Intravesical Microdox versus normal saline bladder instillation for recurrent urinary tract infections: A Randomised Controlled Trial.

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**Background**

Urinary tract infections (UTIs) are the most common outpatient infections, with a lifetime incidence of 50−60% in adult women. Close to 10% of postmenopausal women indicate that they had a UTI in the previous year (1). The high prevalence of recurrent UTIs represents a modifiable determinant for both societal and personal burdens, hence the importance of disease prophylaxis. Consultations for UTIs represent between 1% and 6% of all medical visits (1)

There is now increasing concern regarding progressive antibiotic resistance, and emergence of multi-drug resistant pathogens. Recent data from the Asia-Pacific region has suggested over half of urinary E. coli isolates were resistant to fluoroquinolones (levofloxacin, ciprofloxacin), and >30% were resistant to third-generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime) (2).

Recurrent UTI’s is defined as 3 or more infections in one year. A misperception is that it often is not reinfection, but rather persistence of the same infection. The main reason for persistence is intracellular bacteria and biofilms. (4). Biofilms are highly organised, surface-attached microbial communities formed when micro-organisms become embedded in a mixture of extracellular matrix composed of extracellular DNA, polysaccharides and proteins (5). Biofilms render encased microorganisms resistant to host-defence mechanisms such as phagocytosis, they also hamper the ability of antibiotics to reach bacteria within the biofilm (6). Around 30% of women that develop a urine infection will have persistence of the infection after a short course of antibiotics. (7). Short courses of oral or IV antibiotics can clear dividing extracellular or planktonic microbes but do not eradicate the intracellular bacteria or the biofilm. The bacteria can then increase in numbers with time and symptoms return.

Testing for UTI’s has recently become debatable. The traditional MSU was validated by Kass et al in 1957 and was based on pyelonephritis (8). Unfortunately, recent research has showed that MSU’s are less reliable than previously thought with sensitivity as low as 50% (9). A more sensitive test for UTI’s is likely to be pure symptoms or pyuria on a freshly spun sample. This has now been shown to correlate closely with the patient’s symptoms, cytokine analysis and cytology of the urine (10).

Specificity of MSU’s has been questioned given emerging evidence that documents the presence of urinary microbiota in many adult women. It is clear that the mere presence of an organism without symptoms should not prompt antibiotic treatment (11).

Current first line treatment for recurrent UTI’s is long term low-dose antibiotics (12). A large meta-analysis showed reduction in symptomatic UTI against placebo of 85%. There were, however, more adverse events (AEs) in the antibiotic group (14). The adverse events most commonly included vaginal and oral candidiasis and gastrointestinal symptoms. The incidence of antimicrobial multi-resistance within post-menopausal women suffering from rUTI is around 25% and was shown to rise to more than 80% following prolonged antibiotics (15).

Other preventive oral therapies have also been studied and utilised, such as Hiprex (methenamine hippurate) and oral D-mannose supplements; all with variable effect. Evidence for non-antibiotic treatments is variable. Vaginal oestrogens, D-mannose, immunotherapy, and Hiprex look most promising. Recent evidence suggests that there is little benefit from previously utilised treatments such as Cranberry, Ural, and probiotics (15).

Intravesical gentamicin appears effective for both prevention and treatment of UTIs, with some evidence to suggest it also results in less resistant organisms. However, relapse rates are high after cessation of gemtamicin instillation; one study had a very small number of patients with elevated serum gentamicin levels following intravesical administration. So far, study numbers and long-term data are relatively lacking (16).

Other intravesical instillations have also been postulated to be of benefit, including hyaluronic acid and chondroitin sulphate, as a means of replacing the glycosaminoglycan (GAG) layer lining the transitional epithelium of the bladder wall. This aims to reduce bacterial adhesion to epithelial cells (and therefore bladder colonisation and infection) (17). This treatment has been shown to decrease UTI rate and improve subjective symptoms, but numbers are small and lack long-term follow up. These treatments are expensive, and their utilitisation for prolonged use is questionable.

Historically, intravesical chlorpactin (sodium oxychlorosene – a stabilized organic derivative of hypochlorous acid) has been utilised in the prevention of recurrent UTI due to its potent antimicrobial effect on a wide range of pathogens, including bacteria, viruses and fungi. It has been used in many facets of medicine for infection prevention and treatment, and the bulk of data supporting its use has come from chronic wound and burn care

Microdox is a ready-to-use super-oxidised solution produced by electrolysis of water and USP-grade sodium chloride (18), which contains hypochlorous acid (HOCl). It is stable for 36 months unopened, and 60 days after opening. It displays potent anti-microbial and anti-biofilm efficacy, and is inexpensive with its cost being approximately $30 per 500ml bottle.

Microdox can be self-administered as an intravesical instillation by patients who are taught to self-catheterise. The usual recommended prophylactic treatment is weekly, for prevention of UTIs, but there is no data surrounding optimum dose/frequency. Its use can be up titrated to twice daily in patients being treated for an acute UTI.

Hypochlorous acid is a weak acid formed by dissolution of chlorine in water. HOCl is a small, neutrally charged molecule, meaning it diffuses more easily across cell membranes to target intracellular pathways (19), ultimately resulting in pathogen destruction. HOCl has proven in-vitro cell-killing effects on a multitude of pathogens, including bacteria (both gram negative and gram-positive pathogens), viruses, and fungi (19-21). Perhaps more importantly in regards to UTI pathogens and indwelling catheters is hypochlorous acid’s proven ability to destroy biofilms (18, 22-24). Robson demonstrated complete removal of Staphylococcus aureus biofilm, in addition to removal of 70% of biofilm polysaccharide and >90% of biofilm protein after 5, 7- and 10-minutes contact time with hypochlorous acid (24). HOCl has shown similar efficacy against Pseudomonas biofilms which is highly relevant within the urinary tract, whereas various antibiotic agents have been shown to be less effective in the same setting (25). The placebo chosen in this trial is Normal saline wash, as there is evidence that bladder rinse with normal saline can significantly improve UTI’s in catheterized patients (32)

 Microdox is an inexpensive hypoallergenic treatment that may be superior to antibiotics for prophylaxis of recurrent UTI's. It is likely to have less systemic side effects and it may have an ability to penetrate the bacterial biofilms, something that short-term antibiotic treatments have not been able to do. The main benefit of Microdox would be a reduction in antibiotic resistance, which is of growing concern around the world.

There are currently no published human studies on Microdox for the treatment and prevention of recurrent UTI. The limited data available has mainly assessed chlorpactin rather than Microdox specifically. Nevertheless, the clinical efficacy of hypochlorous acid has been demonstrated in a wide range of other clinical settings, most notably chronic wound care (with a particular emphasis on diabetic ulcers and burns), sternotomy wound infections/cardiac surgery, intraperitoneal infections/sepsis and even in Fournier’s gangrene (26-29). There is also some evidence that HOCl may be more effective against multi-drug resistant organisms than other topical antimicrobial agents (30). Due to limited publications assessing its use within the urinary tract, there is a paucity of information regarding tolerability and side effects related to intravesical hypochlorous acid. Those reported side effects appear to be minimal and localised, including burning/stinging and bladder spasm. It has been postulated that Microdox is hypoallergenic and unlikely to elicit any kind of allergic reaction (31), making it particularly useful in patients with multiple drug allergies who also suffer recurrent infections, especially in the setting of multi-drug resistant organisms.

**Outcomes**

*Primary outcome:* To evaluate the effectiveness of intravesical Microdox in patients with rUTI.

Efficacy will be assessed by the number of symptomatic UTI’s during the 3 month treatment period and 3 months following completion of Microdox, compared to placebo with normal saline bladder instillation.

*Secondary Outcomes:*

• To determine if there is a reduction in pyuria.

• To assess improvement in other lower urinary tract symptoms including frequency, urgency, nocturia, bladder pain, voiding difficulty, flow and incontinence using the validated symptom questionnaire ICIQ-FLUTS

• To determine if causative organisms and sensitivity patterns change during Microdox therapy.

• To evaluate the total number of days spent on antibiotics in both groups.

• To assess the incidence of inpatient care/hospitalization required for UTI’s during the 6 month trial period.

• To evaluate patient tolerability of intavesical Microdox in comparison to normal saline using the validated patient questionnaire

**Hypothesis**

Both Intravesical Microdox and Normal Saline bladder rinse can aid in treatment of recurrent UTI’s. This study is powered to detect a 30% difference between these two treatments.

**Methodology**

This is a multi-centre, double blind, randomized controlled trial to evaluate the clinical benefit of intravesical Microdox bladder instillation treatment compared to normal saline bladder instillation for the prevention of rUTI in women during a 4-month treatment period and the 3 months post treatment follow up.

Recruitment : All women with recurrent UTI presenting to the Urogynaecology Department and meeting the inclusion criteria will be offered participation in the study. Written and verbal patient information will be provided and written consent obtained.

Those women who decline to participate will be offered all available treatment options including the use of intravesical Microdox.

Patients complete ICIQ- FLUTS questionnaire on their first visit and provide a midstream urine for fresh spun (<2 hours) microscopy, culture and sensitivities.

Blinding: The local research nurse will provide the clinical team with the allocated treatment in a de-identified Toomey syringe. The clinical team administering treatment and performing follow up will remain blinded to the allocation. The patients will be blinded to which treatment they are receiving.

50mls Microdox or 50mls normal saline solution is administered directly to the bladder via clean technique with a Toomey syringe or via patient inserted self catheter and Toomey syringe to the bladder once weekly for 4 weeks, then fortnightly for 4 weeks then monthly for 2 months.

Patients will be asked to hold on to the bladder instillation for as long as possible or at least 30min, recording the length of time before voiding.

A fresh spun microscopy (<2hrs) and culture will be sent prior to each instillation.

At 3 months and 6 months, participants will complete the ICIQ-FLUTS, validated TQSM (treatment satisfaction questionnaire for medication) and Visual analogue score on ease of treatment.

If a symptomatic UTI occurs during treatment, antibiotic treatment will be instituted as the sensitivies and clinical discretion of the clinician with length of treatment at least 5 days.

A long term follow up appointment will be made 6 months – 3 yrs following completion of the treatment.

Data collection and Storage:

Data will be collected in a standardized proforma including baseline patient characteristics and demographics

• Length the patient held the Microdox before voiding.

• Symptomatic UTIs in the preceding 12 months and organism/sensitivity patterns

• Other treatment/prophylaxis tried by the patient and its success

• Symptomatic UTI occurrence whilst on Microdox/Normal saline therapy

• Patient adherence to Microdox/normal saline treatment regimen, including ease of use, side effects, adverse reactions

• Monthly Fresh spun urine microscopy to assess for pyuria

• ICIQ- FLUTs questionnaire pre and post treatment.

• Monthly TQSM questionnaire assessing medication tolerability.

• Monthly Visual analogue score for treatment tolerability.

A database will be created and populated with the participant information. The database will be created on the online secure password protected University of Melbourne REDcap database system. Only the primary investigators will have access to the online database. The database will include the demographic information, medical history as well as above information.

Any hard copy data such as questionnaires will be de-identified and only able to be accessed by members of the research team. This will be kept in a secure locked location for 7 years. Data will be deleted and destroyed 7 years after the publication of the study.

**Sample Size Calculation**

There are no other clinical trials to determine efficacy of Microdox in our proposed population sample. The 2017 systematic review by Goddard and Janssen (32) on intravesical hyaluronic acid and chondroitin sulphate has been used to estimate an appropriate clinical difference and calculate sample size.

Sample size has been calculated for a parallel group RCT design with the objective of demonstrating non-inferiority objective and assuming a NIC(non-inferiority criteria) of 10%, and accounting for a typical 10 % drop out from a tertiary outpatient procedure clinic. For a power of 80% and alpha of 0.05, 64 subjects need to be recruited in each arm for a 30 % difference in clinical outcomes calculated as binary measure of rates of patients cured/not cured as per the relevant case definition.

**Study Duration**

Patients will be recruited from 2020 until 2022 or until the sample size is reached.

An interim analysis will be performed after 40 patients are recruited in each arm to determine the safety of the treatment.

Inclusion criteria:

• Women >18 years.

• Women meeting the criteria for recurrent UTI: > 3 documented symptomatic UTIs in the preceding 12 months or 2 or more UTI’s in the preceding 6 months.

• Willing to participate and return for follow up.

Exclusion criteria:

• Permanent IDC, ureteric stents or nephrostomy

• Foreign body causing obstruction or recurrent infection (e.g. untreated bladder stones, upper tract stones, mesh).

**Randomisation and Bias**

Patients will be randomized with equal probability to either Microdox bladder instillation or normal saline bladder instillation using computer generated random allocation. (Randomisation.com)

Balanced baseline characteristics would minimize influence on potential confounders.

Selection bias will be minimised by including all adult female patients with recurrent uncomplicated UTI as eligible participants. We have deliberately set few exclusion criteria to enable the findings of this study to be generalisable. Both treatments have a low side-effect profile. We will stratify randomisation on the basis of menopausal state to ensure equivalent proportions of these groups at differential risk in both arms.

**Statistical analysis**

Information will be analysed in a de-identified manner. SPSS will be used to perform the statistical analysis. Paired non parametric data will be analysed using Wilcoxon signed rank sum test and independent categorical data will be analysed with the chi-squared test.

**Risk**

This research may result in some discomfort during the instillation of the treatment. Care will be taken to minimise discomfort using lignocaine gel for instillation. Avoiding the use of catheters and utilising a Toomey syringe to directly administer the Microdox or normal saline should also decrease discomfort. We will assess the tolerability of the treatment in our questionnaires and visual analogue scale. If a UTI arises during the trial period, this will be treated with standard antibiotics.

Trial flow chart (Fig. 1 )



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