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D-mannose: a promising support for acute urinary tract infections in women. A pilot study

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Abstract. – OBJECTIVE: Urinary tract infections still represent a significant bother for women and result in high costs to the health system. D-mannose is a simple sugar; it seems able to hinder bacteria adhesion to the urothelium. The present study aimed to determine whether D-mannose alone is effective in treating acute urinary tract infections in women and its possible utility in the management of recurrences.

PATIENTS AND METHODS: This is a pilot study, performed between April 2014 and July 2015 at Department of Gynaecological Obstetrics and Urologic Sciences of "Sapienza" University of Rome. A D-mannose compound was administered twice daily for 3 days and then once a day for 10 days. Changes in patients' symptoms, the therapeutic effects and changes in quality of life (QoL) were evaluated clinically and using a specifically validated questionnaire (UTISA). After described treatment, patients were randomized in receiving or not prophylaxis in the next 6 months.

RESULTS: Mean UTISA scores recorded after completing the treatment, compared with baseline scores, showed a significant improvement of the majority of symptoms ($p < 0.05$). D-mannose seemed to have had a significant positive effect on UTIs' resolution and QoL improvement ($p = 0.0001$). As prophylactic agent administered for 6 months, it showed promising results (4.5% *vs*. 33.3% recurrences in treated and untreated patients respectively).

CONCLUSIONS: The results of this study suggest that D-mannose can be an effective aid in acute cystitis management and also a successful prophylactic agent in a selected population; however, more studies will certainly be needed to confirm the results of our pilot study.

Key Words:
D-mannose, Urinary tract infections, Cystitis.

Introduction

Urinary tract infections (UTIs) are extremely common in women, it is estimated that about 11% of women > 18 years experiment at least one episode of UTIs each year[1].

However these data are underestimated, in fact about 50% of UTI do not come to medical attention. Over 65 years of age, the incidence of UTIs tends to increase due to functional and anatomical problems[1,2].

Isolated cases of UTIs are generally well tolerated by patients but in several occasions recurrent UTIs (defined as 2 infections in 6 months or 3 or more infections in 1 year) have a detrimental impact on the quality of life of these women. Recurrent infections occur in 35-53% approximately of women that were treated within one year[2].

A large review has shown that long-term antibiotic prophylaxis (from 6 to 12 months) significantly reduced clinical recurrences comparing with placebo[3]. Despite that, the optimal duration of prophylaxis, the schedule and the adequate doses remain still on debate.

Other studies confirm that the recurrences of UTIs returns to initial levels when prophylaxis is interrupted, with up to 60% of women facing a relapse within 3 months[4-6].

Considering the possible side effects of a long-term anti-microbic therapy and the high recurrence rates when antibiotics are stopped, alternative prophylactic methods as probiotics, cranberry juices and D-mannose have been introduced and studied.

D-mannose is a simple sugar, a monosaccharide extracted from larch rod, closely related to glucose. D-mannose is rapidly absorbed and in about 30 minutes reaches the peripheral organs, then is excreted by the urinary tract[6,7]. It can't be transformed into glycogen, therefore, is not stored in the body[8]. A long-term use of D-mannose, in concentrations up to 20%, has not shown any side effect on human metabolism[9].

The process of bacterial adhesion on the cell surface is a crucial factor for the onset of most

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infections. This happens because specific lectins on bacterial wall are able to bind molecules such as D-mannose and L-fucose distributed on the human cell surface.

Some virulence mechanisms have been described on several pathogenic serotypes of *E. coli* (known as UPEC, Uropathogenetic *Escherichia coli*), *Salmonella* spp., *Proteus mirabilis* and other bacteria involved in UTIs[10,11].

The bladder wall is coated with various mannosilate proteins, such as Tamm-Horsfall protein (THP) that interfere directly with the adhesion of bacteria on the mucosa. THP may fasten to *E. coli* with a specific bond, which may be inhibited by exogenous D-mannose[12]. This evidence suggests that D-mannose could be important in treating UTIs mediated by mannose specific binding, particularly determined by *E. coli* fitted out an exclusive virulence factor called FimH, mostly responsible of UTIs. By inhibiting the adhesion of bacteria to the urothelium, D-mannose mimics urothelial barrier function. Binding free D-mannose in the urine rather then proteins on the vescical cells surface, bacteria are trapped in the urinary flow and consequently eliminated by the urinary tract.

Studies *in vivo* and *in vitro* have demonstrated the ability of mannose-like molecules in reducing bacterial load of 2-times in the urinary tract and over 4-times intravescical[12-14].

A strong scientific rationale seems to sustain the effectiveness of D-mannose in inhibiting bacterial adhesion responsible for UTIs by increasing the clearance of bacteria in the urine, thereby reducing the risk of infection[11,14]. Some authors show an excellent tolerability and safety of D-mannose, during a long-term administration also[9-15].

The aim of our study is to evaluate the efficacy of D-mannose alone in treating and solving acute urinary infections.

Patients and Methods

This is a pilot study on the efficacy and safety of D-mannose for acute uncomplicated cystitis and for preventing recurrences. We enrolled patients between April 2014 and July 2015 in the Department of Obstetrics and Gynaecology of "Sapienza" University of Rome. Women who had acute cystitis and/or history of recurrent UTIs were invited to participate. Written informed consent was obtained by all patients. Institutional Review Board has approved the study.

UTISA (Urinary Tract Infection Symptoms Assessment) validated questionnaire was administered to all enrolled patients[15]. It is a 14-item instrument asking about the severity of seven key UTI-related symptoms (Table I). The questionnaire was developed on the basis of the results of a series of comprehensive reviews to identify the key symptoms associated with UTIs.

Criteria for inclusion in the study were women aged between 18 and 65 years with symptoms of acute cystitis (dysuria, frequency, urgency, supra-pubic pain, nicturia, and haematuria) or asymptomatic with diagnosis of UTI (defined as 10^3 or more colony-forming units – CFU – in 1 mL of clean voided midstream urine). Patients were excluded if they had a history of urinary tract anomalies, acute symptoms > 1 week before the first visit, if they were pregnant, breastfeeding or trying to conceive, if they had symptoms of upper urinary tract infection and symptoms of systemic inflammatory UTI (fever over 38°C, white blood cell count over 12,000), if they were taking hormone therapy, interstitial cystitis or diabetes, use of catheter of intermittent self-catheterisation, or had previously received antibiotic prophylaxis, patients unable to fill the questionnaire.

Mannocist® (Laboratori Farmaceutici Krymi, Rome, Italy) is a soluble drug composed of D-mannose (1.5 g), sodium bicarbonate, sorbitol and silicon dioxide.

D-mannose (Mannocist® – Rome, Italy) was administered twice daily for 3 days and then once a day for 10 days. Changes in patients' symptoms, the therapeutic effects and changes in quality of life were evaluated using UTISA (Urinary Tract Infection Symptoms) score.

Table I. Patients' characteristics.

Age (years), mean ± SD	46.7 ± 5.7
BMI (kg/mq), mean ± SD	22.5 ± 4.1
High education level, n (%)	
Secondary and tertiary education	34 (79.0%)
Sexually active, n (%)	30 (69.7%)
Post-menopause, n (%)	22 (51.2%)
Use of contraceptives, n (%)	9 (20.9%)
Episode of cystitis in the last 6 months, mean ± SD	2.3 ± 1.7
Isolated bacteria in acute cystitis, n (%)	
E. coli	35 (81.4%)
Other	6 (13.9%)
Not available	2 (4.6%)

Table II. The scoring of the severity of the lung tissue injury during the disease process.

Moderate-severe symptoms prevalence (UTISA score 2-3)	Patients, n=43 (%)
Dysuria	27 (70.7%)
Increased frequency	30 (73.2%)
Urgency	26 (63.4%)
Tenesmus	10 (23.2%)
Suprapubic pain	18 (41.8%)
Backache	14 (32.5%)
Hematuria	5 (12.2%)
Nicturia	22 (51.2%)

The primary endpoint was to assess symptom cure according to the UTISA severity subcategories (dysuria, frequency, urgency, supra-pubic pain, gross haematuria), based on improvement from baseline. Each item was scored according to a severity-related scale including "did not have", "mild", "moderate", and "severe". Score ranging from 0 to 3. Treatment success or failure was assessed based on the standard UTISA questionnaire at the 15-day follow-up visit. The impact of these symptoms and of their improvement/worsening on quality of life was also investigated. Additionally a urine culture was performed at the end of the therapy, just to confirm the absence/no of bacteriuria.

Based on their responses to the question, "Since you last completed this questionnaire, have there been any changes in your urinary tract infection symptoms?", patients were classified into the treatment success group (answered "better") or the treatment failure group (answered "about the same" or "worse"). Clinically, patients in the treatment failure group were addressed to start antibiotic administration and therefore re-evaluated. No side effects were recorded during treatment.

After completing the treatment, patients were also consecutively randomized in receiving or not a prophylaxis with D-mannose for 6 months (once a day for a week every other month).

During the study period, patients were encouraged to contact a dedicate team of the department if they had any concerns. Patients were prohibited from using systemic antibiotic agents at any time during the trial.

Statistically Analysis

All values are presented as mean ± standard deviation (SD). Paired, independent *t*-tests and the Pearson's Chi-square test were used to determine the significance of differences before and after treatment. A p-value <0.05 was considered statistically significant.

Results

Forty-three patients of 45 initially enrolled complete the treatment according with the instruction provided (two of them were excluded due to antibiotics use for other infections incurred in the study period). Mean follow up was 11.8 months (range between 8.2 and 14 months). Two of these 43 patients had no resolution of symptoms and they needed the addiction of antibiotic therapy to resolve the infection.

UTISA questionnaire has been administered and filled by all patients.

Patients' characteristics were shown in Table II. All patients included in the study were symptomatic and 88.4% (n = 38) had positive urine cultures. At our first clinical evaluation, most of women had moderate (score 2) or severe (score 3) dysuria (n = 29; 70.7%). Increased frequency was registered in 73.2% (n = 30) while urgency

Table III. Severity of UTIs associated symptoms at baseline (time zero) and at 15-day follow up visit.

Symptoms	Time zero (mean score ± SD)	After 15 days (mean score ± SD)	*p*-value
Dysuria	1.60 ± 1.00	0.31 ± 0.47	0.0001
Frequent voiding	2.16 ± 1.52	0.60 ± 0.63	0.0001
Urgency	1.73 ± 0.92	0.23 ± 0.43	0.0001
Tenesmus	1.16 ± 0.95	0.15 ± 0.36	0.0001
Suprapubic pain	1.47 ± 0.95	0.15 ± 0.36	0.0001
Backache	0.89 ± 1.18	0.57 ± 0.85	0.152
Hematuria	0.34 ± 0.90	0.10 ± 0.45	0.121
Nicturia	1.68 ± 1.35	0.55 ± 0.64	0.008

Table IV. Impact of symptoms' severity on quality of life: comparison between first evaluation and after completing treatment.

Symptoms	Impact on QoL at time zero (mean score ± SD)	Impact on QoL after 15 days (mean score ± SD)	*p*-value
Dysuria	1.50 ± 1.00	0.57 ± 0.75	0.0001
Frequent voiding	2.26 ± 0.82	0.23 ± 0.48	0.0001
Urgency	2.23 ± 1.05	0.31 ± 0.47	0.0001
Tenesmus	1.07 ± 1.04	0.28 ± 0.69	0.0001
Suprapubic pain	1.57 ± 1.13	0.18 ± 0.56	0.0001
Backache	1.02 ± 1.38	0.97 ± 1.34	0.865

*When compared to the BLM experimental group over the same period of time, $p<0.05$; #Comparison of NHUMSCs group and APHUMSCs group over the same period of time, $p<0.050.05$

in 63.4% (n = 26) of patients. Haematuria was reported in 5 women (12.2%) and 2 of them required antibiotics.

Mean scores recorded after completing the treatment, compared with baseline UTISA scores, showed a significant improvement of the majority of symptoms (Table III). No statistical differences were recorded concerning backache, probably because it represents one of the least specific symptoms of UTIs ($p = 0.152$). Also haematuria demonstrated no statistically significant variation in scores; we reckon that haematuria is more often associated with severe infections. In fact, as observed in our study, two of patients with haematuria required antibiotic therapy.

Concerning quality of life assessment, UTIs related symptoms seem to have a detrimental effect on women lives (Table IV).

After 15 days, cultures performed resulted negative in 90.7% of patients (n = 39). Comparing with baseline results of cultures, D-mannose seemed to have had a significant positive effect on UTIs' resolution ($p = 0.0001$).

One month after diagnosis patients were consecutively randomized in two groups: some women received prophylaxis (n = 22) and others remained untreated (n = 21).

Of those treated with D-mannose a week per month every other month, 1 (4.5%) had a recurrence within 6 months (Table V). Despite that, in 7 women (33.3%) of the untreated group recurrences were observed ($p = 0.05$). The mean time to UTIs onset was 43 days (± 4.1 SD) in the group undergoing prophylaxis and 28 (± 5.4 SD) in the other one ($p = 0.0001$). Treatment did not present any side effect also in a long-term schedule.

Discussion

Acute uncomplicated cystitis is a frequent condition that in most cases may be successfully diagnosed and treated[1-3]. Management of acute uncomplicated cystitis is evolving due to increasing antimicrobial resistance confines selections for oral therapy[5,6]. The aim of this study was the evaluation of the efficacy of D-mannose (Mannocist® – Rome, Italy) alone in solving and preventing UTIs in women.

D-mannose is widely accessible for UTI prevention, and the hypothetical mechanism of action is by blocking bacterial adhesion on the uroepithelial cells[8].

Very few studies, even showing promising results, are still present in the literature about the use of D-mannose based compounds as first choice in cystitis' treatment[17-19].

For example, in his study on 33 subjects, Vicariotto[17] reported that typical and uncomfortable symptoms of cystitis, specifically dysuria, fre-

Table V. UTIs recurrences in patients receiving prophylaxis vs untreated patients.

Symptoms	D-mannose group (n=22) (n=21)	Untreated group	*p*-value
Recurrent acute cystitis during prophylaxis, n (%)	1 (4.5%)	7 (33.3%)	0.05
Median time from prophylactic therapy start to cystitis symptom onset, days (mean ± SD)	43 ± 4.1	28 ± 5.4	0.0001

SD: standard deviation.

quent voiding, urgency and supra-pubic pain were significantly improved by using D-mannose and cranberry extract based compound.

In our study, D-mannose attested significant effects on specific symptoms control, such as on dysuria, pollachiuria, urgency, supra-pubic pain, tenesmus and nicturia (Table IV). No statistically significant differences were observed regarding backache ($p = 0.152$) and haematuria ($p = 0.121$).

This is probably related to the fact that backache is not only ever associated with cystitis and haematuria is a trait of more severe urinary infections. Also in other studies[17,19] no significant differences in the prevalence and severity of haematuria were recorded.

As confirmed by our study, UTIs related symptoms affect women's lives deeply; for this reason, symptoms' resolution has to be considered a milestone in UTIs treatment and management.

Nevertheless, no differences in terms of QoL improvement were registered after treatment in symptoms as haematuria, backache and nicturia ($p = 0.178$, $p = 0.865$ and $p = 0.823$, respectively). Lacking their specificity, these symptoms frequently indicate the presence of others diseases.

Avoiding recurrences represents another bedrock of UTIs medical policy. The overall rate of UTIs recurrence was 4.5% in the group treated with D-mannose, lower than the rate of recurrence in patients who did not get prophylaxis (33.3%). In other studies, the rate of recurrence was usually from 15 to 53% in 6 or 12 months period[2,20,21].

The present trial had some limitations. Firstly, it referred to a small sample size. Secondly, a placebo effect could not be excluded from the measurement of the subjective QoL effects during prophylaxis.

On the other hand, the strengths of this study included the demonstration of the efficacy and safety of D-mannose in managing UTIs and its possible role in averting relapses. Moreover, by introducing this single agent use to treat uncomplicated acute cystitis, the duplication of multidrug resistant pathogens might be avoided. Additional studies are needed to support and validate these preliminary results.

Conclusions

Confirming our main endpoint, D-mannose (Mannocist® – Rome, Italy) seems to own good efficacy and to be well tolerated in both pre- and postmenopausal women with history of UTIs. Moreover, D-mannose demonstrated its effectiveness in reducing the incidence of UTI in a 6-month period and consequently in increasing QoL. Given this evidence, its administration might be beneficial in the prevention of UTIs in selected women population.

Randomized clinical trial will be required to validate and confirm the results of this study, considering particularly our small sample size. Our initial findings illustrate that D-mannose might be effective for UTI treatment and prevention in selected patients with uncomplicated acute cystitis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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