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ORIGINAL ARTICLE

# D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial

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**Abstract**
*Purpose* To test whether D-mannose powder is effective for recurrent urinary tract infection (UTI) prevention.
*Materials and methods* After initial antibiotic treatment of acute cystitis, 308 women with history of recurrent UTI and no other significant comorbidities were randomly allocated to three groups. The first group ($n = 103$) received prophylaxis with 2 g of D-mannose powder in 200 ml of water daily for 6 months, the second ($n = 103$) received 50 mg Nitrofurantoin daily, and the third ($n = 102$) did not receive prophylaxis.
*Results* Overall 98 patients (31.8 %) had recurrent UTI: 15 (14.6) in the D-mannose group, 21 (20.4) in Nitrofurantoin group, and 62 (60.8) in no prophylaxis group, with the rate significantly higher in no prophylaxis group compared to active groups ($P < 0.001$). Patients in D-mannose group and Nitrofurantoin group had a significantly lower risk of recurrent UTI episode during prophylactic therapy compared to patients in no prophylaxis group (RR 0.239 and 0.335, $P < 0.0001$). In active groups, 17.9 % of patients reported side effects but they were mild and did not require stopping the prophylaxis. Patients in D-mannose group had a significantly lower risk of side effects compared to patients in Nitrofurantoin group (RR 0.276, $P < 0.0001$), but the clinical importance of this finding is low because Nitrofurantoin was well tolerated.
*Conclusions* In our study, D-mannose powder had significantly reduced the risk of recurrent UTI which was no different than in Nitrofurantoin group. More studies will be needed to validate the results of this study, but initial findings show that D-mannose may be useful for UTI prevention.

**Keywords** Urinary tract infection · Recurrent · Cystitis · D-mannose · Prophylaxis

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## Introduction

Urinary tract infections (UTI) are common, and it is estimated that around 11 % of women aged over 18 have an UTI each year [1]. Simple isolated cases of UTIs do not cause severe problems for patients. On the other hand, recurrent UTIs (defined as 2 infections in 6 months or 3 or more infections in 1 year) carry a significant burden for the patient and result with high costs to the health system. One study showed that recurrent infections occurred in around 35 to 53 % of women that were treated for UTI within 12 months [2], and overall expenditures for the treatment of UTIs in women in the United States, excluding spending on outpatient prescriptions, were approximately 2.47 billion dollars in 2000 [3]. To prevent recurrent UTIs, two main antibiotic regimes are used: long-term antibiotic prophylaxis or postcoital antibiotics [4]. A large review found that long-term antibiotic prophylaxis (lasting from 6–12 months) significantly reduced the proportion of women with clinical recurrence during prophylaxis compared to placebo, but no conclusions could be made

regarding the optimal duration of prophylaxis, schedule, or doses, so currently there is no consensus on when to start the treatment or on how long it should last [5]. Also, it has been shown that the rate of infection returns to initial levels when prophylaxis is stopped, with up to 60 % of patients having a recurrence within 3 months [4, 6]. Possible side effects (although rare), costs, and increasing bacterial resistance to antibiotics are also the downfalls of long-term antibiotic prophylaxis [5, 7, 8], so alternative prophylactic methods such as cranberry juice, probiotics, and D-mannose have been advocated.

D-mannose is a sugar that has an important role in human metabolism, especially in the glycosylation of certain proteins. The supposed mechanism of action is inhibiting bacterial adherence to uroepithelial cells. In vitro experiments have shown that D-mannose binds to the type 1 pili of enteric bacteria blocking their adhesion to uroepithelial cells, and reduction in bacteriuria levels have been confirmed in in vivo animal models [9–13]. Although the anti-adhesive effect of D-mannose has been clearly established, and many D-mannose powders have been available on the market for prevention of UTIs in human and animals for some time, no clinical trials have been conducted to assess its effectiveness. This led us to conduct a randomized clinical trial to determine the effect of regular intake of D-mannose powder on reducing the rate of recurrent UTI compared to standard Nitrofurantoin prophylaxis and no intervention.

## Patients and methods

This was a prospective, randomized controlled study comparing efficacy of daily D-mannose powder intake for preventing recurrent urinary tract infection.

We recruited patients between October 2010 and October 2012 in Zabok county general hospital and five local general practice centers. Women who had acute cystitis and a history of recurrent cystitis were invited to participate. All patients provided written informed consent for involvement in the study. CONSORT flowchart of the study is shown in Fig. 1.

Criteria for inclusion in the study were age over 18 years, and positive history of recurrent cystitis defined as at least two episodes of acute cystitis in the last 6 months and/or 3 episodes of acute cystitis in the last year. Patients were excluded if they were pregnant, breastfeeding or trying to conceive, had symptoms of upper urinary tract infection and symptoms of systemic inflammatory response (fever over 38 °C, white blood cell count over 12,000), had a history of urinary tract anomalies, interstitial cystitis or diabetes, if they were taking hormone therapy, contraception, or had previously received antibiotic prophylaxis.

Diagnosis of UTI was based on $10^3$ or more colony-forming units (CFU) in 1 ml of clean voided midstream urine, and at least two of the following lower urinary tract symptoms (LUTS): dysuria, frequency, urgency, suprapubic pain, nocturia, and hematuria.

Midstream urine samples were taken, with patients not voiding for at least 3 h earlier and after washing the genital area with sterile water wipe. Urine culture samples were stored at 4 °C and analyzed within 24 h in the county Public Health Department.

Initial UTI was treated with Ciprofloxacin 500 mg twice daily for 1 week, after which the control urine samples were analyzed. Patients with less than $10^3$ CFU/ml in urine culture and no LUTS were considered cured and were randomly divided by throwing the dice in one of the three groups according to the prophylaxis they would receive during the following 6 months: group 1 received 2 g of D-mannose powder (U-tract™, Progressive Laboratories, USA) diluted in 200 ml of water once daily in the evening (as recommended by the manufacturer), group 2 (active control) received 50 mg of Nitrofurantoin (Ninur®, Belupo, Croatia) once daily in the evening, and group 3 (control) that did not receive anything.

Each woman completed an inquiry form giving demographic data, medical history, and nutritional status at entry. For compliance assessment, patients recorded the intake of prophylaxis on a self-report sheet.

When during prophylaxis a participant reported symptoms suggesting UTI, a clean voided midstream urine sample for culture was obtained. We used $10^3$ or more CFU/ml as criterion for recurrent infection. In cases of recurrence, prophylaxis was stopped, antibiotic therapy was prescribed, and the patients were not re-entered in the study. The prophylaxis was discontinued after 6 months (end of study). All patients were contacted by telephone to attend the control appointment 6 months after the start of prophylaxis. The primary study endpoint was the number of patients in each group without recurrent UTI after 6 months.

Statistical analysis was conducted using MedCalc statistical software version 10.3 (copyrighted by MedCalc Software bvba 1993–2010).

The sample size was calculated based on the projection that intervention would decrease cystitis recurrence by 20 %, from 30 % in patients without prophylaxis to less than 10 % in patients receiving prophylaxis. A standard sample size calculation gave 62 patients per group (using a two-sided 5 % significance level) for >80 % power.

We used one-way analysis of variance to determine the significance of differences between groups. Risk of UTI was estimated per group in intent to treat analysis. Time to first recurrence of infection was presented as a Kaplan–Meier curve, and differences between groups were assessed

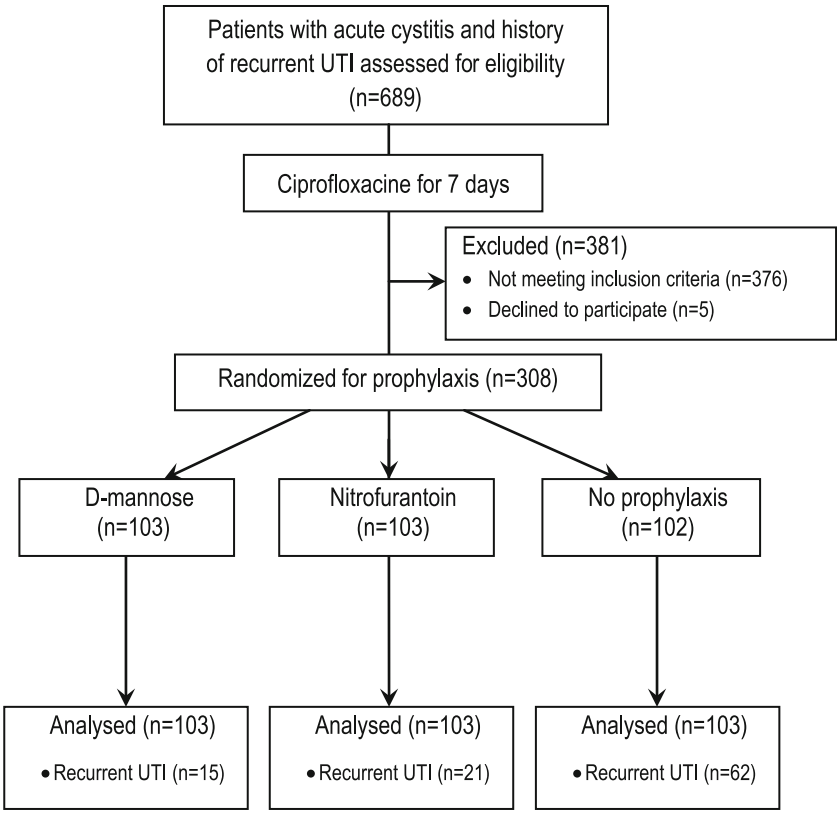


**Fig. 1** CONSORT flowchart of the study protocol

using the log-rank test. Cox regression analysis was used to control for the baseline risk factors for infection.

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki, and within local laws and regulations. The study was approved by the institutional review board in all investigative centers.

## Results

The study included a total of 308 women with acute cystitis and positive history for recurrent cystitis episodes. The groups were similar in their baseline characteristics with regard to the risk of urinary tract infection (Table 1). There were no dropouts from the study. Median patient age was 49 years (range 20–79). Overall, 146 patients were postmenopausal (47.4 %), and median BMI was 28.5 (24.8–33.4). The most commonly isolated bacteria during acute cystitis phase was Escherichia coli in 236 patients (76.6 %), followed by Enterococcus faecalis (17, 5.5 %), Klebsiella pneumoniae (12, 3.9 %), Streptococcus agalactiae (8, 2.6 %), Proteus mirabilis (7, 2.3 %), and Citrobacter freundii (4, 1.3 %) (Table 2). Two microorganisms were isolated in 24 patients (7.8 %). There was no significant difference among groups in isolated microorganisms. Median number of CFU per culture was $10^4$/ml and did not differ among groups. During the prophylactic therapy period, 98 patients (31.8 %) had recurrent UTI and median time from starting the prophylaxis to onset of symptoms was 30 days (range 20–41) (Table 2). The time from starting the prophylaxis to onset of symptoms did not differ significantly between groups. The number of recurrent cystitis episodes was significantly higher in no prophylaxis group compared to D-mannose group and Nitrofurantoin group ($P < 0.001$). Patients in D-mannose group and Nitrofurantoin group had a significantly lower risk of recurrent cystitis episode during prophylactic therapy compared to patients in no prophylaxis group (RR 0.239, 95 % CI 0.146–0.392, $P < 0.0001$ and RR 0.335, 95 % CI 0.222–0.506, $P < 0.0001$, Fig. 2). This is an absolute risk reduction of 45 % compared to the control group. The difference between D-mannose and Nitrofurantoin group was not significant. After standardization for baseline UTI risk factors including age, history of urinary tract infection, and intercourse frequency, the two explaining variables for the prevention of recurrence were intake of D-mannose and Nitrofurantoin prophylaxis ($P = 0.016$, Cox regression analysis).

During prophylactic therapy, 37 patients out of 206 receiving prophylaxis (17.9 %) reported side effects but they were mild and did not require stopping the prophylaxis (Table 2). Patients in D-mannose group had a

**Table 1** Characteristics of patients included in the study

| | D-mannose group ($n = 103$) | Nitrofurantoin group ($n = 103$) | No prophylaxis group ($n = 102$) | *P* |
|---|---|---|---|---|
| Age median (IQR) | 49 (38–56) | 48 (29–58) | 52 (38–56) | 0.06 |
| Education level, *n* (%) | | | | 0.49 |
| Elementary school | 6 (5.8) | 10 (9.7) | 12 (11.8) | |
| High school | 89 (86.4) | 85 (82.5) | 80 (78.4) | |
| Higher education | 8 (7.8) | 8 (7.8) | 10 (9.8) | |
| Sexually active, *n* (%) | 69 (67.0) | 79 (76.7) | 68 (66.7) | 0.20 |
| Intercourse frequency a month median (IQR) | 5 (0–6) | 5 (2–6) | 5 (0–6) | 0.40 |
| Use birth control, *n* (%) | 42 (40.7) | 45 (43.7) | 39 (38.2) | 0.45 |
| Postmenopausa, *n* (%) | 52 (50.5) | 42 (40.8) | 52 (51.0) | 0.25 |
| BMI median (IQR) | 28.5 (22.5–33.2) | 28.5 (25.8–33.6) | 28.6 (24.8–34.5) | 0.24 |
| Cystitis episodes in the last 6 months median (IQR) | 2 (2–5) | 2 (1–5) | 2 (1–5) | 0.68 |

**Table 2** Causative microorganism of the initial UTI and events during prophylaxis

| | D-mannose group ($n = 103$) | Nitrofurantoin group ($n = 103$) | No prophylaxis group ($n = 102$) | *P* |
|---|---|---|---|---|
| Isolated bacteria in acute cystitis *n* (%) | | | | 0.98 |
| *E. coli* | 81 (78.6) | 78 (75.7) | 77 (75.5) | |
| Other | 13 (12.6) | 18 (17.5) | 17 (16.7) | |
| Two microorganisms | 9 (8.8) | 7 (6.8) | 8 (7.8) | |
| Recurrent acute cystitis during prophylaxis, *n* (%) | 15 (14.6) | 21 (20.4) | 62 (60.8) | 0.001 |
| Median time from prophylactic therapy start to cystitis symptoms onset (days) median (IQ range) | 43 (15–50) | 24 (15–36) | 28 (20–42) | 0.12 |
| Complications during prophylaxis, *n* (%) | 8 (7.8) | 29 (27.2) | | 0.001 |
| Diarrhea | 8 (100) | 10 (34.4) | | |
| Nausea | | 6 (20.7) | | |
| Headache | | 3 (10.3) | | |
| Skin rash | | 1 (3.6) | | |
| Vaginal burning | | 9 (31.0) | | |

significantly lower risk of side effects during prophylactic therapy compared to patients in Nitrofurantoin group (RR 0.276, 95 % CI 0.132–0.574, $P < 0.0001$).

## Discussion

The aim of this study was to determine whether D-mannose powder is effective for recurrent UTI prophylaxis in women. D-mannose is widely available for UTI prevention, and the supposed mechanism of action is by blocking bacterial adhesion on the uroepithelial cells. This has been confirmed in vitro and in animal models, but no clinical trial has been undertaken to test its efficacy in clinical practice.

In our study, D-mannose powder was equally efficient in UTI prevention as standard Nitrofurantoin prophylaxis during 6 months. Both groups that received prophylaxis had a significantly reduced rate of recurrent infection compared to the group that did not receive prophylaxis. The overall rate of UTI recurrence was around 30 %, and the rate of recurrence is higher than expected in patients who did not receive prophylaxis (60 %), since in other studies the rate of recurrence was usually from 15 to 53 % in 6 or 12 months period [2, 14, 15]. This can probably be due to several factors such as population characteristics and methodology of other published studies. In our study, half of the participants were postmenopausal, population was rural with lower educational level, and median BMI shows that most were overweight, all characteristics supposed to increase the rate of UTI [2, 16, 17]. Nevertheless, this does not influence the validity of our findings because we also did an analysis for projected UTI recurrence rate of 30 %

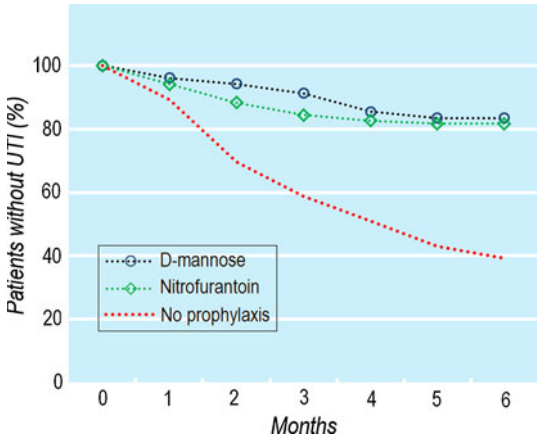


**Fig. 2** Kaplan–Meier plot showing the percentage of patients remaining cystitis-free during the 6-month clinical trial period

in no prophylaxis group. In that case, the difference between both active and no intervention group would still remain significant with $P = 0.01$.

Recurrence rates without prophylaxis in similar studies vary substantially, from 15 to 53 %, but this can be due to different methodology and characteristics of recruited population. For example, one Finnish study [15] reported recurrence of around 35 % after 6 months of follow-up, but the criterion for diagnosing recurrent UTI was $10^5$ or more CFU/ml in urine culture, while our criterion was $10^3$ or more CFU/ml. Also, in several studies [14, 15], patients were recruited for prophylaxis after the first episode of UTI, while we recruited only patients who had a known history of recurrent UTI with at least two episodes in the previous 6 months or three in previous 12 months. All of the mentioned factors can partially explain the higher number of recurrent UTIs in our study. For initial UTI treatment, we prescribed 7 days of Ciprofloxacin because we attempted a bacteriological cure, and such regimen is most likely more efficient [18].

Side effects were more common in patients that used Nitrofurantoin than in patients that used D-mannose, but all reported side effects were mild and did not cause the patients to stop the prophylaxis. The clinical importance of this finding is low because Nitrofurantoin is generally well tolerated by patients with low resistance in *E. coli* (less than 3 %) and complications rarely occur during long-term prophylaxis [19, 20].

There are several limitations to the study. One possible shortcoming of the study lies in the fact that it was not blinded. We estimated that blinding was not necessary in our case because the main followed event (recurrent UTI) was diagnosed based on patients' self-report on recurrent LUTS and confirmation of UTI by positive urine culture, objective finding that minimizes potential bias. Secondly, because of the study design, we could not calculate the total number of recurrences per patient since we did not re-enter the patients into the study after the antibiotic treatment of recurrent infection.

The results of our study show that D-mannose can be an effective prophylactic agent in selected population which can have practical importance. However, more studies will certainly be needed to confirm and validate our results, based on the experience with cranberry products and UTI prevention. It has been shown in multiple in vitro studies that cranberry products inhibit bacterial adherence to uroepithelial cells [21, 22], similarly to D-mannose. But in clinical practice diverging, results have been reported and the usefulness of cranberry products in preventing UTIs has still not been established. Latest Cochrane Database review on the topic concluded that cranberry products cannot currently be recommended for the prevention of UTIs [23], although there are many good-quality studies that clearly showed its effectiveness. A possible cause of opposing results among studies is that in many of them used various cranberry products without clearly defined potency, dosing and active ingredient content which is a well-known problem with all natural remedies. The pharmacokinetic studies that would determine the exact dosage and regimen for D-mannose are also lacking, and should be undertaken.

## Conclusion

In our study, D-mannose powder was shown effective in preventing UTI during 6-month prophylaxis. The recurrence rate did not differ between patient who took standard Nitrofurantoin prophylaxis and those who took D-mannose powder. More studies will be needed to validate the results of this study but initial findings show that D-mannose may be useful for UTI prevention in selected patients.

**Conflict of interest** All authors state that they have no conflict of interest.

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