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ORIGINAL ARTICLE

Efficacy of antibiotic prophylaxis in patients undergoing cystoscopy: a randomized clinical trial

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Abstract
Objective To establish the efficacy of antibiotic prophylaxis prior to cystoscopy in outpatients in decreasing the incidence of post-procedure urinary tract infection.
Study design and setting A randomized clinical trial in patients (men and women) older than 18 who underwent cystoscopy for any non-urgent indication. The intervention was Levofloxacin 500 mg single dose, and the control was placebo 500 mg single dose made with similar characteristics. The primary outcome was urinary tract infection (UTI) measured 3–10 days after the procedure. It was performed as per protocol analysis.
Results Hundred and thirty-eight patients in each study arm completed the trial. The incidence of UTI in the intervention group was 0.7 % and in the placebo group was 3 % ($p = 0.17$), and no significant differences were found. The incidence of asymptomatic bacteriuria in the intervention group was 5.8 % and in the control group was 14.5 % ($p = 0.01$).
Conclusions No significant differences were found in the use of prophylactic antibiotic compared to placebo to reduce the incidence of UTI in patients who undergo cystoscopy as an outpatient procedure with sterile urine demonstrated by urine culture.

Keywords Urinary tract infection · Cystoscopy · Clinical trial · Antibiotic prophylaxis

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Introduction

Urinary tract infection (UTI), the most common of nosocomial infections, has been clearly studied in both ambulatory and hospitalized patient populations. Among the procedures used in the field of urology, cystoscopy is accepted by most patients; however, it could lead to some complications such as UTI, which could increase costs to the health system, the resistance of microorganisms, and morbidity to the patient [1–3].

The effectiveness of preoperative antibiotic prophylaxis in reducing surgical site infection and UTI has been shown in randomized clinical trials, but there is wide variation in the use of prophylaxis before procedures that involve the urinary tract [4]. The most common etiologic agents involved in UTI are *Escherichia coli*, *Proteus* spp., *Klebsiella* spp., and enterococcus [5, 6].

There is a systematic literature review aimed to prophylactic antibiotic use in urological procedures [7]. Nine studies were found and four met the inclusion criteria for the review. All four studies identified were assessed to have potential biases, and the authors of the systematic review concluded that there is insufficient evidence to suggest the use or non-use of antibiotic prophylaxis in patients undergoing cystoscopy [7]. There is little evidence for the use of antibiotics for ambulatory patients who undergo cystoscopy, but in the presence of risk factors such as immunosuppression, bacteriuria, or permanent urethral

catheter or manipulation of the urinary tract, prophylactic antibiotics have been advised [8, 9].

The primary purpose of the present randomized controlled trial was to establish the efficacy of antibiotic prophylaxis prior to cystoscopy in outpatients in decreasing the incidence of post-procedure UTI.

Methods

A multicenter randomized controlled trial was performed in two cities in Colombia (Cali and Bogota).The participating centers were: Urological Salus Clinic (Cali), Hospital Universitario San Ignacio (Bogota), ESENSA Foundation (Cali), Farallones Maternal and Child Clinic (Cali), and Colsubsidio Clinic (Bogota).

Inclusion criteria

We included men and women 18 years or older who underwent cystoscopy for any non-urgent indication on an outpatient basis. All eligible patients had to have negative urine culture results before the procedure and provide written informed consent prior to participation.

Exclusion criteria

We did not include patients who could not be followed up, had any allergy to antibiotics, were taking other medication which could interact with the study drugs or for the purpose of prophylaxis for other health conditions (e.g., prosthetic heart valve, heart murmur, prosthetic orthopedic or vascular), were taking antibiotics at the time of the procedure, had a history of permanent urethral catheter. We also excluded patients with immunosuppression, spinal cord injury requiring intermittent catheterization, or who required a urethral catheter after the study procedure.

Sample size

A sample size calculation was performed for comparison of categorical variables in two independent samples (two-tailed hypothesis), taking into account the primary outcome variable: UTI incidence. We anticipated incidences of 10 % in the control group and 2.5 % in the antibiotic group. With an alpha of 5 %, the planned sample size was 136 patients in each arm in order to achieve 80 % power.

Randomization

We used permuted block randomization with variable-sized blocks to ensure a similar number of patients in each group. A statistician outside the research group generated the computerized random sequence independently. The statistician coded the sequence and maintained the code until the end of the study.

Treatment assignments were kept in sealed, opaque, consecutively numbered envelopes, which were opened in the order of patient arrival at each center in order to conceal the allocation to which study group each patient would be assigned. A nurse assistant and physician administered the drugs at each center.

Intervention

Experimental group

A prophylactic antibiotic (single dose of 500 mg oral levofloxacin), was administered 30–60 min before the procedure.

Control group

A placebo tablet similar in appearance to the antibiotic administered to the experimental group was administered 30–60 min before the procedure.

After the administration of the antibiotic or placebo tablet, physicians performed the procedure (cystoscopy). The cystoscope was immersed in 10 % chlorhexidine Opa for 5–10 min prior to the procedure. Immediately following the procedure, the instruments were washed and immersed again in the chlorhexidine. This process was standardized for each participating center.

Definition of outcomes

Primary outcome

Incidence of urinary tract infection (UTI) was defined as the presence of irritative symptoms of urinary tract with a positive urine culture $>10^5$ CFU/mL for a microorganism in a midstream sample of urine, with or without systemic symptoms (P.e. fever).

Secondary outcome

The incidence of bacteriuria was defined as the result of a positive urine culture $>10^5$ CFU/mL for one microorganism in a midstream sample of urine, without systemic symptoms or irritative symptoms of the urinary tract.

During the follow-up appointments (between the third and tenth day after the procedure), patients were evaluated for the presence of lower urinary tract symptoms and a complete physical examination was performed to assess their clinical status. A questionnaire was implemented to assess the primary and secondary outcomes and patient

safety. A urine culture was taken on the third day after the cystoscopy. The sample was sent for analysis to a standard laboratory. In some patients, it was necessary to get the results by phone and if necessary an appointment was suggested to evaluate any important results. Patients were treated according to their clinical status and diagnoses.

Blinding

Patients, researchers, and treating physicians were blinded to whether or not patients received antibiotics or placebo, as well as there was a management protocol defined in terms of primary and secondary outcomes. Different codes were assigned to the drug and placebo (P.e. A and B) for blinding.

An external laboratory (Tecnoquímicas®) manufactured the placebo tablet of identical presentation and weight to Levofloxacin 500 mg tablet. There was no conflict of interest with any of the researchers involved in the study.

Statistical analysis

An exploratory analysis was initially performed. The χ^2 or Fisher exact test was used for categorical variables and a *T* test was used for continuous variables. We also reported the RR, the absolute risk reduction (ARR), and number needed to treat (NNT). A per protocol analysis was performed which included only patients who complete the assessment for primary and secondary outcome. The analysis was performed in the statistical program Stata 11®.

Ethical considerations

This study was reviewed and approved by the Ethics Committee of the University of Valle (Cali, Colombia). There was no conflict of interest with any of the researchers involved in the study. This trial is publicly registered in the Australian New Zealand Clinical Trials Registry ACTRN12611000750987.

Results

During March 1, 2011, and April 30, 2012, 290 patients were candidates for inclusion in the study. Of these, 5 patients were not eligible and were not included in the study; thus, 285 patients were randomized. No urine culture was performed for 9 (3.2 %) patients after the procedure (3 patients in the antibiotic group and 6 patients in the placebo group). There were no significant differences between the nine patients lost to follow-up and those who remained in the study. The analyses include 138 patients in each study arm (see Fig. 1).

Both intervention and control groups were comparable at baseline (presented in Table 1).

With regard to urinary infection as a primary outcome, the risk in each group is described in Table 2, and there was no statistically significant difference between groups ($p = 0.17$; RR 0.25; 95 % CI 0.028–2.2).

Results for asymptomatic bacteriuria are described in Table 2. Patients in the antibiotic group had significantly less asymptomatic bacteriuria than those in the placebo group following the procedure ($p = 0.01$; RR 0.4; 95 % CI 0.18–0.87; ARR = 0.09; and NNT = 11).

It was found that all UTI episodes were localized to lower urinary tract; there were no episodes of upper urinary tract infections.

No patient had an adverse event related to the procedure (i.e., episodes of urinary retention, urinary sepsis, or bladder perforation).

With regard to the adverse effects that may occur for the drug: emesis, diarrhea, headache, delirium, hallucinations, convulsions, and rash were not found. The remaining events can be reviewed in Table 3.

In a subgroup analysis of patients at high risk for UTI according to literature, there was no significant difference in recurrent UTI group ($p = 0.8$) nor in diabetes mellitus group ($p = 0.39$) as clinically important history.

Discussion

The aim of this study was to determine the efficacy of prophylactic antibiotic use in the prevention of UTI post-cystoscopy, compared with placebo. The overall risk of UTI was 1.8 % in the present study, which is comparable to the literature [10]. The risk of UTI in the experimental group was not statistically different when compared with the control group ($p = 0.17$). This study found no difference between groups in the primary outcome, questioning the necessity for the use of the antibiotic before the procedure in patients with sterile urine.

Jimenez et al. performed a randomized clinical trial with good internal and external validity. This was an experiment of 2,284 patients, divided into two groups, ceftriaxone versus placebo [11]; some of the differences were as follows: larger sample size, the antibiotic used, and the route of administration; results are not consistent with ours because they concluded ceftriaxone lowers the incidence of UTI.

Johnson et al. conducted a clinical trial with 2,500 patients, and three interventions were implemented: placebo, ciprofloxacin, and trimethoprim/sulfa. They blended

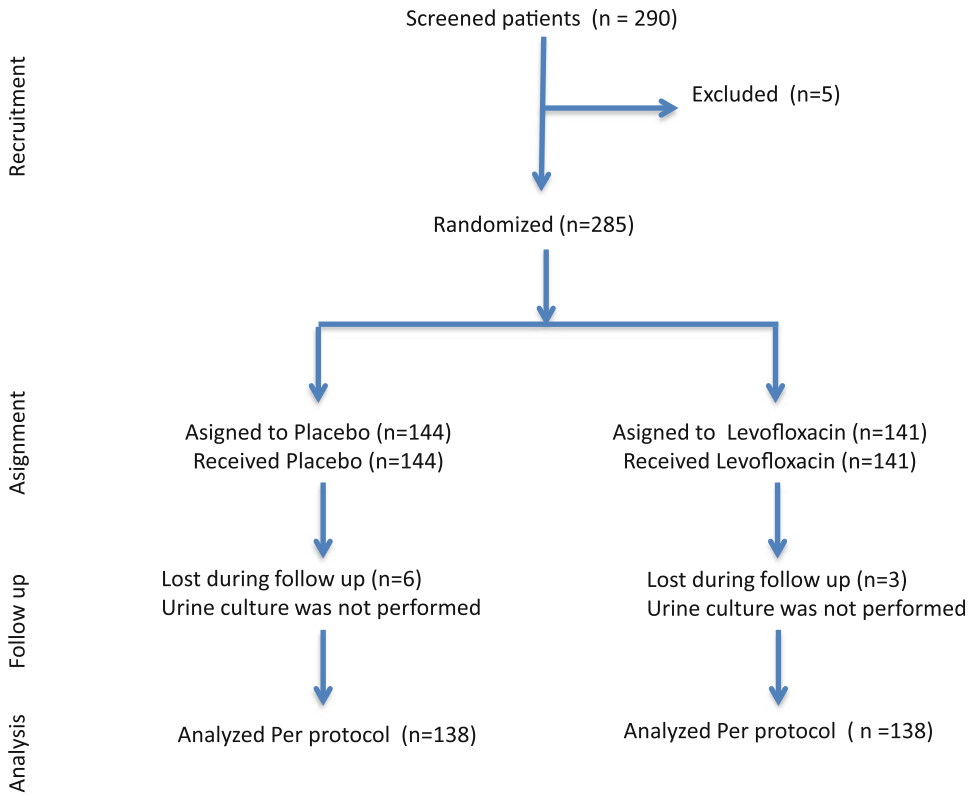

Fig. 1 Flowchart progress through the various stages of clinical trial

patients with positive urine culture at the beginning of inclusion and the UTI outcome was not stated [12].

Tsugawa et al. [13] conducted a clinical trial with a few patients, without a clear system of randomization, and found no difference in both groups, according to our study.

Rane et al. [14] assessed 162 patients (intramuscular gentamicin versus placebo), there was no evidence of urine culture, UTI, or bacteriuria, and it was just urinalysis so it would not be comparable to this study.

Christiano et al. [10] developed a clinical trial comparing oral ciprofloxacin versus intravenous cefazolin but mixed different endourological procedures, for example: transurethral prostate resection, ureteroscopy, cystoscopy, etc. They found no differences in UTI, according to the present.

Cam et al. developed an experiment with 100 patients per arm, 22 patients with positive urine culture prior to treatment. They included different endourological procedures and positive urine culture prior to the procedure [15]. They found no differences in bacteriuria; this was not according to the actual study.

Wilson and colleagues conducted an experiment with 112 patients randomized to norfloxacin and 122 patients to placebo. There was no description of randomization and statistical analysis and an interim analysis found low incidence of infection and no differences. Fifty-eight patients had positive urine culture pre-procedure [16].

Finally, Cutajar et al. [17] conducted an experiment with 70 patients undergoing endoscopic procedures, methods were not described, sample size was not calculated, and up to 11 % had bacteriuria before the procedure. They found out that norfloxacin lowered the incidence of bacteriuria.

According to this latter description, the present study is pertinent and relevant because of the following:

1. No positive urine culture was found before the procedure, this allows having patients with sterile urine before, and it will make the patients and their results comparable.
2. UTI is the primary outcome and was considered according to literature (symptoms and urine culture).
3. No other procedures were accepted; it was just for cystoscopy, different from some studies described before.
4. This article is about an oral medication, which is important in clinical settings.

Just two clinical trials are well designed according to an updated literature review: Jimenez et al. and our study, both have different conclusions but a practicing cystoscopist could apply these results in clinical practice easily and confidently.

Regarding asymptomatic bacteriuria, it is important to ask: What is the clinical relevance of using prophylactic antibiotics to decrease bacteriuria if ultimately it has no

Table 1 Comparison of two intervention groups regarding sociodemographic characteristics ($n = 276$)

Variable	Placebo ($n = 138$)	Levofloxacin ($n = 138$)	p value
Age			
	59 (SD 14.8)	58 (SD 15.4)	0.78
Gender			0.7
Masculine	94 (68.1)	90 (65.2)	
Femenine	44 (31.9)	48 (34.8)	
City			1
Cali	95 (68.8)	94 (68.1)	
Bogota	43 (31.2)	44 (31.9)	
Socioeconomic stratum			0.85
0	4 (2.9)	6 (4.4)	
1	12 (8.7)	16 (11.6)	
2	52 (37.7)	49 (35.5)	
3	52 (37.7)	45 (32.6)	
4	10 (7.3)	13 (9.4)	
5	6 (4.4)	5 (3.6)	
6	2 (1.5)	4 (2.9)	
Sexual activity			0.7
No	51 (37)	47 (34)	
Yes	87 (63)	91 (66)	
Medical history			0.84
None	80(58)	81 (59)	
Chronic obstructive pulmonary disease	1 (0.7)	2 (1.5)	
Arterial hypertension	44 (32)	43 (31)	
Stroke	1 (0.7)	1 (0.7)	
Chronic pelvic pain	2 (1.5)	5 (3.7)	
Sickle cell disease	3 (2.2)	1 (0.7)	
Other	7 (5.1)	5 (3.6)	
Any kind of cancer history			0.38
No	124 (90)	129 (93.5)	
Yes	14 (10)	9 (6.5)	
Diabetes mellitus history			0.71
No	122 (88.4)	119 (86.2)	
Yes	16 (11.6)	19 (13.8)	
Pregnancy			0.47
No	43 (97.7)	48 (100)	
Yes	1 (2.3)	0	
Recurrent UTI history			0.13
No	111 (80.4)	121 (87.7)	
Yes	27 (19.6)	17 (12.3)	
Double pig tail in situ			0.4
No	106 (76.8)	99 (71.7)	
Yes	32 (23.2)	39 (28.3)	
Taking antithrombotics			1
No	134 (97.1)	134 (97.1)	
Yes	4 (2.9)	4 (2.9)	
Renal stone disease			0.82
No	128 (92.7)	126 (91.3)	
Yes	10 (7.3)	12 (8.7)	
Cystoscopy indication			0.8
Prostatic hyperplasia	49 (35.5)	44 (31.9)	
Urinary incontinence	8 (5.8)	7 (5.1)	
Double pig tail withdrawal	33 (23.9)	39 (28.3)	
Chronic pelvic pain	6 (4.4)	11 (8)	
Lower urinary tract symptoms	7 (5.1)	3 (2.1)	
UTI recurrent	12 (8.7)	10 (7.3)	
Hematuria	8 (5.8)	8 (5.8)	
Urethral stricture	4 (2.9)	6 (4.4)	
Bladder tumor control	7 (5.1)	8 (5.8)	
Bladder-vagina Fistula	2 (1.5)	0	
Cervical cancer classification	1 (0.7)	0	
Urethral–vaginal mass classification	1 (0.7)	1 (0.7)	
Renal tumor (upper urothelial cancer suspected)	0	1 (0.7)	

clinical implication, unless the patient requires another endourological procedure and there are so many different elements that generate a bacteriuria?

The following are findings from different studies described above: Jimenez et al. [11] and Tsugawa [13] found no statistically significant differences, but other studies like Johnson et al. [12], Rane et al. [14], and Cutajar [17] found a decrease in the incidence of asymptomatic bacteriuria in the intervention group, which would be in accord with the present study. However, all these investigations except for Jimenez's study have low internal validity.

Other outcomes evaluated in the study were complications and adverse effects of medication, and the following are described below:

Urethral symptoms such as pain, hematuria, and the presence of storage symptoms are rare in patients undergoing cystoscopy (about 3 %) [1–3]; in the present study, we found a similar distribution: hematuria and lower urinary tract symptoms in 1.8 and 5.4 % of patients, respectively. This implies that complications are similar in our Colombian environment related to the world.

Adverse events that could be expected for the drug were as follows: nausea, emesis, diarrhea, headache, delirium, hallucinations, convulsions, rash, and pruritus among

Table 2 Number and percentage of asymptomatic bacteriuria and urinary infection in experimental and control group ($n = 276$)

Variable	Placebo ($n = 138$)	Levofloxacin ($n = 138$)
Urinary infection		
No	134 (97.1)	137 (99.3)
Yes	4 (2.9)	1 (0.7)
Asymptomatic bacteriuria		
No	118 (85.5)	130 (94.2)
Yes	20 (14.5)	8 (5.8)

others. In the actual study, nausea (0.7 %) and pruritus (0.7 %) were found, which allows us to conclude that the drug is safe in this clinical situation.

The most common agents in post-cystoscopy UTI are *E. coli*, *Proteus* spp., *Klebsiella* spp., and enterococcus [5, 6]. According to the present research, *E. coli* (58 %), *Klebsiella* (8.8 %), and *Enterococcus* (17.6 %) were found. Given the variability of laboratories in which the cultures were taken, it was not possible to get the information to determine the susceptibility patterns of these microorganisms, but this is well described in the literature. This study only had information about one patient that had an infection with an ESBL-positive microorganism, but it was in the group of asymptomatic bacteriuria.

According to this research, in patients with negative urine cultures, which undergo a cystoscopy, it is not necessary to use antibiotics to prevent urinary infections. In actual clinical practice, this result is important because this could prevent the use of antibiotics around the world in this kind of procedure, and so it would reduce bacteria resistance and costs to the health system; however, it is important to discuss some relevant points:

This research had 3.2 % loss in both groups with comparable characteristics, which generated post-randomization exclusion with no effect on the analysis of the study. Another important topic is that the "non-significance" or "no differences" could be due to the absolute rate of UTI, which was lower than expected in a calculated sample size and this could be considered as a limitation.

Not considering a specific time for those urine cultures before the procedure was found as a weakness, but in this study it was accepted up to 1 month from the date of the result to perform the procedure. No specific time was found in literature and this could be another related issue, as it is very widely accepted from 10 to 30 days.

Even if the following is not a central part of this article, it would be important to discuss what the patient's preferences are about choosing prophylactic antibiotic. We tried to search some articles but none were found; in general practice, people accept doctor's decisions if they are supported by literature and explained in common words

Table 3 Secondary outcomes and adverse events in experimental and control group ($n = 276$)

Variable	Placebo ($n = 138$)	Levofloxacin ($n = 138$)
Cystoscopy		
Abnormal	69 (50)	57 (41.3)
Normal	69 (50)	81 (58.7)
Urinary tract obstruction		
No	77 (57.8)	86 (62.3)
Yes	61 (44.2)	52 (37.7)
Post-void residual		
No	133 (96.4)	134 (97.1)
Yes	5 (3.6)	4 (2.9)
Lower urothelial tumor		
No	131 (94.9)	133 (97)
Yes	7 (5.1)	4 (2.9)
Bladder biopsy		
No	138 (100)	136 (98.5)
Yes	0	2 (1.5)
Cystolithiasis		
No	136 (98.6)	137 (99.3)
Yes	2 (1.5)	1 (0.7)
Fever		
No	137 (99.3)	137 (99.3)
Yes	1 (0.7)	1 (0.7)
Urine culture		
Negative	114 (82.6)	128 (92.8)
Positive	24 (17.4)	10 (7.2)
Microorganism		
E. Coli	13 (54.2)	7 (70)
Klebsiella pneumoniae	2 (8.3)	1 (10)
Enterococo	5 (20.8)	1 (10)
Proteus mirabilis	1 (4.2)	0
S. aureus	0	1 (10)
Other	3 (12.5)	0
ESBL microorganism		
No	24 (100)	9 (90)
Yes	0	1 (10)
Lower urinary tract symptoms		
No	131 (94.9)	130 (94.2)
Yes	7 (5.1)	8 (5.8)
Hematuria		
No	137 (99.3)	134 (97.1)
Yes	1 (0.7)	4 (2.9)
Admitted to hospital		
No	138 (100)	137 (99.3)
Yes	0	1 (0.7)
Nausea		
No	138 (100)	137 (99.3)
Yes	0	1 (0.7)

Table 3 continued

Variable	Placebo ($n = 138$)	Levofloxacin ($n = 138$)
Pruritus		
No	137 (99.3)	138 (100)
si	1 (0.7)	0

to the patient, and this is why this article is important, so that the patient can deeply understand the need to get an antibiotic.

Conclusion

No significant differences were found in the use of prophylactic antibiotic (levofloxacin) compared to placebo to reduce the incidence of UTI in patients who undergo cystoscopy as an outpatient procedure with sterile urine demonstrated by urine culture.

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