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Lactiale Uro in the prevention of postmenopausal urinary infection: LACMUS study results

For citation: *Počki*. 2020;9(4):215-220. doi: [10.22141/2307-1257.9.4.2020.218235](https://doi.org/10.22141/2307-1257.9.4.2020.218235)

Abstract. Background. The purpose was to assess the efficacy and safety of Lactiale Uro, a product containing two strains of *Lactobacilli* plus cranberry extract and vitamin A, in preventing recurrent urinary tract infections (UTIs) in postmenopausal women (LACMUS study). **Materials and methods.** This was a randomized, prospective, multicenter study. Subjects received Lactiale Uro twice daily for 26 weeks after recovery from UTI; the control group didn't receive the product. The primary endpoint was the proportion of subjects with recurrent UTI episodes at the end of the study. **Results.** Seventy-seven women were screened; 65 were enrolled; 61 completed the study. After 26 weeks, a significantly lower number of women experienced recurrent UTIs with Lactiale Uro compared to no treatment (9.7 vs 23.3 %; $P < 0.05$). Lactiale Uro produced statistically significant improvements, such as lower rates of UTI episodes (12.9 vs 36.6 %; $P < 0.05$); longer time to first UTI episode (136 vs 27 days; $P = 0.0038$); shorter duration of active UTI episode (5 vs 11 days; $P = 0.0199$); and shorter duration of antibacterial therapy for an active UTI episode (4 vs 10 days; $P = 0.0462$). **Conclusions.** Lactiale Uro was safe and effective for the prevention of recurrent UTIs in postmenopausal women. These data require further well-designed trials to clarify possible benefits.

Keywords: *Lactobacilli*; urinary tract infection; postmenopausal period

Introduction

Treatment of recurrent urinary tract infections (UTIs) is an urgent problem. Three most important causes of recurrences in females: anatomical and functional disorders, sexually transmitted infections and postmenopause associated with a number of changes that cause a decrease in resistance to intestinal pathogens [1].

Current guidelines offer a variety of approaches to reduce UTI recurrences, including the use of natural herbal components. However, their use has no certain evidence base. For example, cranberries are considered effective when containing minimum 36 mg of proanthocyanidin (PAC) A (level of evidence: 1b, grade of recommendation: C) [2]; a lower dose is not effective. This was one of the reasons for the exclusion of cranberry products from the guidelines of the European Association of Urology (EAU) in 2014 [3].

However, combined cranberry-containing products are still popular due to their safety and quite convincing efficacy. Our attention was drawn to a study conducted by P. Koradia et al. in premenopausal women with recurrent UTIs, which results were presented in 2019 [4]. This study demonstrated the effectiveness of Bio-Kult Pro-Cyan in the prevention of recurrent UTIs in premenopausal women.

A similar product, Lactiale Uro produced by JSC Farmak, is available on the Ukrainian market. Each capsule contains a concentrate of lactic acid-producing bacteria containing *Lactobacillus acidophilus*, *Lactobacillus plantarum* 5.0×10^8 colony-forming units; cranberry extract containing 18 mg of PAC 254 mg; vitamin A 160 μ g. We designed a study “LACTiale uro in the prevention of postMenopaUSal urinary infection” — LACMUS. The study is an independent test of the efficacy and safety of the product similar to Bio-Kult Pro-Cyan, based on the study conducted by P. Koradia et al. (2019).

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Purpose of the study: to investigate the efficacy of Lactiale Uro in the prevention of recurrent UTIs in postmenopausal women.

Materials and methods

An open-label, prospective, randomized, multicenter, comparative study, LACMUS, was conducted in 61 patients (mean age 56.1 ± 1.5 years): 31 women were in the Lactiale Uro group and 30 in the control group not receiving Lactiale Uro.

The study design was completely reproduced from the original study by P. Koradia et al. [4], which became a prototype, with the only amendment — all patients were documented postmenopausal. The mean time after the last menstruation was 3.2 ± 1.5 years. In addition, the studied product Lactiale Uro had a different composition, compared to BKPro-Cyan, and contained vitamin A.

The primary endpoint was the proportion of subjects with recurrent UTI episodes at the end of the study.

Inclusion criteria: non-pregnant menopausal women aged 49 to 65 years who have experienced > 2 episodes of uncomplicated acute cystitis within the last 6 months, or > 3 episodes of uncomplicated acute cystitis within the last 12 months. Each subject enrolled in the study had to be available for the duration of the study, follow the final protocol and avoid using any supplements/products containing cranberries or probiotic supplements during the specified follow-up period. Each person had to have a negative pregnancy test at screening.

Exclusion criteria: active UTI; use of any antibiotic for 2 weeks after screening; known allergy to any ingredient in the study product; use of any natural product within a month prior to the study; positive pregnancy test; presence of the menstrual cycle; concomitant use of corticosteroids, anticoagulants, antidepressants, other mood-stabilizing drugs, or any medications that may interact with the supplement; significant comorbidities or conditions, including psychiatric, cardiac (including poorly controlled hypertension), renal (including anatomical disorders, catheterization, kidney stones, or kidney transplantation); hepatic (including hepatitis B or C), neurological, endocrine, metabolic (including diabetes) or lymphatic diseases, which, according to the investigator, may adversely affect the subject's participation in the study; immunodeficiency disorders (including human immunodeficiency virus); and active participation in

any clinical trial within one month after the beginning of the study.

Drug administration: immediately after recovery from UTI, the next day after the last dose of an uroantiseptic (antibiotic), Lactiale Uro, 1 capsule twice daily with meals, was prescribed as a prophylactic treatment according to the instructions for use. Prescription was based on the manufacturer's instructions, which specified the period of administration as 14–21 days or as prescribed by a doctor.

The duration of the study was 6 months, 26 weeks of active follow-up of the patients. For the first month of treatment, JSC Farmak provided free Lactiale Uro as an encouraging step. The patients did not receive any fees for the inclusion or participation in the LACMUS study.

The efficacy of Lactiale Uro was assessed based on the number of patients from the group who did not develop recurrent UTIs, which was determined according to the criteria of the EAU, 2019 [5]. Lactiale Uro was not discontinued in cases of UTI exacerbation.

Each patient gave an informed consent for treatment. The local ethics committee did not evaluate the study because it did not use a pharmacological agent, as Lactiale Uro is a dietary supplement. However, each doctor who prescribed the product confirmed the possibility of its long-term use, provided a monitoring of women according to the study protocol.

At the end of the study, each patient answered 3 questions about quality of life, including:

- comfort regarding urogenital system;
- satisfaction with the absence of UTI recurrence;
- general impression on the efficacy of UTI treatment.

The evaluation was performed using a 10-point score.

Statistical processing was carried out using Chi-Square Test Calculator [6]. However, for a better comparison with the prototype, we used the same approach, i.e. descriptive statistics was used to compare findings in the two treatment groups, and these included counts and percentages for categorical data. Continuous data were summarized using mean, standard deviation (SD), median, and range (minimum and maximum values) [4].

Results and discussion

At the end of the study, 31 subjects and 30 patients from the control group were included in the analysis (Table 1).

According to Table 1, 84.4 % of the selected patients were included in the study, 91.8 % completed the study

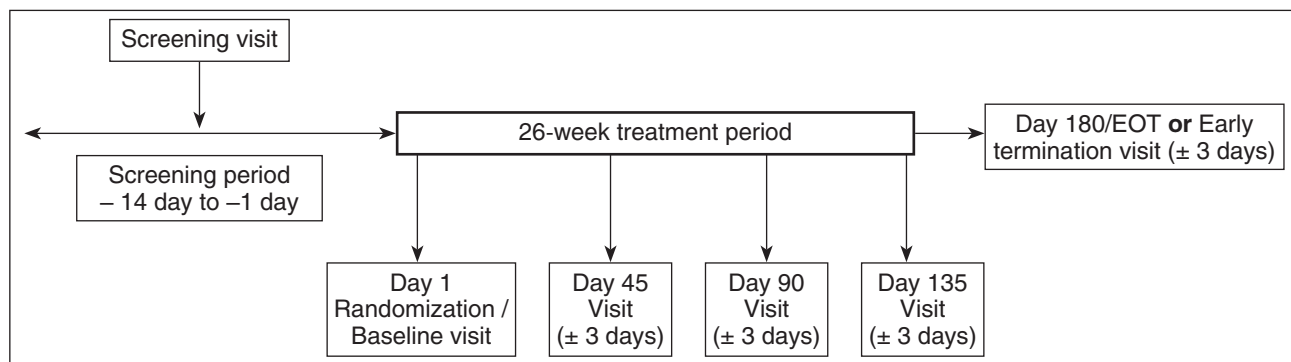


Figure 1. Study design by P. Koradia et al., 2019 [4], with amendments

protocol. Four patients discontinued the study for organizational reasons.

Statistical analysis comparing the efficacy of treatment is shown in Table 2.

According to Table 2, the use of Lactiale Uro resulted in a significant reduction in the number of both UTI episodes and women who experienced them. The number of recurrent episodes decreased almost fourfold (3.66). This effect was quite expected, as the amount of cranberry active substance complied with the evidence-based recommendations of the European Association of Urology (2013). Further cancellation of the recommendations regarding cranberries, in our opinion, is based on incorrect prescriptions and disregarded risk factors for the process exacerbation.

Apart from cranberries, there are many approaches in the reduction of UTI recurrences, in particular, development of autovaccines [7] or officinal preparations [8]. These measures are aimed at pathogen eradication through the body immune defense. However, adding active ingredients to cranberries can help the immune system to form local re-

actions. This is exactly what we observed in the analysis of recurrence characteristics in the LACMUS study.

Table 3 shows the number of UTI episodes, time to their occurrence, duration and the need for antimicrobial therapy. The presented data have significant differences, which indicate the efficacy of the used approach to Lactiale Uro administration. A very important parameter was the presence of bacteriuria at the end of the study, it was observed in 2 patients from the study group and 7 patients from the control group ($X^2(2, n = 61) = 2.074, p = 0.16776$).

However, our data showed the results not as impressive as those of the selected prototype [4]. When we started the study, we expected a higher percentage of women to be able to maintain a recurrence-free course. Possible explanations may be the excessive number of risk factors in postmenopausal patients compared to premenopausal ones and possible non-compliance of the individuals with the treatment schedule for Lactiale Uro during 5 months of self-administration of the product at their own expense.

At the same time, the use of Lactiale Uro as a biological supplement showed very promising results: an almost

Table 1. Subjects' data

Number of subjects	Lactiale Uro	No product	Total
Screened, n			77
Screen failure, n			12
Randomized, n	32	33	65
Completed the study, n (%)	31 (96.8)	30 (90.9)	61 (93.8)
Population analysis, n (%)			
FAS	31 (97.8)	30 (100.0)	61 (100)
PP	28 (90.3)	28 (93.3)	56 (91.8)

Notes: n — number of subjects in the given category; FAS — full analysis set; PP — per-protocol.

Table 2. Proportion of subjects with recurrent UTI episodes at the end of 26 weeks of treatment (primary endpoint)

Population/visit	Lactiale Uro	No product	Lactiale Uro vs No product (P-value)
FAS population, number of subjects	31	30	
Visit 6 (week 26): n (%) [number of recurrent UTI episodes]	3 (9.7) [4]	7 (23.3) [11]	
Chi-square test, 95% CI	5.08 [0.85]	4.92 [0.88]	Comparing number of patients $X^2(2, n = 61) = 2.074,$ $p = 0.149793$ number of episodes $X^2(2, n = 61) = 4.642,$ $p = 0.31184$
PP population, number of subjects	28	28	
Visit 6 (week 26): n (%) [number of recurrent UTI episodes]	3 (10.7) [4]	7 (25.0) [11]	
Chi-square test, 95% CI	5.00 [0.80]	5.00 [0.80]	Comparing number of patients $X^2(2, n = 56) = 1.948,$ $p = 0.162821$ number of episodes $X^2(2, n = 61) = 4.4612,$ $p = 0.34661$

twofold reduction in the number of women with recurrent UTIs during supplement administration was impressive. Discontinuations of treatment due to side effects of the product and quality of life assessments regarding urogenital complaints were also important. The mean score of satisfaction regarding the urogenital system was 7 out of 10 in those taking Lactiale Uro and 4 out of 10 in those who were not prescribed this therapy. Presumably, a long-term use of *Lactobacilli*, contained in the product, and vitamin A helped maintain a healthy microflora of the vagina.

Administration of herbal products can significantly improve the course of UTI, sometimes competing with antibiotic therapy [9]. Such studies have recently become more active, which is associated with an increase in antibiotic re-

sistance [10]. However, it should be noted that at least 3 factors contribute to recurrences in postmenopausal women: estrogen depression, changes in the anatomy of the urinary tract, and decreased sexual activity [11, 12].

The LACMUS study, in our opinion, has become a litmus test that demonstrates the capabilities of a dietary product in achieving medical goals. Excellent tolerability of Lactiale Uro, an almost 4-fold reduction in the number of UTI episodes and improvement of the quality of life in postmenopausal women demonstrate the right choice in the search for optimal health status in women over 49 years. However, further research may provide additional data on the efficacy and feasibility of a long-term use of the product.

Table 3. Secondary efficacy endpoints at the end of 26 weeks of treatment

Parameter	Lactiale Uro	P-value	No product
Summary of UTI episodes at the end of 26 weeks of treatment			
FAS population	N = 32		N = 33
Number of episodes			
Visit 6 (week 26), n (%) 0	31 (96.8)		30 (90.9)
1	2 (6.45)		5 (16.6)
2	2 (6.45)		6 (20.0)
PP population	28		28
Visit 6 (week 26), n (%) 0	27 (96.4)		28 (100)
1	2 (7.4)		5 (17.9)
2	2 (7.4)		6 (21.4)
P-value FAS population (Fisher's exact test) for 0 and 1 UTI [95% CI]		0.152	
P-value FAS population (Fisher's exact test) for 0 and 2 UTI [95% CI]		0.093	
Time (days) to first episode of UTI from randomization			
FAS Population, N	31		30
n	4		11
Mean (SD)	136		27
Median	24.3		18.4
P-value (Student's t-test) [95% CI]		P = 0.003810 (t = 3.58)	
Duration (days) of active UTI episode			
FAS Population, N	31		30
n	4		11
Mean (SD)	5		11
Median	1		2
Min, Max	4, 6		4, 30
P-value (Student's t-test) [95% CI]		P = 0.019916 (t = 2.68)	
Duration (days) of antibiotic treatment for an active UTI episode			
PP Population, N	28		28
Number of subjects with an active UTI episode and requiring antibiotic course	4		10
P-value (Fisher's exact test) [95% CI]		0.046289	

Notes: N — number of subjects in given analysis population; n — number of subjects with UTI episode.

A product similar to Lactiale Uro, Pro-Cyan (BKPro-Cyan), containing probiotic strains (*Lactobacillus acidophilus* PXN 35, *Lactobacillus plantarum* PXN 47) and cranberry extract (36 mg/d PACs), is available on the world market for the prevention of recurrent uncomplicated UTIs in premenopausal women. However, various products with similar compositions, based on the presented and prototype studies, are expected to be effective in pre- and menopausal women.

Limitations of the study: small number of patients, lack of placebo control.

Conclusions

1. Lactiale Uro in the LACMUS study showed a significant reduction in the number of recurrent UTI episodes in postmenopausal women compared to those who did not receive it. Lactiale Uro was very well tolerated during a 6-month course; there were no discontinuations of the product.

2. Lactiale Uro showed a significant reduction in urogenital complaints in women with recurrent UTIs, which is probably due to the comprehensive action of the product.

3. The above findings allow us to consider Latiale Uro as an effective agent for the prevention of recurrent UTIs in postmenopausal women, administered as 1 capsule twice daily for at least 6 months.

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript. JSC Farmak sponsored the first month of Lactiale Uro administration, as well as summary and presentation of the materials of the investigator-initiated study.

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Received 18.10.2020

Revised 07.11.2020

Accepted 17.11.2020 ■

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Лактіале Уро в профілактиці сечової інфекції в постменопаузі: результати дослідження LACMUS

Резюме. Мета: оцінити ефективність і безпеку Лактіале Уро, препарату, що містить два штами *Lactobacilli*, екстракт журавлини та вітамін А, в запобіганні повторним інфекціям сечових шляхів (ІСШ) у жінок у постменопаузі (дослідження LACMUS). **Матеріали та методи.** Це було рандомізоване проспективне багатоцентрове дослідження. Суб'єкти отримували Лактіале Уро двічі на день протягом 26 тижнів після одужання від ІСШ; контрольна група препарат не отримувала. Первин-

ною кінцевою точкою була частка пацієнтів із повторними епізодами ІСШ у кінці дослідження. **Результати.** Сімдесят сім жінок пройшли обстеження, у дослідження увійшли 65, а завершила його 61 пацієнтка. Через 26 тижнів у значно меншій кількості жінок відзначені повторні ІСШ при прийомі Лактіале Уро порівняно з тими, хто не отримував лікування (9,7 проти 23,3 %; $P < 0,05$). Використання Лактіале Уро обумовлювало статистично значущі покращення, такі як нижчі показники

епізодів ІСШ (12,9 проти 36,6 %; $P < 0,05$); довший час до першого епізоду ІСШ (136 проти 27 днів; $P = 0,0038$); менша тривалість активного епізоду ІСШ (5 проти 11 днів; $P = 0,0199$); і менша тривалість антибактеріальної терапії активного епізоду ІСШ (4 проти 10 днів; $P = 0,0462$). **Висновки.** Лактиале Уро був

безпечним та ефективним у профілактиці повторних ІСШ у жінок у постменопаузі. Ці дані вимагають подальших добре розроблених досліджень для з'ясування можливих переваг.

Ключові слова: *Lactobacilli*; інфекція сечових шляхів; постменопаузальний період

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Лактиале Уро в профілактике мочевої інфекції в постменопаузе: результаты исследования LACMUS

Резюме. **Цель:** оценить эффективность и безопасность Лактиале Уро, препарата, содержащего два штамма *Lactobacilli*, экстракт клюквы и витамин А, в предотвращении повторных инфекций мочевых путей (ИМП) у женщин в постменопаузе (исследование LACMUS). **Материалы и методы.** Это было рандомизированное проспективное многоцентровое исследование. Субъекты получали Лактиале Уро дважды в день в течение 26 недель после выздоровления от ИМП; контрольная группа препарат не получала. Первичной конечной точкой была доля пациентов с повторными эпизодами ИМП в конце исследования. **Результаты.** Семьдесят семь женщин прошли обследование, в исследование вошли 65, а завершила его 61 пациентка. Через 26 недель у значительно меньшего количества женщин отмечены повторные ИМП при приеме Лактиале Уро по сравнению с

теми, кто не получал лечения (9,7 против 23,3 %; $P < 0,05$). Использование Лактиале Уро обуславливало статистически значимые улучшения, такие как низкие показатели эпизодов ИМП (12,9 против 36,6 %; $P < 0,05$), более долгое время до первого эпизода ИМП (136 против 27 дней; $P = 0,0038$), меньшая продолжительность активного эпизода ИМП (5 против 11 дней; $P = 0,0199$) и меньшая длительность антибактериальной терапии активного эпизода ИМП (4 против 10 дней; $P = 0,0462$). **Выводы.** Лактиале Уро был безопасным и эффективным в профилактике повторных ИМП у женщин в постменопаузе. Эти данные требуют дальнейших хорошо разработанных исследований для выяснения возможных преимуществ.

Ключевые слова: *Lactobacilli*; инфекция мочевых путей; постменопаузальный период