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Prevention of recurrent urinary tract infections in post-menopausal women using a non-antibacterial approach; a randomised, double-blinded, crossover, placebo-controlled trial of aspirin.

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| Associate Investigators:Professor Ajay RaneProfessor of GynaecologyMs Swati MuruganProject Background:Urinary tract infections (UTIs) are the commonest bacterial infections. They range from cystitis to life-threatening urosepsis. (1) Recurrent UTIs are also common, particularly in women. Recurrent UTIs are debilitating, leading to high usage of medical resources including frequent prescription of antibiotics. (2) There is an increasing frequency of antibiotic resistance among recurrent UTI causative organisms that are unresponsive not only to the routine antibiotics used for UTI, but increasingly, to more potent antibiotics reserved for severe infections. (3) Suppressive antibiotics for recurrent UTI are not totally effective, (4) are associated with substantial toxicity (5) and select resistant bacteria.Searching Google for ‘support groups for urinary tract infection’ results in about 1,670,000 results in 0.42 seconds with 516,000 results in Australia found in 0.58 seconds. This is indicative of the level of distress experienced in patients who have UTIs. Reducing painful conditions like UTI has the potential to substantially improve the lives of these people seeking support from communities of others with the same experience. Figures are available from the USA for the economic impact of treatment for uncomplicated UTI such as cystitis that is the common form of recurrent disease. Direct costs include the costs of outpatient doctor visits, antimicrobial prescriptions as well as the nonmedical costs associated with travel, sick days, and morbidity. Approximately 11.3 million women in the United States had at least 1 presumed acute community acquired and treated UTI in 1995. Direct costs were estimated at $659 million and indirect costs $936 million. The estimated annual cost of community-acquired UTI in the USA is approximately $1.6 billion.It is obvious then that reducing recurrent UTI has major benefits for patients and the health care system. The additional costs of treating bacteria resistant to multiple antibiotics are substantial.The bacteria that cause UTI are predominantly gram-negative, most commonly *E. coli*. Uropathogenic *E. coli* strains produce type I fimbriae; ‘arms’ of the bacteria, that allow it to attach to the lining of the urinary tract. (6) These and other fimbriae are also involved in biofilm formation that is required for infections of urinary catheters as well as recurrent UTI. These bacterial factors; type I fimbriae production and biofilm formation in *E. coli* (7) and other uropathogens, (8) are both reduced by salicylic acid, the biometabolite of aspirin, and this drug may be useful in prevention of recurrent UTIs. The minimum salicylic acid concentration required for Type I fimbrial suppression is 0.1-0.5mM. (7) This is exceeded by 300mg doses of aspirin as 30% (9) of the total dose is excreted in alkaline urine. (10) The safety of the 300mg dose has been precisely determined in large-scale studies. The rate of major haemorrhage (requiring transfusion or hospitalisation) in patients taking greater than 200mg aspirin/day is 2.29%. This Is significantly higher than those on doses <100mg, but even here the rate of major haemorrhage (1.56%) remains substantial. (11) These risks must be balanced against the morbidity of recurrent UTIs and the toxicity of prophylactic antibiotics like nitrofurantoin. We will trial both doses of aspirin and hope to show that 100mg is as effective as 300mg.Recurrent UTIs are distressing for patients, interfering with their ability to lead productive lives, restricting their ability to work or carry out other daily tasks. If we are able to identify a treatment to reduce the frequency of recurrences of UTI using aspirin then this will be of great benefit to many patients. Aspirin is a safe and cheap medication. If aspirin is shown to be effective for UTI prevention in post-menopausal women it may be generalised, after more research, to other patient groups such as patients with indwelling catheters. The extremely limited cost of such an intervention is obviously very attractive to patients and the health care system in general. Additional health savings may accrue such as due to reduction in GP visits and overall use of antibiotics.Beyond reduction in highly symptomatic recurrent UTIs, a contribution to reduction in antibiotic resistance will be extremely beneficial. Aims: Our aim is to perform a randomized, crossover, double-blinded, placebo controlled trial to determine whether aspirin reduce the frequency of recurrent urinary tract infections.Our endpoints are:Primary; * To assess for a difference in frequency of UTI in subjects randomized to aspirin or control

Secondary;* To assess the time to first breakthrough UTI in subjects randomized to aspirin or control
* To assess the safety of aspirin in these subjects

Sample size: Recent trials for recurrent UTIs intervention have shown that the rate of microbiological recurrence is 70% at one year, with a time to first recurrence of between 19 and 180 days. (12) (13) We have chosen a clinically relevant effect size of 30% reduction in the frequency of recurrences of UTI over one year. Using a crossover design, this allows us to have an adequately powered study with 95% two-sided significance with 33 participants in each of the two intervention arms and 65 in our control group (predicted odds ratio 0.29). With this sample size we are able to proceed to a Phase III trial. We will aim to recruit 43 participants in each of the trial arms and 86 controls to allow for 30% drop out and to increase the trial’s power to detect smaller differences in recurrence rate. The total number of participants will be 172.Participant recruitment strategy: Professor Rane assesses at least 5 patients with recurrent UTI per week in his outpatient clinic at Mater Hospital. He will also commence an outpatient clinic at THHS in the next month. Via these sources there will be more than adequate numbers of potential participants for the trial.Timeline: The following milestones are in place* Trial Commencement – April 2016
* Recruitment completion – September 2016
* Trial completion – September 2017 [12 months on trial / placebo with crossover at 6 months]
* Analysis results completion November 2017

Recruitment strategy:Professor Rane’s Obstetrics and Gynaecology Training Fellow will be responsible for recruitment.Inclusion criteria: Post-menopausal women who have a documented history of at least three UTIs per year. Exclusion criteria: * Increased bleeding risk.
* Hypersensitivity to aspirin.
* Requirement for surgery to correct anatomical abnormalities predisposing to UTI.
* Dependence on intermittent self-catheterisation.
* Medical illness requiring continued aspirin treatment.

Trial regimen: * Aspirin, either 100mg or 300mg, or matching placebo tablets along with one Ural sachet (to optimize excretion of salicylic acid into alkaline urine) taken at night. All trial medications will be taken before bed at night to maximize bladder dwell time.
* NSAID use (which may have anti biofilm effects similar to aspirin) will be avoided with panadol or panadeine used preferentially for analgesia.
* The total duration of the trial will be ≤2 years with a minimum period on trial of 1 year for each participant.
* Stopping rules will be in place including; severe haemorrhage, hypersensitivity and onset of ischaemic heart disease or cerebrovascular disease requiring aspirin prophylaxis.

Trial procedures. * Participants will be interviewed by Professor Eisen and Swati Murugan prior to commencement on the trial medications. This will occur at a monthly clinic run during the recruitment phase of the trial. Participants who have provided consent will be reviewed at the next available clinic.
* Allocation to trial arm will be managed by the unblinded trials pharmacist who will open a sealed envelope to reveal the daily dose of aspirin and the sequence of aspirin and placebo.
* As the recruitment is at a single site, randomisation will be a simple process consisting of random numbers being allocated to an ordered list of aspirin dose and placebo sequence combinations. This list when then be sorted into descending numbers to determine randomisation order.
* Trial participants in this cross over trial will act as their own controls.
* The unblinded clinical trials pharmacist will manage the transition from aspirin or placebo to placebo or aspirin after participants have been on the study treatment for 6 months.
* Participants will be given standard advice regarding perineal hygiene and behavioural approaches for prevention of recurrent UTI.
* The type of prophylactic antibiotic at study entry and after breakthrough UTI will be guided by identified pathogen and its susceptibility pattern.
* Trials medication will be provided for 2-month periods and participants will have 2-monthly clinic reviews at THHS. This clinic review will be with Professor Eisen and Swati Murugan.
* A monthly, interval telephone call will be made to discuss trial medication compliance, details of recurrent UTIs and declared haemorrhage.
* Participants will be provided with an information sheet to give to their general practitioners on their next visit to promote their understanding of trials requirements including; promoting compliance with study medications, the need to perform mid stream urine (MSU) cultures prior to prescribing empiric antibiotics for symptomatic UTI and documentation of revealed haemorrhage. There is no necessity for trial participants to be regularly reviewed by their GP as part of this trial. They will see their GP only as required for investigation and management of possible UTI.
* Investigation and treatment of recurrent UTIs by the participant’s GP will be according to protocols described in the Antibiotic Guidelines, Version 15, 2014. Mid-stream urine cultures are taken followed by susceptibility-directed antibiotics for treatment of proven cystitis.
* Study participants will be provided with preprinted pathology request forms for MSU. These forms will have Professors Eisen and Rane address so that results are sent to these investigators automatically. Bacterial isolates grown from MSUs will be retrieved from private pathology laboratories. These isolates will have been placed in enriched media for long-term storage.

Data management plan. Data will be entered into an electronic case report form (Appendix 1) that will automatically populate a relational database. AUSLAB data and private pathology data will also be automatically linked with the database.Statistical analysis: Differences in the frequency of UTIs in the treatment and placebo groups will be measured using comparison of means by unpaired t-test. Cox-proportional hazards survival analysis will determine the impact of aspirin on time to the first recurrence of UTI. Analyses will be by Intention To Treat.Stopping Rules;If participants develop* Major bleeding consisting of gastrointestinal haemorrhage or intracranial haemorrhage.
* Hypersensitivity to aspirin shown by new onset or worsening of asthma and nasal polyps
* Requirement for surgery to correct anatomical abnormalities predisposing to UTI.
* Dependence on intermittent self-catheterisation.
* Medical illness requiring continued aspirin treatment.

Then aspirin will be ceased. The decision to cease will be made by the Primary Investigator in conjunction with the participant’s GP.Reporting of Severe Adverse Events (SAEs)If participants develop* Major bleeding consisting of gastrointestinal haemorrhage or intracranial haemorrhage.
* Hypersensitivity to aspirin shown by new onset or worsening of asthma and nasal polyps

The PI will notify the HREC and Research Governance Office within 24 hours.Dissemination of ResultsAll named investigators and Professor Rane’s Fellows will be included as authors on manuscripts arising from this trial.Trial participants will be provided with a plain language statement of results of the trial. They will be informed that they can discuss further management with Professors Eisen, Rane and their GPs. |
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