hematuria, pain and a decrease in the frequency of urination.

In our study, a domestic preparation of instylan-hyaluronic acid gel of non-animal origin was used as a protector of the intercellular matrix of the bladder's urothelium. As a result, the successful elimination of symptoms of HC was also demonstrated. During the observation period of up to 12 months, the effect of the therapy - a complete remission or partial response was maintained in 94% of patients who reported significantly lower frequency of urination compared with the initial data, as well as a decrease in the severity of pain syndrome.

Conclusion

Intravesical instillations with hyaluronic acid are an effective option for treating patients with HC induced by radiation therapy. As a result of using the Instylan drug, bleeding of the bladder wall significantly reduced, the intensity of pelvic pain and the frequency of urgent urination reduced in the absence of adverse reactions. The positive effect of the therapy persisted for at least 12 months.

References:

1. Payne H., Adamson A., Bahl A. et al. Chemical- and radiation-induced haemorrhagic cystitis: current treatments and challenges // BJU Int. 2013; 112 (7): 885-897.

2. Sommariva M. L., Sandri S. D., Ceriani V. Efficacy of sodium hyaluronate in the management of chemical and radiation cystitis // Minerva Urol Ne- frol. 2010; 62 (2): 145-150.

3. Kim A., Lim B., Song M., Choo M.-S. Pre-treatment features to influence the effectiveness of intravesical hyaluronic acid instillation in refractory interstitial cystitis/painful bladder syndrome // Int Neurourol J 2014; 18: 163-167.

4. Engeler D., Baranowski A. P. , Borovicka J., Cot- trell A., Dinis-Oliveira P. et al. Guidelines on Chronic Pelvic Pain. European Association of Urology, 2014.

5. Miodosky M., Abdul-Hai A., Tsirigotis P. et al. Treatment of post-hematopoietic stem cell transplantation hemorrhagic cystitis with intravesicular

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ISSN 2311-7931

sodium hyaluronate. Bone Marrow Transplant 2006; 38: 507-511.

6. Thompson A., Adamson A., Bahl A., Borwell J. et al. Guidelines for the diagnosis, prevention and management of chemical- and radiation induced cystitis. British Association of Urological Surgeons // Journal of Clinical Urology 2014; vol. 7, no. 1: 25-35.

7. Denton A. S., Clarke N. W., Maher E. J. Non-surgical interventions for late radiation cystitis in patients who have received radical radiotherapy to the pelvis // Cochrane Database Syst Rev 2002; (3): CD001773.

8. Peeker R., Fall M. Treatment guidelines for classic- and non-ulcer interstitial cystitis // Int. Urogyne- col J. Pelvic Floor Dysfunct. 2000; 11: 23-32.