

ORIGINAL CONTRIBUTION

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Canephron® N in the treatment of recurrent cystitis in women of child-bearing Age: a randomised controlled study

Maksim Sabadash^{1*} and Alexander Shulyak²

Abstract

Background: The aim of this study was to investigate the effect of the herbal medicine Canephron®N, particularly regarding its ability to prevent recurrences of cystitis, associated with E.Coli in women of child-bearing age.

Methods: Ninety patients were randomised into two treatment groups. Both, the test group ($n = 45$) and the control group ($n = 45$), received an antibacterial therapy (fluoroquinolones) for 7 days determined by urine culture. Furthermore, in both groups general recommendations on preventing cystitis were made (sufficient liquid consumption, avoidance of hypothermia etc.). The test group received an additional Canephron®N therapy for 3 months (2 tablets, three times a day).

Control examinations were conducted on day 7 and after 3, 6 and 12 months; or immediately in the case of a recurrent episode. The following cystitis symptoms were recorded at each time point: pain in the bladder, burning and stinging during urination, urinary urgency and frequent urination in small amounts. The criteria for defining a recurrent episode of cystitis were rebound lower urinary tract infection symptoms with pyuria and positive bacteriological urine culture.

Results: Canephron®N in addition to fluoroquinolones helps to reduce cystitis symptoms after 7 days better compared to treatment with fluoroquinolones only, as well as pyuria after 3, 6 and 12 months and urine levels of *E. coli* at 3 and 12 months.

The frequency rate of recurrent episodes of cystitis was in the test group always lower than in the control group with a statistically significant difference at 6 months (8.9% vs. 17.8%) and at 12 months (15.5% vs. 35.5%). At 12 months, the mean score of the LUTI Symptom Severity Index was 6 ($p \leq 0.05$) in the control patients and 3 ($p \leq 0.05$) in the test patients. This may indicate that the relapses were less severe in the test group.

Conclusion: Treatment with the herbal medicine Canephron®N is a novel treatment method of alleviating the symptoms of cystitis and especially for reducing the rate of recurrent cystitis episodes.

Keywords: Herbal medicine, Cystitis, Pyuria, Canephron®N

Background

Cystitis is an infectious and inflammatory process in the bladder wall, primarily localised in the mucosa. This is usually associated with lower urinary tract infection (LUTI) [1]. Cystitis is an unpleasant condition, but never causes death or irreversible bladder changes [2]. Typical signs of cystitis are inconvenient and frequent urges to urinate. The

patients may also experience pain in the lower abdomen, haematuria and urinary urgency. Furthermore, the urine may be turbid and have an unpleasant odour.

Escherichia coli is the main pathogen causing cystitis in 85% of community-acquired LUTIs and 50% of hospital LUTIs. Bladder infections are normally treated by antibiotic therapy [1, 3]. If the symptoms are mild, antibacterials may be prescribed upon completion of a bacterial urine culture.

In men with normal urinary tract anatomy LUTIs are rare [4], but one third of women under 24 years have had

* Correspondence: Sobodash@ukr.net; maxsabadash@i.ua

¹Institute of Urology of NAMS of Ukraine, 04053Str. V. Vinnichenko, 9-a, Kiev, Ukraine

Full list of author information is available at the end of the article

at least one LUTI episode requiring antibiotic treatment in their life. About half of all women suffer from cystitis at least once during their lifetime, and more than half of them develop one or two recurrences. In most cases, recurrent episodes occur because of sexual intercourse, and may also be associated with the use of spermicides, but in certain cases the underlying causes are unclear. Recurrent episodes may be prevented with prophylactic antibiotics, although there is a risk that resistances may be developed [5, 6].

Herbal medicines may be used to circumvent the development of antibiotic resistance, particularly in long-term prevention of episodes of recurrent cystitis. One of the herbal medicines for the prevention of recurrent episodes of UTI is Canephron®N (Bionorica, SE, Germany). This is a fixed combination of herbal medicine components – centaury grass, lovage root and rosemary leaves – and acts against infection and inflammation in the urinary tract. It exhibits in-vitro both bactericidal and bacteriostatic effects on a wide range of uropathogens and inhibits bacterial adhesion to the urothelium, improves urodynamics and inhibits inflammatory reactions [7, 8]. The improvements in urodynamics are linked to mild diuresis [9] and spasmolysis [10].

Canephron®N has been shown to exhibit high efficacy in the prevention of chronic/recurrent infectious and inflammatory pathology of the urinary tract [reviewed in [10]]. We now present the first randomised long-term study of Canephron®N in the prevention of recurrent episodes of cystitis in women of child-bearing age.

Methods

The aim of this study was to investigate the effect of the herbal medicine Canephron®N on the clinical course of acute recurrent cystitis in women of child-bearing age, associated with *E. coli*. The study was designed as open labeled, randomised controlled study, in which the standard treatment with fluoroquinolones (ofloxacin) – the control group – was compared with standard treatment plus Canephron®N.

The study enrolled 90 women aged from 18 to 45 years. All of them had been diagnosed with acute recurrent cystitis caused by *E. coli* (with episode rates of up to twice every 6 months or 3 times a year). The patients were examined and treated at the SE “Institute of Urology of the NAMS of Ukraine”.

The study was conducted in accordance with the principles laid down in the Declaration of Helsinki and approved by local Ethics committee.

The following methods of examination were used on admission:

- blood chemistry and urine analysis;
- standard bacterial urine culture and antibacterial susceptibility test;

- ultrasound examination of bladder and kidneys;
- LUTI Symptom Severity Index (see Table 1).

Patients were excluded from study participation if they exhibited:

- malformation of the urinary system;
- intracellular sexually-transmitted pathogens, and pathogens other than *E. coli*;
- individual intolerance of Canephron® N components;
- calculi impairing urodynamics, dendritic urolithiasis;
- type 1 or type 2 diabetes mellitus;
- hematuria, chronic renal impairment and other pathologies of the urinary system that might enhance the risk of relapse;
- ≤ 3 or ≥ 9 points in total on the main 3 LUTI Symptom Severity Index (see Table 1).
- Association of cystitis with sexual activity (postcoital cystitis)

The patients were randomly assigned to test ($n = 45$) and control ($n = 45$) groups.

Both, the test group and the control group received an antibacterial therapy (ofloxacin 200 mg/2 times daily) for 7 days determined by urine culture. Furthermore, in both groups general recommendations on preventing cystitis were made (sufficient liquid consumption, avoidance of hypothermia etc.).

Additional to these standard treatments, the patients in the test group received a Canephron®N therapy for 3 months (2 tablets TID for 3 months),

After the initial examination, all patients returned for a control examination on day 7 and for further examinations at 3, 6 and 12 months; or immediately in case of a recurrent episode. The following cystitis symptoms were recorded at each time point: pain in the bladder, burning and stinging during urination, urinal urgency and frequent urination in small amounts.

Pyuria was measured up to 12 months. A bacterial count for *E. coli* was conducted on culture at each examination and the relapses of cystitis were recorded for a follow-up period of up to 12 months.

Table 1 LUTI Symptom Severity Index

Points	Assessment of background symptoms ^a
0	None
1	Mild (causing no effect upon daily activities or sleep)
2	Moderate (minor effect upon daily activities or sleep)
3	Severe (major effect upon daily activities or sleep)
4	Very severe (daily activities or sleep is impossible)

^a Background symptoms: dysuria, pollakiuria (frequency), urgency

Table 2 Cystitis symptoms in the two treatment groups, on admission and after 7-day treatment

Groups	Test group n = 45		Control group n = 45	
	On admission	After 7-day treatment course	On admission	After 7-day treatment course
Examination time				
Symptoms				
Pain in the bladder	26 (57.7%)	3 (6.7%)	23 (51.1%)	5 (11.1%)
Burning and stinging during urination	45 (100%)	6 (13.3%)	45 (100%)	9 (20%)
Urinal urgency	38 (84.4%)	2 (4.4%)	39 (86.6%)	5 (11.1%)
Frequent urination in small amounts	45 (100%)	6 (13.3%)	45 (100%)	9 (20%)

The criteria for recurrent episodes of acute cystitis were rebound LUTI symptoms with a positive bacteriological urine culture.

To prevent distortion of the results due to errors with urine sampling technique, urine samples for bacterial culture in acute cystitis were taken using Nelaton Fr 6 catheter. At month 3, 6 and 12 - midstream urine was taken without catheter.

All results were expressed as quantities and percentages, if appropriate. Statistical comparisons were conducted using the Student's *t* test, with a two-sided 95% confidence interval (95% CI), $p \leq 0.05$.

Results

The incidence of the main symptoms of cystitis (pain in the bladder, burning and stinging during urination; urinal urgency; frequent urination in small amounts) were essentially the same in the test and control groups (Table 2), which confirmed the comparability of the groups. All four symptoms improved in both groups after 7 days of treatment, although there was a tendency for a greater improvement in the test group than in the control group. The only statistically significant difference between the two groups was in the symptom of urinal ssurgency.

Pyuria (6 or more leucocytes in the field of view of the microscope) was initially present in all patients in both groups. During the follow-up period, pyuria was always more frequent in the control group than in the test group (see Fig. 1). This difference was statistically significant at 3 months (31.1% vs. 6.7%, $p \leq 0.05$), 6 months (31.1% vs. 6.6%, $p \leq 0.05$) and 12 months (31.1% vs. 4.4%, $p \leq 0.05$). The differences between the groups remained constant after 3 months.

The culture data for *Escherichia coli* were analysed separately for bacteriuria (E. Coli titer $\geq 10^3$ CFU/ml) and for no bacteriuria.

Initially, all patients in both groups (100%) showed bacteriuria. During the follow-up were constantly fewer patients with bacteriuria in the test group than in the control group. This difference was statistically significant at 3 months and at 12 months (Table 3).

The rate of recurrent episodes of acute uncomplicated cystitis was always lower in the test group than in the

control group (see Fig. 2). This difference was statistically significant at 6 months (8.9% vs. 17.8%) and at 12 months (15.5% vs. 35.5%).

During the 12-month period, the mean score of the LUTI Symptom Severity Index of the recurrent cystitis episodes was 6 in the control patients and 3 in the test patients.

Discussion

This randomised controlled study was performed in women of child-bearing age who were suffering from an acute episode of recurrent cystitis. Patients in the test group received an identical treatment as patients in the control group, but were additionally treated with the herbal medicine Canephron®N (2 tablets TID for 3 months).

During the first 7 days of treatment, the symptoms of cystitis improved in both groups. There was a tendency for better results for the test group than for the control group but the difference was only statistically significant in symptom of urgency (4.44% vs. 11.1%).

Pyuria was significantly lower in the test group 3, 6 and 12 months after the end of antibiotic treatment (Fig. 1). Presence of bacteriuria was also lower during this period (Table 3). Finally, the rate of recurrent episodes of acute cystitis was also lower in the test group after 6 and 12 months (Fig. 2).

During the 12-month period, the mean score of the LUTI Symptom Severity Index of the recurrent cystitis

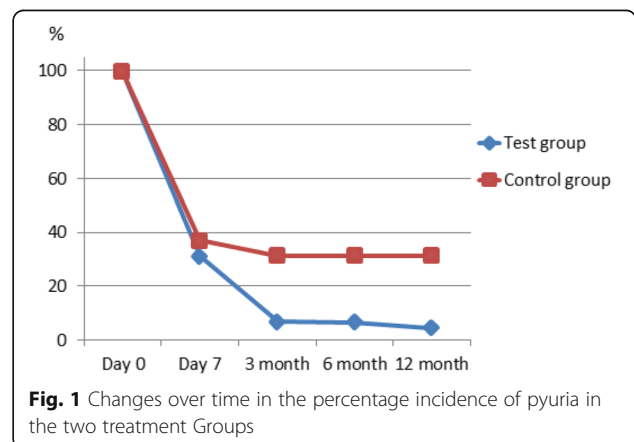


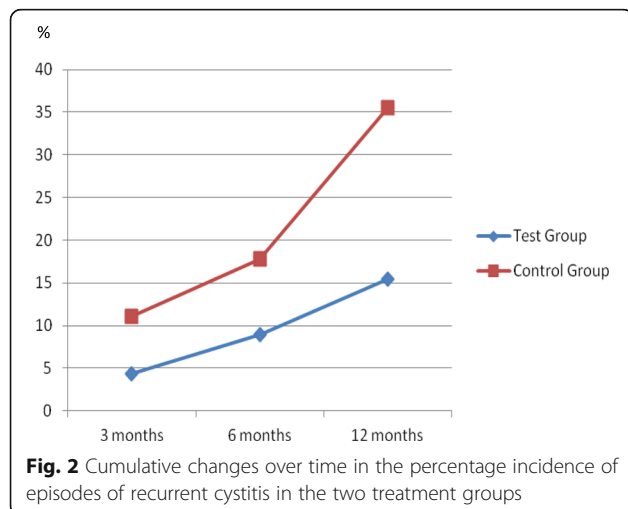
Table 3 Prevalence of bacteriuria and no bacteriuria (*E. coli* titer > 10³ CFU/ml) in the two treatment groups

Groups	Test group n = 45				Control group n = 45			
	Day 7	Month 3	Month 6	Month 12	Day 7	Month 3	Month 6	Month 12
Prevalence of bacteriuria	33.3	13.3	13.4	13.4	42.2	28.9	33.3	47.2
No bacteriuria (<i>E. coli</i>)	66.7	86.7	86.6	86.6	57.8	71.1	66.7	52.8

episodes was 6 in the control patients and 3 in the test patients. This may indicate that the recurrences were less severe in the test group than in the control group.

These effects may be related to the pharmacological activity possessed by Canephron®N, including diuretic, spasmolytic, anti-inflammatory, antibacterial and nephroprotective effects [10]. Taking into account the variability of chemotypes of medicinal plants and methods of production of herbal remedies it is important to note, that Canephron® N is a fixed combination of standardised herbal medicine components – century grass, lovage root and rosemary leaves in which special attention is paid to question about standardization and reproducibility of ingredients. It is more difficult to explain the differences between the groups at 6 and 12 months after treatment, when the patients were no longer receiving Canephron®N. It might be postulated that the physiological effects caused by Canephron®N (e.g. less inflammation) last for longer than the immediate presence of the components of the herbal medicine. Anyway reducing the frequency of recurrent episodes of cystitis can be explained by sustained positive changes in the urinary tract and possibly a change in the nature of the relationship microorganism/macro-organism. This issue could be investigated by further pharmacokinetic studies.

The limitations of this study include the lack of blinding to the patients and the physician at any time, the lack of characterisation of the individual components of the herbal medicine and the lack of more detailed studies of urological function.



Conclusion

In women of child bearing age suffering from acute recurrent cystitis, the herbal medicine Canephron®N can reduce the rate of episodes of recurrence, as well as bacteriuria and pyuria. To generalize the results, additional studies are needed, including longer-term studies and studies in older women.

The present data indicate that Canephron®N is a novel and effective treatment of recurrent cystitis. Because of the complex composition of Canephron®N, there may be less risk that bacterial resistance will develop than during antibiotic treatment of the same condition. This possibility should be also examined.

Abbreviation

LUTI: Lower urinary tract infection

Authors' contributions

MS performed the selection of patients, conducted treatment and observation during the period of the study, collected of the study results data, participated in writing of the manuscript. AS developed the study design, performed statistical analysis, monitoring of the study. Conducted analysis and review of study-results, participated in writing of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Institute of Urology of the NAMS.

Participants signed an informed consent form.

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Author details

¹Institute of Urology of NAMS of Ukraine, 04053Str. V. Vinnichenko, 9-a, Kiev, Ukraine. ²Institute of Urology Cystitis in Women, 04053Str. V. Vinnichenko, 9-a, Kiev, Ukraine.

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