Abstract

Objective: To assess the feasibility of using D-Mannose, a natural food supplement, in patients with multiple sclerosis (MS) reporting recurrent urinary tract infections (UTIs) as a preventative.

Methods: A single-centre, open-label, feasibility study enrolled patients with MS, using and not using urinary catheters, experiencing recurrent UTIs (≥3/year or ≥2/6 months). Participants were given D-mannose powder 1.5 grams twice daily for 16-weeks and were instructed to monitor suspected UTIs at home using urine dipsticks. Diaries were used to record compliance, number of prescriptions of antibiotics received for UTIs, results of urine dipsticks and cultures.

Results: Overall, 22 patients with MS, median age 50 years (46-59) were enrolled: 10 were not using catheters and 12 were using catheters. The compliance rates for using D-Mannose and dipsticks for testing suspected UTIs were 100% and 90.2% respectively. Sixty-one episodes of suspected UTIs were recorded, 19/61 (31.1%) were confirmed UTIs and 29/61 (47.5%) prescriptions of antibiotics were made. The number of monthly proven UTIs decreased both in catheter users and non-users ($p<0.01$). No adverse effects were reported.

Conclusion: Using D-mannose in patients with MS experiencing recurrent UTIs and self-monitoring for infections is feasible and safe. Further studies are required to establish efficacy. *CinicalTrials.gov (identifier NCT02490046).*

Keywords: multiple sclerosis; recurrent urinary tract infections; D-Mannose; compliance; antibiotics; dipsticks

Introduction

Urinary tract infections (UTIs) commonly occur in patients with multiple sclerosis (MS) reporting lower urinary tract (LUT) dysfunction and are reported in 30% (ranging from 13% to 80%) of patients.[1–3] Factors that predispose to UTIs have been poorly investigated in patients with MS, though postulated risk factors are incomplete bladder emptying, the use of a catheter, either intermittently or indwelling, and female gender.[4] Infections occur more often in the MS population compared to the general population.[5] and is one of the top three non-neurological causes for hospitalization, with a reported rate of 30-50% of all inpatient admissions.[5,6] Recurrent UTIs are associated with significantly raised morbidity and mortality rates, triggering of relapses and have a detrimental impact on quality of life.[7] Despite this, only a few options are available for preventing recurrent UTIs, antibiotic prophylaxis being the most common despite the lack of studies in MS.[8,9] The use of oral antimicrobial prophylaxis for preventing UTIs in neurological patients with LUT dysfunction was not supported in a meta-analysis by Morton et al.[10] and is currently not recommended as a routine by NICE (National Institute for Health and Care Excellence).[11] Moreover, there are several disadvantages to using antibiotics over long periods including adverse reactions, increasing risk for bacterial resistance and costs.[10] Therefore, alternative prophylactic agents have been explored. Studies evaluating cranberry extracts have reported conflicting results[12,13] with one specifically looking at patients with MS (n=171)[14] not showing any significant reduction in UTI rates.

D-mannose is a monosaccharide isomer of glucose naturally found in the body and plays a role in human metabolism through the glycosylation of proteins. There is evidence to suggest that D-mannose inhibits bacterial adherence to urothelial cells.[15] In vitro experiments have shown D-mannose binding to FimH adhesion located at the tip of type 1 fimbria of enteric bacteria.[15] During bacterial colonization, FimH binds to carbohydrate-containing glycoprotein receptors on the epithelium of the urinary tract.[16] D-mannose shares similarity in

structure to these urothelial glycoprotein receptors and therefore acts by competitively inhibiting bacterial adherence. In vivo experimental studies in rat UTI models have shown that D-mannose can significantly reduce bacteriuria by a factor of 10 on the first and third days after D-Mannose inoculation, and by a factor >100 on days 5 and 7.[17] A randomised controlled study that compared D-mannose, nitrofurantoin and no treatment in a group of 98 women with recurrent UTIs demonstrated that D-mannose powder significantly reduced the risk of recurrent UTIs by 45%, comparable to the effects of prophylactic nitrofurantoin.[18] Moreover, side effects were significantly lower in D-mannose users compared to the nitrofurantoin group. More recently, a pilot study conducted in women without neurological disease demonstrated safety and efficacy of D-mannose compared to trimethoprim/sulfamethoxazole prophylaxis.[19] Therefore, D-Mannose seems to be a viable option for the prevention of UTIs in a susceptible population. The objective of the study was to assess the feasibility of using D-Mannose in patients with MS reporting recurrent UTIs in preventing UTIs.

Materials and methods

Participants

This prospective single-site open-label feasibility study enrolled patients with MS with LUT symptoms (ie. urinary urgency, frequency, urinary incontinence, incomplete bladder emptying) and reporting recurrent UTIs between February 2015 and August 2015 after obtaining written informed consent. Two groups of patients were considered: those who were not using urinary catheters and those who were using catheters. The inclusion criteria included: clinically stable MS (relapsing or progressive) for at least three months, a history of recurrent UTIs (defined as having ≥ 2 proven UTIs in the preceding six months or ≥3 proven UTIs in the preceding one year[20] and age between 18 and 65 years. Exclusion criteria included pregnancy or patients planning to become pregnant during the study period, females

of childbearing potential with no effective contraception, patients with history of congenital urinary tract anomalies, interstitial cystitis, diabetes mellitus, current UTI or vaginal infection and any known allergies to D-mannose. Data including demographic characteristics, past medical history, vital signs, weight, physical examination, concomitant medications, symptoms of a UTI and standardised validated questionnaires to assess LUT symptoms (International Consultation on Incontinence Questionnaire- Overactive Bladder ICIQ-OAB,[21] Short-Form- Qualiveen SF-Qualiveen[22] and EuroQoL five-dimensional 5-level version EQ5D-5L[23]) were collected at baseline and week 16.

Protocol

Participants were asked to take D-Mannose powder (Nature supplies, D-Mannose Ltd, Co Durham, UK) 1.5 grams twice daily, added to any beverage, for 16 weeks. Patients were not on any other prophylactic measures for preventing recurrent UTIs during the course of the study. Patients maintained a diary to record usage of D-Mannose and any side effects. Compliance was assessed through weekly returns of the usage diary, phone calls at weeks 1 and 8 of the treatment, and by weighing and counting containers at week 16.

Participants were instructed to self-monitor suspected UTIs. At the initial study visit they were educated about the symptoms and signs of UTIs including the presence of cloudy malodorous urine, haematuria, fever, feeling unwell, painful micturition, recent worsening of urgency/frequency/incontinence, suprapubic/flank pain, loin or abdominal discomfort, leakage between intermittent self-catheterization, catheter blockage, reduced appetite, and otherwise unexplained deterioration of pre-existing neurological condition or mobility and/or increasing spasticity [3]. They were taught to use combined rapid urinalysis reagent strips (urine dipsticks) (Nature supplies, D-Mannose Ltd, Co Durham, UK) and read the results for leukocyte esterase and nitrites. General practitioners (GPs) were informed about the study

and were asked to evaluate participants with abnormal urine dipsticks (positive leukocytes and/or nitrites) for suspected UTIs including sending a sample to the lab for culture, and commence antibiotics, according to standard clinical practice.[24] Participants maintained a UTI diary where the date of suspected UTIs, symptoms, results of urine dipsticks, results of culture and the name of antibiotics prescribed and the duration of treatment were recorded. Patients were asked to continue D-Mannose if they developed a UTI.

Endpoints

The primary endpoint was the D-mannose compliance over the 16-week course recorded on the compliance diary and expressed as a percentage. A weekly compliance rate of 100% signifies that the patient took D-Mannose twice a day for seven days. An overall compliance rate to D-Mannose was calculated based on the weekly compliance rates of each patient.

Additional endpoints assessed the number of episodes of suspected UTIs, number of proven UTIs, the number of antibiotic prescriptions, results of urine dipstick test and accuracy of the test, urine culture results, safety of D-Mannose and the wish to continue D-Mannose at the end of the study.

Statistical analysis

Reported values were expressed as mean and ranges, median and interquartile range or as frequency and their corresponding percentages. Student's t test and Wilcoxon's sign rank test were used to compare variables, as appropriate. A P-value of <0.05 was considered significant. All analyses were performed using GraphPad prism version 5.0a (GraphPad Software, 2007 La Jolla, CA, USA).

The study was approved by local ethic approval (NRES Committee London-City Road & Hampstead, REC number 14/LO/2262) and registered with CinicalTrials.gov (identifier NCT02490046).

Results

Overall, 25 patients were screened and 22 patients (18 female, 4 men), median age 50 years (46.2-59) were enrolled in the study (3 patients excluded because two of them were planning pregnancy and one was recently diagnosed with diabetes). Participants were split into two groups: group 1 included patients with MS who were not using catheters (n=10) and group 2 those who were using catheters (n=12; 9 using intermittent-self catheterizations and 3 suprapubic catheters). The baseline characteristics are shown in table 1. One patient was lost to follow-up in group 1 and two early withdrawals occurred in group 2 (one patient experienced an MS relapse immediately after inclusion and before starting D-Mannose, one patient known to have epilepsy required hospitalization for seizures).

In group 1 (n=10), the mean compliance rate was 99.7% (range 97.8-100; median 100% (IQR 99.7-100). Seven patients had a compliance rate of 100%. The most common reason cited for not taking D Mannose was a failure to remember (n= 2) and generally feeling unwell (n=1). One patient mistakenly understood that D mannose should be stopped if a UTI occurred and was lost to follow up at week 11. No significant changes were observed in SF-Qualiveen, ICIQ-OAB, EQ5-5DL, EDSS scores or weight over the study period.

In group 2 (n=11), the mean compliance rate was 99.4% (range 93.7-100; median 100% (IQR 100-100). Nine patients had a compliance rate of 100%. The reason cited for not taking D Mannose was failure to remember (n=1), feeling sleepy (n=1), feeling sick (n=1) and seizure recurrence in an epileptic patient known to have frequent seizures (n=1). No adverse reactions to D-Mannose were reported. No significant changes were observed in SF-

Qualiveen, ICIQ-OAB, EQ5-5DL, EDSS scores or weight over the study period.

Overall, 61 episodes of possible UTIs were recorded based on symptoms and signs. In 55/61 (90.2%), patients used urine dipsticks at home and recorded the results in the UTI diary. There were no recorded difficulties in using dipsticks, however in 6/61 (8.8%) episodes patients did not feel confident in their ability to interpret the results of dipsticks and therefore visited their GP for advice. In 80% of episodes when the dipstick test was negative, patients felt confident about not having an infection and symptoms resolved without further investigations or treatments. Eight patients (4 in each group) remained free of UTIs during the study period.

Nineteen out of the 61 episodes (31.1%) were confirmed UTIs by culture. The median total number of symptomatic UTIs proven by urine culture was lower in group 1 (0.5 (0-1)) compared to group 2 (1 (0-2)) (table 2). The number of monthly proven UTIs significantly decreased in both groups ($p<0.01$), by 75% in group 1 (0.5 to 0.12) and by 63% in group 2 (0.67 to 0.25).

A total of 29 prescriptions for antibiotics were made between these 61 episodes of suspected UTIs (47.5%). Antibiotics were prescribed without bacteriological evidence of UTIs in 10/61 (16.4%) episodes. The median number of prescriptions was 1 (0-2.2) in group 1 and 2 (0-3) in group 2 (table 2). Table 3 shows the accuracy of the dipstick test for the diagnosis of culture-proven UTIs. In patients not using a catheter, the specificity and positive predictive value of a test being positive both for leukocytes and nitrites was high (100%) compared to patients using a catheter (58% and 54% respectively). In patients using a catheter, a test being negative for both leukocytes and nitrites had a specificity of 83%.

At the end of the study, eight patients (80%) in group 1 and ten patients (90.9%) in group 2 expressed a desire to continue taking D-Mannose.

Discussion

In this study, we report that it is feasible for patients with MS experiencing recurrent UTIs to use D-Mannose, and that this was very well tolerated without any safety concerns. Indeed, the compliance for using D-Mannose was high (99.7% in group 1 and 99.4% in group 2). Moreover, the number of proven UTIs was reduced and the number of prescriptions of antibiotics was low. Notably, most patients in our study population were females and had a high EDSS score; these are two factors that have been reported to increase the likelihood of UTIs in MS.[3] Awareness about D-mannose is growing and only recently has it become available in the United Kingdom over the Internet. Randomized controlled trials suggested a benefit of using D-mannose in non-neurological women experiencing recurrent UTIs.[18,19] However, no clinical trials have been undertaken to test feasibility of using D-mannose amongst neurological patients.[3,25] D-mannose is safe product, classed as a food supplement, with no significant safety signals identified in open label studies, with only diarrhoea rarely reported.[18,19] The results of our study were in line with these reports.

Our preliminary results seem to suggest a significant reduction in number of UTIs (by 75% in patients without catheter and by 63% in those without) though as the study was designed to evaluate only feasibility, no conclusions could be drawn about efficacy, however the results are encouraging and clearly, a randomized controlled study designed to evaluate efficacy is required.

The study additionally used a model of follow-up using home-based self-monitoring of UTIs based on patient education and urinalysis using dipsticks. Urine dipsticks test appear to be a rapid and cost-effective test to help test for the diagnosis of UTIs. Testing for nitrites and leukocyte esterase has been shown to be useful to screen for an infection, associated with a high negative predictive value.[26] We chose to incorporate home-based urinalysis in this study as urine dipsticks are often used already by patients with MS in our service. In patients not using catheters, the specificity and positive predictive value of a positive result for both

leukocyte esterase and nitrites were high. However, the relevance of a positive result for one of these tests is uncertain and indeed in both groups, urine cultures were most often negative. A review with the GP is still advisable, as relying only on the urine dipstick test results in such a situation may result in might result in higher rates of overtreatment.[27]

In patients using catheters, the value of the dipstick tests is less clear, because of the high prevalence of abnormal findings and asymptomatic bacteriuria.[20] In this group in particular, symptoms and signs would guide the decision-making process.[3]

In an emerging health care system of shared decision making,[28] the decision to use antibiotics for a UTI is based on a set of complex processes including need recognition, information search and evaluation processes governed by the relationship and interactions between the physician and the patient.[29] Matching this patients in our study were first instructed to recognize symptoms and signs of UTIs.[3] They were asked to go to their GP in case of positive dipsticks, severe symptoms or if they did not feel confident in reading the results of the dipsticks. In 55 of the 61 episodes of suspected UTIs, the urine dipstick test was performed at home (90%), and in about 80% of the time when the dipstick test was negative, the patients felt confident to self-manage without seeking the advice of the GP and symptoms resolved without further investigations or treatments. These results suggest that it is indeed feasible for patients with MS to self-monitor UTIs at home after being educated about symptoms of UTIs and using urine dipsticks. This should be studied in a larger population of patients with MS however before being adopted in a care pathway.

Conclusion

Recurrent UTIs are a significant problem in patients with MS and current available options are limited. This study demonstrates the feasibility of using D-mannose in patients with MS experiencing recurrent UTIs and self-monitoring for infections, without any safety concerns.

The use of D-mannose seems to be associated with a reduction in the number of UTIs and further studies are required to establish efficacy. A self-monitoring of UTIs at home after being educated about symptoms of UTIs and using urine dipsticks is a feasible care pathway strategy to adopt in patients with MS without catheter use and needs to be assessed in a larger population.

Abbreviations:

UTI: urinary tract infection

MS: multiple sclerosis

LUT: lower urinary tract

MS: multiple sclerosis

GP: general practitioner

Conflict of interest:

The Authors declare that there is no conflict of interest.

Tables

Table 1. Patients' baseline characteristics

Table 2. Number of prescriptions of antibiotics and of UTIs during the 16 weeks of treatment by D-Mannose

Table 3. Accuracy of the urine dipstick tests

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Table 1. Patients' baseline characteristics

Characteristics	Group 1 Without catheter (n= 10)	Group 2 With catheter (n= 12)
Age, years	51 (48-59.5)	48.5 (41.7-58.7)
Gender, n (male/female)	0/10	4/8
Time since MS diagnosis, years	14.5 (8.7-25.2)	15.5 (3.7-20.5)
Type of MS - **primary progressive** - **relapse remitting** - **secondary progressive**	 2 5 3	 2 7 3
EDSS score	6.2 (5.5-6.5)	6.2 (6-7)
Lower urinary tract symptoms - **storage symptoms** - **voiding symptoms** - **mixed**	 7 3 0	 7 3 2
Number of UTIs per month in the preceding 6 months	0.5 (0.4-0.7)	0.7 (0.5-1)

Data are expressed in median, interquartile range (25^{th}-75^{th} percentile)

MS: multiple sclerosis, EDSS: Expanded disability status scale, UTI: urinary tract infection

Table 2. Number of symptomatic UTIs and antibiotic prescriptions in pwMS during 16-weeks treatment with D-Mannose

	Group 1 without catheter (n= 10)	Group 2 with catheter (n= 12)
Number of symptomatic UTIs per month	0.1 (0-0.2)	0.2 (0-0.5)
Number of antibiotic prescriptions	1 (0-2.2)	2 (0-3)
Total duration of antibiotic therapy (days)	7 (5.5-7)	7 (7-10)

Data are expressed in median, interquartile range (25^{th}-75^{th} percentile)

UTI: urinary tract infection; PwMS: people with multiple sclerosis

Table 3. Accuracy of urine dipstick tests when culture was performed (n= 37)

	Group 1 PwMS without catheter (n=10)			Group 2 PwMS with catheter (n=12)		
	Leukocytes (+) *and* nitrites (+)	**Leukocytes (+) *or* nitrites (+)**	**Leukocytes (-) *and* nitrites (-)**	**Leukocytes (+) *and* nitrites (+)**	**Leukocytes (+) *or* nitrites (+)**	**Leukocytes (-) *and* nitrites (-)**
Sensitivity	50%	50%	NA*	60%	10%	30%
Specificity	100%	0%	NA*	58%	58%	83%
Positive predictive value	100%	29%	NA*	54%	17%	60%
Negative predictive value	71%	0%	NA*	64%	44%	59%

*NA: not applicable- urine culture was not sent when the dipstick was negative for both leukocytes (leukocyte esterase) and nitrites

PwMS: people with multiple sclerosis