

**COMPARATIVE STUDY ON THE EFFECTIVENESS OF NOKAMEN
FOR PREVENTING EXACERBATIONS OF CHRONIC RECURRENT
CYSTITIS IN WOMEN**

Litvinec E.A., Litvinec V.E.

DVNZ "Ivano-Frankivsk National Medical University"

The purpose of the study: to study the efficacy and safety of using Nokamen phytocomplex for preventing exacerbations of chronic recurrent cystitis.

Materials and methods. We have carried out an open monocentric, comparative study which involved 60 women aged 20-65 years with chronic recurrent cystitis. In order to prevent the exacerbation of chronic recurrent cystitis based on a random sample, the patients were divided into II groups. Nokamen phytocomplex at a dose of 1 tablet 2 times a day for 3 months was intended to the main group (30 patients). The second group (30 patients) - the comparison group took an tincture of phytomixture "Kidney" at a dose of 50 ml 3 times a day for 3 months also.

Results. Analysis of the results has shown that the use of Nokamen phytocomplex within 3 months after the treatment of the last episode of exacerbation of chronic cystitis significantly reduces the incidence of relapses in comparison with phytomixture. Thus, in the main group of patients receiving Nokamen, an exacerbation of chronic cystitis was reported in 6 months - in 3 (10.0%) patients, while in the comparison group – in 18 (60.0%) patients.

Conclusion. This study has shown that the use of a balanced phytocomplex of Nokamen for 3 months compared with phytomixture is more effective in preventing exacerbations of chronic recurrent cystitis. So, it can be recommended for wide use as a highly effective and safe remedy.

Key words: chronic recurrent cystitis, Nokamen, phytomixture.

Cystitis is an infectious and inflammatory process in the wall of the bladder, which is localized predominantly in the mucous membrane [2, 5, 6]. The prevalence of acute cystitis in Ukraine is 314 per 100 thousand people, and chronic cystitis - 135 per 100 thousand people. Most patients are young women and women in the pre-menopausal period. If the infection of the bladder is constantly repeated (periodic relapse of its inflammation), the chronic cystitis, which has the ICD-10 code - N30.1-N30.2 can be diagnosed. Chronic recurrent cystitis or chronic cystitis with frequent exacerbations is the most common pathology diagnosed in women of reproductive age [1, 3, 5].

Based on the statistics, every third to fourth woman in the most active reproductive and working age (20-40 years old) experiences acute cystitis, and in one third it becomes recurrent. More often, recurrence occurs within the first three months after the first episode [2, 5]. Another study, which covered a wider age range of women (17-82 years), has shown even more global problem. Recurrent cystitis occurs in 45% of patients during the first year. Among the women 55 years of age and older, each second suffers from repeated exacerbations [10].

Women are highly susceptible to relapse of cystitis, which can be explained by such factors as: anatomical and physiological features of the female body (short and wide urethra, proximity to the reservoirs of opportunistic bacteria); gynecological diseases associated with inflammation and hormonal components that disturb vaginal dysbiosis; frequency of sexual acts, and contraception peculiarities. A significant factor of the bladder infection is a sexual intercourse. The variability of the location of the urethra outer opening creates a high probability of vaginal ectopia, while the urethra opens directly into the vestibule of the vagina. This results conditions for the retrograde passage of the vaginal contents into the bladder during sexual intercourse. In addition, the common "complication" of the onset of sexual activity is the formation of gimenourethral junctions, resulting urethra hypermobility, which is displaced in the vagina during coitus. Non-observance of sexual hygiene causes a cystitis attack almost after every sexual intercourse [2, 3, 5].

Adhesion (sticking) of certain types of bacteria to the epithelium of the bladder plays the important role in the development of cystitis. Spicy food and prolonged retention of urination, which can lead to persistent functional disorders, in which the consistency between the bladder muscles are lost, also contributes to chronic cystitis [5, 6, 7].

Most relapses occur in the first 3 months after a treatment of the previous episode. Within 6 months after the first episode of urinary tract infection (UTI), 27% of young women develop at least one culture-confirmed relapse, and 2.7% have at least 2 relapses. After a treatment of an uncomplicated cystitis the disease recurs for 1 year in almost half of women [2, 5]. If the causative agent of cystitis was *E. coli*, relapses occur in 36% of women under 55 years of age and in 53% of women over 55 years of age within 1 year [6]. Frequent relapses of cystitis are found in 10-15% of women over 60 years of age [10].

The cystitis occurs due to the presence of pathogens and dystrophic congestive processes in the wall of the bladder. In most cases, cystitis is caused by gram-negative bacteria, about 80% of which is *Escherichia coli*. The second most common pathogen (11%) is *Staphylococcus saprophyticus*. The other causes are mainly *Enterococcus faecalis*, *Klebsiella spp.* and *Proteus spp.* In the etiology of cystitis, urogenital infections caused by *Chlamydia trachomatis*, *Ureaplasma urealiticum* and *Trichomonas vaginalis* play a significant role [4, 5].

Deformation and deep damages of the bladder wall layers cause a decreased capacity of the bladder and its partial dysfunction.

The diagnosis of recurrent cystitis is verified if within six months there were at least two exacerbations of the disease or three or more during the year. There are two cases for the development of relapse. 1) Persistence of infection. In this case, the infectious agent gets into the mucous membrane of the bladder or urethra and parasites it, causing the exacerbations regularly. 2) Reinfection. In this case, there is a repeated infection. The first exacerbation of the disease ends with complete elimination of the bacteria, but the cause of relapse is a new infectious agent. This

may be the same or another type of bacteria that has again entered the urinary tract [2, 10].

Prophylactic treatment is indicated to the patients with frequently recurrent cystitis (> 2 exacerbations for 6 months and > 3 exacerbations for 1 year). Such therapy involves several approaches: prolonged prophylactic administration of one of the antibiotics in low doses every 10 days for 3 months; for patients whose exacerbations are associated with sexual intercourse, the antibiotic after coitus with a gradual dose reduction is recommended [5, 7].

An analysis of 108 studies has shown that as a result of the prophylactic use of antibiotics, the probability of relapse decreased 8-fold, however, at the end of the course, in 3 months, 60% of patients again experienced exacerbations. In addition, side effects have been developed in the form of intestinal dysbiosis and oral and vaginal candidiasis [10].

At present, there is a certain opinion regarding this method of prevention: if it is possible to do other ways, antibiotics may not be used until reception.

This condition is associated with a significant proliferation of polyresistant bacteria, their increased virulence, the activation of their own conditionally pathogenic microflora in conditions of reducing the body's defence and infection with hospital bacteria. Other important components of the problem are that over the past 40 years, fundamentally new classes of antibiotics have not appeared in the pharmaceutical market and in clinical practice. In addition, the number of antibiotic therapy side effects increase [6].

Resistance of bacteria to antibacterial agents is the main factor limiting antibiotic therapy and one of the reasons for unsuccessful treatment with antibacterial drugs. Every year around 20,000 articles are published about the spread of antibiotic resistance, which indicates the relevance of this problem [7].

Thus, losing the fight against infections strategically, humanity is forced to resort to tactical maneuvering. In these conditions, the role of phytotherapy, directly aimed at suppressing the development of pathogenic microbial pathogens in the urinary tract, is increasing.

Also, the negative side of most pharmacological drugs is their nephrotoxicity, the ability to sensitize and allergenize the body, especially when prolonged use. Taking into account the mentioned above, the attention was paid to phytotherapy in the treatment of patients with chronic cystitis [6, 8, 9]. The advantages of phytotherapy in the treatment of this pathology are as follows:

- phytopreparations have a pronounced therapeutic effect and a much smaller spectrum of side effects;
- wide range of therapeutic effects and minor toxicity allow long-term use of phytopreparations without the risk of severe complications (hepatotoxic, nephrotoxic, inoculation);
- pharmacodynamics of phytopreparations is quite rich (antiseptic, anti-inflammatory, analgesic, antispasmodic, diuretic and others), which allows to influence on several pathological chains;
- the effect of phytocomplexes is more natural and "soft". There is a modulating effect of these drugs on the immune system and metabolism due to the presence of biologically active substances, vegetable oils, vitamins, antioxidants, etc.

That is why Nokamen, produced by ANANTA Company, due to its complex of the necessary pharmacological mechanisms with a multifaceted effect on the genitourinary system, is very interesting. However, the effectiveness of this remedy in preventing relapses of chronic cystitis was not studied.

The purpose of the study: to study the efficacy and safety of using Nokamen phytocomplex for preventing exacerbations of chronic recurrent cystitis.

Materials and methods.

We have carried out an open monocentric comparative study which involved 60 women aged 20-65 years with chronic recurrent cystitis. Each patient had at least 2 relapses of cystitis at intervals of 2-4 months. In most cases, the exacerbations were caused by hypothermia, a substitution for the sexual partner, frequent sexual contacts and acute infections. The episodes of exacerbation of chronic cystitis were treated on the eve in all the patients included in the study. In

order to prevent the exacerbation of chronic cystitis, the patients were divided into II groups on the basis of a random sample. The main group (30 patients) was treated with Nokamen at a dose of 1 tablet twice a day for 3 months. Nokamen phytocomplex has the following balanced composition of the active substances: Crataeva nurvala bark – 100 mg, Saxifraga ligulata rhizome – 60 mg, Butea frondosa flowers – 40 mg, Dolichos biflorus seed – 40 mg, sodium carbonate – 20 mg, Boerhavia diffusa root – 70 mg, Asphaltum – 70 mg, Tribulus terrestris fruit – 100 mg, Rosmarinus officinalis whole plant extract – 20 mg, Rubia cordifolia root extract – 20 mg.

The second group (30 patients) - the comparison group took a tincture of phytomixture "Kidney", at a dose of 50 ml 3 times a day for 3 months. The composition of this phytocomplex contains the following plants: field horsetail (*Equisetum arvense*), corn stigma, tickseed, knotweed (*Polygonum aviculare*), currant leaves, bearberry (*Arctostaphylos uva-ursi*).

The criteria for the patients' inclusion in the study were as follows: the diagnosis of chronic recurrent cystitis, the age of patients 20-65 years, the patient consent for the study.

The criteria for exclusion from the study were as follows: malformations of the urinary system; the presence of concomitant disease, which is not provided for in the protocol and can affect the pharmacokinetics and pharmacodynamics of the drugs used in the study, as well as affect the interpretation of data; the presence of neuropsychiatric pathology in patients, which may also affect the complicity between the patient and the physician; patients intolerant to the drugs used in the study; refusal to participate in the study.

All patients involved in the study were examined using the following methods: examination of complaints and anamnesis, objective physical examination; clinical blood test; clinical urine analysis; Nechiporenko urine analysis; urine culture test; daily proteinuria; Zimnitsky test; biochemical blood test (urea, creatinine, liver tests); ultrasound examination of the abdominal cavity and genitourinary system.

Statistical comparison between groups was performed using t-test. Differences were considered as significant when $p < 0.05$.

During the study period, detection and registration of possible side effects were performed.

During the study the safety and tolerability evaluation, based on the study of the incidence of adverse events in the context of drug administration, was carried out. If there was a reasonable suspicion that an adverse event is associated with the study drug, it was considered as a side effect.

The criteria for assessing the tolerance were the patients' personal feelings in the background of using the study drug and the medical examination of possible allergic rash, peripheral edema, tachycardia and unforeseen adverse reactions.

Degrees of evaluation: good tolerance - the absence of side effects or insignificant severity side effects, which do not require the treatment cessation or change of the drug's dosage; satisfactory tolerance - the presence of adverse reactions that are mild or moderate, requiring the drug's reduction dose; poor tolerability - the presence of adverse reactions requiring the drug cessation. All patients involved in the study have completed the full course of the planned examination and treatment.

Patient groups were comparable in age, severity of clinical symptoms and concomitant pathology. Comparison of the initial data of laboratory studies has shown the uniformity of the main group and the comparison group.

Patient monitoring was carried out in order to determine the duration of remission within 6 months.

All patients were examined after their information consent in accordance with the GCP IHC requirements.

Results and Discussion.

The study was carried out at the urological department of the regional clinical hospital in Ivano-Frankivsk on the clinical basis of the Urology Department, DNEZ "Ivano-Frankivsk National Medical University". The age of the patients ranged from 20 to 65 years, on average 34.5 ± 2.6 .

The analysis of the results has shown that the use of Nokamen phytocomplex within 3 months after the treatment of the last episode of exacerbation of chronic cystitis significantly reduces the incidence of relapses. Thus, in the main group of patients receiving Nokamen at a dose of 1 tablet twice a day for 3 months, any exacerbation of chronic cystitis was not reported. But in 4 months only 1 (3.3 %) patient experienced the exacerbation, in 5 months - 2 (6.6%) patients, and in 6 months - 3 (10.0%) patients. In the comparative group, after 2 months, the exacerbation of chronic recurrent cystitis was reported in 2 (6.6%) patients, in three months - in 5 (16.6%) patients, in four months - in 9 (30.0%) , in 5 months - in 12 (40.0%), and in 6 months - 18 (60.0%) patients experienced the exacerbation chronic recurrent cystitis (Table 1).

Table 1

Frequency of exacerbations of chronic recurrent cystitis during 6 months of observation

	1 month	2 months	3 months	4 months	5 months	6 months
Main group (Nokamen), n=30	0	0	0	1 (3.3 %)	2 (6.6 %)	3 (10.0 %)
Comparative group, n=30	0	2 (6.6 %)	5 (16.6 %)	9 (30.0 %)	12 (40.0 %)	18 (60.0 %)

Any adverse reaction has not been observed when using Nokamen and phytomixture "Kidney".

Thus, the obtained data demonstrate that Nokamen phytocomplex is an effective remedy for the prevention of exacerbations of chronic recurrent cystitis.

Conclusions

1. This study has shown that the use of Nokamen for 3 months compared with phytomixture is more effective for preventing exacerbations of chronic recurrent cystitis.

2. Nokamen has no side effects and is well tolerated by patients, so it can be recommended for wide use as a highly effective and safe remedy for preventing chronic recurrent cystitis.

References:

1. Vozianov S.O. Resources and main indicators of the urological service of Ukraine for 50 years / S.O. Vozianov, N.O. Saidakova, L.M. Startseva // Urology. - 2015 – No. 2. - P. 9-19.
2. Vozianov A.F. Atlas: guide on urology: 3 volume. / A.F. Vozianov, A.V .Lyulko. - Dnipropetrovsk: RIA "Dnepr-VAL", 2001 - P. 1905.
3. Acute uncomplicated cystitis in women. Primary care / S.P. Pasechnikovka // Series «Library of Health of Ukraine». - K .: LLC "Doctor-Media", 2012.- P. 64.
4. Pasechnikov S.P. Monitoring of the species spectrum of causative agents of urinary tract infections and their sensitivity to antibacterial drugs in the urological department / S.P. Pasechnikov, N.A. Saidakova, V.S. Gritsay, V.V. Kuznetsov // Urology. - 2011.- Volume 15, No.2.– P. 9-16.
5. Pasechnikov S.P. Nonspecific cystitis: modern principles of diagnosis and treatment / S.P. Pasechnikov, M.V. Mitchenko // Health of Ukraine 21st Century. - 2017. No.8 (405). – P. 50-51.
6. Shulyak O.V. Evaluation of the preventive potential of Kanefron N in the treatment of recurrent cystitis in women of reproductive age / O.V. Shulyak, M.E. Sabadash // Health of woman. - 2015 – No. 10. – P.51-55.
7. Bonkat G. Guidelines EAU: guide lines on urological infections / G. Bonkat, R. Pickard, R. Bartoletti [et al.]. – 2017. – P. 106.
8. Dingermann T., Loew D. Urologika // Phytopharmakologie. — Stuttgart. Wiss. Verlagsgesellschaft Stuttgart, 2003. — P. 250-258.

9. Naber K.G. Efficacy and safety of the phytotherapeutic drug Canephron® N in prevention and treatment of urogenital and gestational disease: review of clinical experience in eastern europe and central asia // Research and reports in Urology. — 2013. — No. 5. — P. 39-46.
10. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect. Dis.Clin.North. Am. – 2014. – No. 28. – P. 1-13.