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Short - versus - long course antibiotics in catheterized patients undergoing transurethral resection of prostate

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Abstract

Introduction: The duration of peri-operative antibiotic treatment for patients undergoing Trans Urethral Resection of the Urostate (TURP) and who have been catheterized pre-operatively, remains undecided. The efficacy of a short-versus a traditional long-course antibiotic regime was investigated in preventing post-operative bacteriuria for catheterized patients undergoing TURP at a single centre.

Methodology: A randomized single blind, single centre clinical trial was conducted between September 2017 and May 2018. Patients were randomized into two groups (1:1). The control group received peri-operative antibiotics for 8 days and the intervention group for 3 days. Urinalysis and urine culture were performed pre-operatively, and post-operatively on day 2 and days 9 to 11, following TURP. All patients were followed up for 30 days after surgery for signs and symptoms of infectious complications.

Results: A total of 83 patients were enrolled in the study. 78 patients were evaluable until day 2 and 66 until days 9 to 11. The incidence of bacteriuria at days 9 to 11 following TURP were 40 % and 38.7% in the intervention (short-course) and control (long-course) groups respectively (RR 1.03, 95% CI 0.097 to 2.573). The incidence of Symptomatic Urinary Tract Infections (UTI) at the same time was 11.4% and 9.7% in intervention and control groups respectively (RR 1.27, 95% CI 0.10 to 2.57). None of the patients enrolled in the study developed clinical sepsis nor required re-admission during the follow up period.

Conclusion: A short- course antibiotic is as effective as a long course in preventing infectious complications in catheterized patients undergoing TURP.

Keywords: Antibiotic; Catheterized; Prostate surgery; Antimicrobial stewardship

1. Introduction

Benign prostatic hyperplasia (BPH) is one of the commonest medical conditions affecting elderly men. It occurs in 8 % of men at the age of 40 years rising to 50% and 90% by the age of 60 and 80 years respectively [1].Transurethral resection of the prostate (TURP) remains the gold standard surgical procedure for the management of BPH. Worldwide, TURP is one of the most commonly performed Urological procedures (150,000 per year in US) [2]. It is the commonest urological operation at our institution with over 300 procedures each year.

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Infectious complications are common following TURP and include asymptomatic bacteriuria (ABU), symptomatic urinary tract infections (UTI) and clinical sepsis. The incidence of asymptomatic bacteriuria ranges from 6 -64 %, symptomatic UTI from 1.7% to 21.6%, and sepsis from 1-4% [3-5].Data from other colleagues in sub-Saharan Africa shows an incidence of 15% for symptomatic UTI [6].

A short course and even single dose antimicrobial prophylaxis has been shown to be effective in reducing post-operative infections in low risk patients undergoing TURP [7,8]. However, most randomized clinical trials (RCT) which studied short course antimicrobial prophylaxis excluded patients with bacteriuria and indwelling catheter[3- 10]. Therefore, the exact duration of antibiotic prophylaxis for men with a pre-operative urinary catheter, who are at higher risk of sepsis complications, is still debated. Moreover, the world-wide misuse of antibiotics is associated with an increase in drug resistance, secondary morbidity and increase in health care costs [9-11] .This demands a rational use of antibiotics and antimicrobial stewardship programs.

The current practice in our institution has been to give a long peri-operative course of antibiotic coverage to patients undergoing TURP and considered at higher risk of septic complications. This include pre-operatively catheterized men who are in majority (60% from Kilimanjaro Christian Medical Centre theatre registry). We therefore wanted to study whether a short-course antibiotic given peri-operatively was as effective in preventing post-operative septic complications in this patient group.

2. Methodology

2.1. Study design and settings

This study was designed as a randomized, single blind clinical trial, conducted between September 2017 and May 2018 at the Kilimanjaro Christian Medical Centre (KCMC), Moshi, Tanzania.

All men with Bladder Outlet Obstruction (BOO) and treated with indwelling catheter and admitted for TURP during the study period, were included. Exclusion criteria were patients with renal failure, uncontrolled diabetes mellitus, known HIV positivity and patients who had received antibiotics in the seven days prior to surgery. In addition, patients with bacteria resistant to gentamicin and/or ciprofloxacin identified in urine culture were excluded. Written informed consent was obtained prior to randomization. Patients were randomized into routine long (control) and short (intervention) course peri-operative antibiotic course. Computer generated randomization used blocks of 4 and allocation ratio 1:1 and was delivered to the clinical research team using a sealed envelope technique. Other doctors, nurses and laboratory technician were blinded to treatment allocation.

2.2. Antibiotic regimen

The control (long-course) group received intravenous gentamicin 160 mg thirty minutes before surgery and 2 further doses on postoperative day 1 and 2 followed by oral ciprofloxacin tablet 500 mg twice a day for five days. The intervention (short-course) only received intravenous gentamicin 160 mg thirty minutes before surgery and 2 further doses on post-operative day 1 and 2. Catheter removal took place 48 hours following TURP in both control and intervention groups. Patients were discharged on day 2 post-operatively unless the patient experienced fever or other complications which required further hospital investigation and care. Compliance with antibiotic treatment in the control group, after discharge, was determined by telephone follow-up. All other treatments were similar between control and intervention groups.

2.3. Study outcome

The primary outcome was the incidence of post-operative bacteriuria. Secondary outcomes were incidence of symptomatic UTI, fever and clinical sepsis.

2.4. Investigations

Routine pre-operative blood tests included full blood count, creatinine, blood glucose, and prostate specific antigen. In addition an abdominal pelvic ultrasound, and urine culture and sensitivity were performed pre-operatively. Urine culture and sensitivity is a routine investigation for catheterized patients prior to surgery. Post-operatively physiological clinical signs (temperature, pulse rate, blood pressure, and respiratory rate) were recorded twice a day. Urinalysis, culture and sensitivity were performed on day 2 (following catheter removal) and between day 9 and 11 post-operative. After discharge, patients were followed up by telephone for 30 days, for symptoms and signs of sepsis.

Blood film for malaria parasites and blood cultures were performed if patients develop a pyrexia greater than 38.5^0C for more than 24. Bacteriuria was defined as urine culture growth of ≥ 10^5 colony forming units /ml. Symptomatic UTI was defined as symptoms related to UTI and significant urine bacterial growth. Sepsis was defined as suspected urinary infection and the presence of the systemic inflammatory response syndrome, SIRS [5].

2.5. Sample size calculation

The lack of similar studies in countries with limited resources in general and Sub-Saharan Africa in particular made it difficult to identify practical statistical figures to base the sample size calculations on. We therefore opted to use observations from earlier studies [13]. Considering the observed difference in postoperative bacteriuria in preoperatively catheterized/bacteriuric patients at 25% (35% in short-course versus 10% in long-course regimens) and using the formula for non-inferiority in randomized clinical trials [14]. The sample size at a confidence level of 95% was determined at 80. 10% were added to compensate for loss of follow-up.

2.6. Statistical calculations

Continuous variables were analyzed during student's t test for parametric and Man Whitney U test for non-parametric data. Categorical variables were analyzed using chi square test and fisher's exact test. A p value of < 0.05 was considered statistically significant. All analyses were performed using SPSS version 20.

3. Results

Peri-operative clinical characteristics of patients recruited to short- and long- courses were equivalent and are summarized in Table 1.

Table 1: Perioperative clinical characteristics

Parameters	Short Course antibiotics n=41 (51%)	Long course antibiotics n=39 (49%)	P value
Age, yrs, mean (SD)	71.71 (10.7)	74.21 (7.7)	0.2
Creatinine μmol/L mean (SD)	79.54 (15.7)	82.28 (17.3)	0.46
Haemoglobin g.dl mean (SD)	13.33 (1.4)	13.26 (1.4)	0.83
Preoperative duration of catheterization,days,median (range)*	35.50 (174.0)	61.00 (331.0)	0.13
Pre-operative urine culture *** Positive bacteriuria n (%)	24.00 (58.5)	27.00 (69.2)	0.32
Weight of resected tissue, g median (range)* n=68	23.00 (75.0)	22.50 (81.0)	0.65

SD, standard deviation; *Mann-Whitney U test, *** χ^2 test

During the study period, a total of 83 patients met the inclusion criteria and were enrolled in the study (see Figure 1). After enrollment three patients were withdrawn from the study since surgery was cancelled because of high blood pressure (n=2) and surgery no longer required (n=1), because of a revised diagnosis of neurogenic bladder following diagnostic endoscopy. Six (7.5%) patients went into urine retention following catheter removal. 9 patients were lost to follow up (11.3 %). Data was available post-operatively for 78 (97.5%) patients until day 2 (39 intervention and 39 control), and 66 (82.5%) patients until days 9 to 11 (35 intervention and 31 control group).

Pre-operative asymptomatic bacteriuria was present in 58% (24/41) and 69% (27/39) of the short- and long-course groups, respectively (p=0.32).

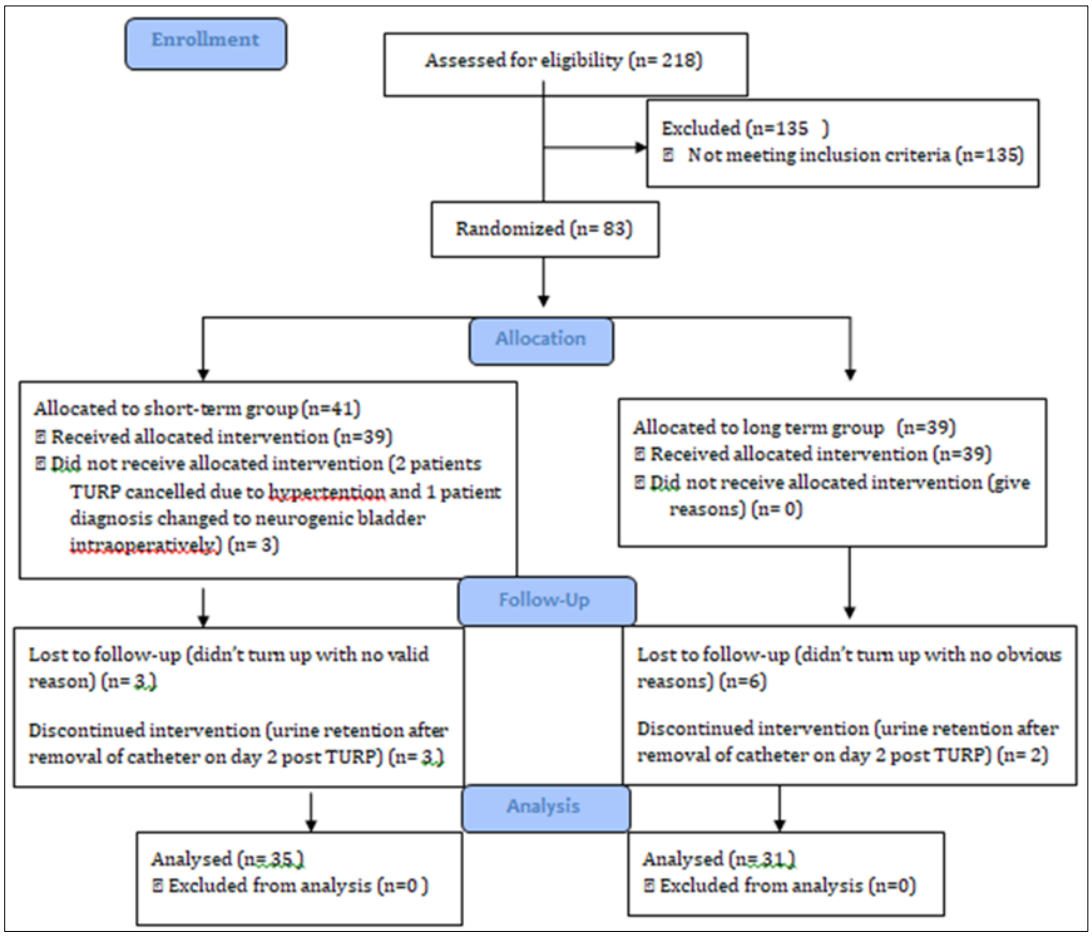

Figure 1 Flow chart with total number of enrolled patients and the number of patients who were evaluable up to end of study

Table 2 Incidence of bacteriuria day 2 post TURP

Antibiotic prophylaxis group	n=78	Bacteriuria Incidence n (%)	Relative Risk (RR)	95% CI	P value
Short course	39	2(5.10)	0.5	0.10-2.57	0.68***
Long course	39	4(10.30)			

*** Fisher's exact value

Table 3 Incidence of Bacteriuria day's 9-11 post TURP

Antibiotic prophylaxis group	n=66	Bacteriuria Incidence n (%)	Relative Risk (RR)	95% CI	P value
Short course	35	14 (40.0)	1.03	0.10 -2.57	0.92
Long course	31	12 (38.7)			

CI, confidence interval; n (%), proportion of patients with bacteriuria

Data for post-operative bacteriuria and symptomatic UTI are shown in tables 2, 3 and 4. One patient in each of the short- and long- course antibiotic groups experienced fever days 9-11 following TURP (p=1.00). No patients in the study developed SIRS or were re-admitted to hospital due to sepsis complications, within one month following TURP.

4. Discussion

Life expectancy has markedly changed in Sub-Saharan Africa during the last decades. With an aging population, the pathology is also changing and the number of men with BPH are steadily increasing [15].

The majority of patients undergoing TURP at KCMC are elderly, presenting in a late stage with BOO and indwelling catheter treatment since weeks or months. They often come from far away villages. This group of men and the perioperative antibiotic coverage is the focus of this study.

Most guidelines recommendations on antimicrobial prophylaxis in conjunction with TURP are based on two systematic reviews and one more recent multi-center study [7, 8, 10, 16] including only patients with pre-operative sterile urine. Therefore, the majority of international guidelines give no high level of evidence regarding the optimal peri-operative antimicrobial regimen in patients with BOO and catheter treatment.

These men will be colonized with a variable bacterial flora most frequently gram negative uro-pathogens but also gram positive contamination [13]. Bacteriuria is a well-established risk factor in conjunction with endo-urological interventions, which is highlighted in international documents and guidelines such as the European Association of urology [17] and the Infectious Diseases Society of America [18]. The level of contamination of the surgical field (i.e. urethra, prostate, and bladder) during TURP for this elderly catheterized group of men is considered as contaminated. This is different from those without pre-operative bacteriuria/catheterization who undergo a clean-contaminated procedure [19].

It is good practice to prevent infectious complications after contaminated endo-urological procedures, as the risk of febrile UTI and sepsis is clearly increased [13, 16-19]. The European Association of Urology (EAU) guidelines on urological infections recommends in this category of men medical control of bacteriuria for 3 to 5 days followed by peri-operative antibiotic coverage [17].

Routine practice at our institution has been for many years to give a long antibiotic course (eight days). However, such regimen increase the risk of bacterial resistance and drug side events, is associated with higher costs. To avoid an overuse of antimicrobial agents, we decided to investigate the efficacy of a three day peri-operative course in this *contaminated* group of men undergoing TURP, with the intention of preventing infectious complications related to the procedure rather than to eradicate all bacterial strains in the surgical field which has shown to be difficult [13].

This study demonstrates that a short-course was not inferior to a long-course in the targeted group of men with Acute Urinary Retention (AUR). This was true for both the recurrence of bacteriuria and the incidence of symptomatic UTI at 9-11 days after TURP. There was no significant difference in postoperative pyrexia between the two groups, no patient with sepsis and no re-admission within 30 days after surgery.
However, bacteriuria recurs after surgery in some 40% of the patients. The exact reason is not well understood. It can be speculated that the microbes are harbored within the urogenital organs affected by chronic and acute inflammation, and detected in the urine, usually without symptoms [13, 19, 20].

Antibiotic resistance is a global challenge and a rational use of antimicrobial agents is nowadays highly recommended. Antimicrobial Stewardship programs have been developed to educate and improve the use of antimicrobial agents [19]. This study is in line with the efforts to curb the overuse and misuse of antibiotics without jeopardizing the patients' health and the outcome. The urological experience is limited [21-22]. By showing that these two aims are reached, the institution can challenge historical recommendations and modify the routines and encourage other institutions to work in the same direction. The consequences in terms of reduced antibiotic prescription is obvious and as such contribute to reduce both the risk of antibiotic resistance development and hospital costs. Only one type-procedure as TURP can save in our institution in one year five kilogram of ciprofloxacin that could be saved for more needing patients. Extrapolating to the whole African continent and beyond, the environmental and economic benefits is enormous.

The study has limitations due to sample size principally, caused among others to limited resources. However, the size was large enough to demonstrate the non-inferiority of a short-term antibiotic course as compared with the established long-term regimen in protecting this defined patient group from infectious complications in conjunction with TURP. The next step would be to further reduce the length of the course to 24 hours even in this contaminated group of men. A large multi-center study within the East, Central and Southern Africa region, supported by international urological and infectious diseases associations, would help deliver evidence-based recommendations for the sub-Saharan region and for a global audience.

5. Conclusion

A short course antibiotic regime is as effective as a long course in preventing infectious complications in catheterized patients undergoing TURP. We recommend the introduction of the short course regime as routine practice in these patients, which would significantly reduce the perioperative misuse of antibiotics and the risk of antibiotic resistance development. Further larger studies are needed to confirm whether even shorter antibiotic courses are efficacious and safe.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declared that they have no competing interests.

Statement of ethical approval

Approval for this study was obtained from Kilimanjaro Christian Medical College Research Ethics Committee with reference number 2109. The trial was retrospectively registered Pan Africa Clinical Trial Register with registration number PACTR201808161376054. All patients provided written informed consent before participation of study.

Statement of informed consent

Written informed consent was obtained from all patients before enrolment in this study.

Authors' contributions

OJM designed the study; OJM, JSN, PR, FB and AKM, inputs in the study design and conduct; OJM data collection; OJM, EM and AKM input in the analysis; OJM, SJN, EM and AKM read the final manuscript for scientific content of the paper. All authors read and approved the final manuscript. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors short Biography

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