Comparison of three different antibiotic protocols in transurethral resection of bladder tumour and the possible infectious risk factors: A non-randomized, prospective study

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Abstract

Introduction: We sought to investigate three different antibiotic protocols in transurethral resection of a bladder tumour (TURBT), and the possible infectious risk factors of this surgery.

Methods: We conducted a non-randomized, prospective study, gathering cases of patients in whom TURBT had been performed. The sample was divided into three groups based on those who received antibiotics as: a single preoperative dose (Group A); a preoperative dose, plus a long protocol during the hospitalization (Group B); a preoperative dose, plus a long protocol during the hospitalization, plus five days at home (Group C). Intra- and post-operative data that could be relevant to infections was gathered.

Results: A total of 219 patients were included. In the multivariate analysis, it was observed that the patients in Group A were more prone to re-hospitalization due to fever than were those from Group C (odds ratio [OR] 11.13; p=0.03). Furthermore, the cases with tumour necrosis and those who entered surgery with a urinary catheter were more prone to have a temperature above 37.5ºC (OR6.74; p=0.02 and OR6.4; p=0.04, respectively), as well as have an increased risk per every additional tumour in the cystoscopy (OR 1.32; p=0.01). Those who received mitomycin had a lower chance of a positive urine culture (OR 0.29; p=0.01), contrary to those patients with over two days of hospitalization (OR 4.11; p<0.01) and those who entered surgery with a urinary catheter (OR 12.35; p=0.02).

Conclusions: Those patients that only received a single dose of antibiotic before TURBT may have an increased risk of re-hospitalization due to fever in comparison to those who received prolonged antibiotic protocols. In addition, there are perioperative factors in this surgery that predict the risk of infectious complications.

Introduction

The benefit of different antibiotic protocols to prevent infections has been studied in diverse surgical endourological techniques. In the ureterorenoscopy, for example, the usage of preoperative prophylaxis has been seen as beneficial in cases of proximal and impacted lithiasis, but not in cases of exclusive diagnostic procedures or in the treatment of distal lithiases in healthy individuals.[1] That notwithstanding, the transurethral resection of the prostate tumour (TURPT) is probably the best-studied procedure regarding antimicrobial prophylaxis, with at least two meta-analyses and several randomized, prospective studies. It has been concluded that there is a relative risk reduction of 65% and 77% for bacteriuria and septicaemia, respectively, with the use of antibiotic prophylaxis in TURPT.[2,3] Besides the TURPT, there are no well-designed prospective studies that contribute any important conclusions about the benefit of preoperative antibiotic usage in endourological techniques.[4,5]

In the specific case of the transurethral resection of a bladder tumour (TURBT), despite the frequency of this intervention, there is a lack of consensus about the use and preoperative benefit of antibiotics. The European Association of Urology clinical guidelines explain that there is no evidence in favour of the use of antibiotics in TURBT because the studies do not distinguish between resection and fulguration, between single or multiple tumours, and between the presence or absence of necrosis. It is because of this that the recommendation transmitted is to distinguish between clean-contaminated TURBT (standard cases) or contaminated TURBT (cases with bacteriuria and necrotic tumours), where the use of antibiotics in case of a contaminated surgery is practical. The greatest benefit of the preoperative use of antibiotics is observed in high-risk patients, ample resections and tumours with necrotic characteristics, according to these guidelines.[4,6] Nevertheless, the American Association of Urology, references only one dated clinical study, which concludes that three antibiotic doses diminish bacteriuria.

It is concluded in these guidelines that there are no other similar clinical studies on this aspect.[6,7]

The main objective of this study was to compare three different antibiotic protocols in the preoperative of TURBT and to observe if there were more infectious complications between them. A secondary objective was to set pre-, intra- and postoperative factors that increase the risk of developing infectious complication after TURBT.

Methods

Study design and source of data

This was a non-randomized, prospective, comparative study, gathering all cases of patients subjected to TURBT between October 2015 and June 2016 at our centre. There was and is no existing protocol for antibiotic use in TURBT in our service. Consequently, every urologist uses the one deemed best according to experience. Each surgeon used the same antibiotic protocol in all the patients they treated, with no individualization. To analyze the objective of the study, the sample was divided into three groups depending on the antibiotic protocol indicated, according to each surgeon's criteria. The first group included those patients that received only one preoperative prophylactic dose (Group A), the second one included those cases that received a preoperative dose and continued doses during the entire hospitalization, regardless of the number of days (Group B), and a third group that received a preoperative antibiotic, continued the treatment during hospitalization, and continued it for five days after the medical release (Group C). All patients were asked for a urinary culture at the moment of medical release, in the first micturition after the removal of the urinary catheter, and another culture a week afterwards.

The present study was approved by the ethical committee of the Hospital Clínico Universitario of Valencia (Valencia, Spain), and by the Spanish Agency of Medicine and Sanitary Products (AEMPS).

Surgical protocol

The patients did not have a routine urine culture prior to the intervention. In all cases, the preoperative antibiotic dose was administered 30 minutes prior to the intervention. The antibiotic used was cefuroxime, and in the case of allergies to any beta-lactam, ciprofloxacin was used. Only in a situation of allergies to both groups was a different drug used. In the cases of prolonged antibiotic protocols, the same one was used during the entire period. During the postoperative period, the use or omission of antibiotics depended on the surgeon's criteria, as noted before.

The patients received spinal or general anesthesia, in accordance with the criteria of the anesthetist. The surgical material used was a Storz resector with a 26 Ch sheath. In all cases, monopolar energy was used (handling 5 mm of width), with glycine as the instillation liquid. When finishing the resection, a Foley catheter of 20 Ch or 22 Ch was left with a continuum physiological serum wash in all cases. During the hours following the intervention, a single dose of 40 mg of intravesical mitomycin was administered, following the surgeon's criteria. The catheter was removed when the hematuria was minimal, as per the urologist's determination.

Study variables

The basal characteristics of all patients were registered: age, sex, and comorbidities. Intraoperative variables noted were the kind of antibiotic used; entering surgery with a bladder catheter; the size of the tumour (taking as reference the 0.5 cm of width of the resection loop); the presence of the macroscopic necrotic characteristics of the tumour; the duration of the surgery in minutes; bladder perforation during the TURBT (understood as the visualization of perivesical fat); the stenosis of the urethral meatus; the stenosis of the urethra (independent of location and length); and the false urethral pathway during the introduction of the resector.

Postoperative variables recorded included: the administration or not of postoperative mitomycin; the days of hospitalization; the postoperative days with catheter; the need of manual washings through the catheter or of catheter replacement during the hospitalization; the registering of a temperature during the stay at the hospital equal to or greater than 37.5 ºC; the need to visit the emergency room during the first month after surgery because of symptomatology of the inferior urinary tract; and the need to re-hospitalize due to fever ≥38 ºC during the first month after surgery. We decided to use the temperature higher than 37.5 ºC during the hospitalization as an indicator of infectious complications because we think that shows an infection and not only inflammation secondary to surgery even without the presence of infection.

Whether the urine cultures were positive or negative, both the one solicited at the time of release and the one the week after were recorded, as was the microorganism isolated. A urinary culture was considered positive if it contained over 10^5 UFC/ml, for both men and women. The stage of the tumour according to the TNM and the degree according to the WHO classifications of 1973 and 2016 were noted as well.

Statistical analysis

A descriptive analysis was performed with the basal characteristics of the sample. For assessment of the main objective, a univariate analysis was performed comparing among the three groups those variables considered to indicate or relate

to infection: positive in any of the two solicited cultures for each patient, temperature ≥37.5 ºC during hospitalization, the need to visit the emergency room due to symptomatology of the lower urinary tract, and the re-hospitalization due to fever ≥38 ºC during the first month after the intervention.

For the secondary objective, the same four variables that may indicate infection were related though a univariate analysis with the rest of the pre-, intra- and postoperative variables of the study in order to see if these intra- and postoperative factors could prevent infection in TURBT. Those variables with a tendency to be significant ($p<0.2$) were included in the same way in a multivariate analysis.

For the univariate analyses, a Chi-squared test was used to compare percentages. A Mann-Whitney U-test or a Kruskall-Wallis test was performed in order to compare averages. For the multivaraite, binary logistic regression was performed. Furthermore, the minimal sample size to establish differences between groups A, B, and C was calculated, in case these existed. A sample size of 167 cases was calculated in order to find differences with a level of signification of $p<0.05$. All the calculations were performed with the SPSS v. 20.0 software (IBM Corp. Released 2011, Armonk, NY, U.S.).

Results

A total of 219 patients were included, 61 (27.9%) in Group A, 54 (24.7%) in Group B, and 104 (47.5%) in Group C. The baseline characteristics of the sample were homogeneous between the groups. The data can be observed in Table 1. As "oncological antecedent," we accept any type of neoplasm other than bladder cancer. The percentages of kinds of microorganisms isolated in the cultures can be consulted in Supplementary Table 1. The three most frequent were *E. faecalis* (in 5.7% of the total of 438 cultures of the study), *E. coli* (4.56%), and *Pseudomona* (1.82%). The mean length of stay in Groups A, B, and C was 2.33±1.53, 3.78±4.61, and 2.62±1.68 days, respectively.

The univariate analysis is shown in Table 2. It must be highlighted that up to 9.8% of the patients that received a single preoperative dose had a re-hospitalization within a month due to a fever ≥38 ºC at home (compared to 1.9% and 1% in the other groups). The multivariate analysis, shown in Table 3, reveals that the patients in Group A had 11.53 times more chances of re-hospitalization within a month due to fever than did those in Group C. There were no differences in the percentages of positive cultures in any of the three groups, with Group A being the one with the lowest percentage (18%) and Group C the one with the highest (31.7%).

The analyses corresponding to the relationship between pre-, intra- and postoperative factors with infectious complications are shown in Table 4. The results corresponding to stage and tumour degree are not shown in Table 3 because they are not statistically significant (these analyses can be seen in Supplementary Tables 2A and 2B). The multivariate analysis (Table 3) shows that those patients that were administered mitomycin postoperatively had a lower chance of a later culture being positive than those who did not receive chemotherapy (odds ratio [OR] 0.35; p=0.02). Still, those patients with over two days of hospitalization (OR 4.11; p≤0.01) and those who went into surgery with a urinary catheter (OR 12.35; p=0.02) had an increased risk of a positive urinary culture. Regarding the possibility of developing a temperature ≥37.5 ºC during hospitalization, tumoural necrosis (OR 7.48; p=0.01), the number or tumours (OR 1.32; p=0.01), and entering surgery with a catheter (OR 6.48; p=0.04) were all associated.

Discussion

TURBT is a urological procedure with a low rate of complication and mortality in comparison to other techniques. It is estimated that the complications oscillate from 4–6%, with urinary tract infection and hematuria being the most frequent.[8] Nevertheless, the mortality rate has been calculated at 1.3% within 30 days, and at 3.3% within 90 days.[9] Even though risk factors that have an influence on the development of general postoperative complications have been established, such as a low serum albumin, high blood levels of creatinine, low body weight, the location of the tumours in the bladder dome, or the status of the surgeon as resident doctor, the factors that predispose the appearance of infectious complications have not been clearly established.[9,10] Due to the frequency with which this surgery is performed, and the lack of evidence on the optimal use of preoperative antibiotics, the results of the following study may be of interest to the urological community.

Few of the current literature strictly recommend the use of antibiotics in TURBT preoperative, partially because of the lack of studies on the topic. Alsaywid et al, undifferentiating between TURBT and TURPT, affirm that the antibiotic prophylaxis in TURBT diminishes the postoperative bacteriuria from 17.6% to 6.8%, the symptomatic urinary infection from 10.1% to 2.9%, and the postoperative bacteremia from 6.1% to 2.1%.[3] Other authors distinguish different situations within TURBT in order to recommend the use of antibiotic prophylaxis or not, or the use of long antibiotic protocols. As such, in cases of small tumours, prophylaxis may not be recommended, while it is recommended in the case of big or necrotic tumours.[11] Regarding the prolonged antibiotic use for several days after the TURBT, there is no published evidence. Currently, there are only two existing clinical studies on the topic, both with small samples. In one of them, a single preoperative dose with pefloxacin was compared to placebo. The study included 61 patients and observed that the bacteriuria rate in the placebo group was significant at 24.1%, compared to 9.4% in the pefloxacin group, with no significant statistical

Table 1. Baseline characteristics of the sample

Variable	Group A (preop)	Group B (preop + hospitalization)	Group C (preop + hospitalization + home)	Total	p
Age	71.36±11.54	71.52±11.27	77.25±11.14	70.88±11.25	0.74*
Sex					
Male	48 (78.7%)	46 (85.2%)	87 (83.7%)	181 (82.6%)	0.61**
Female	13 (21.3%)	8 (14.8%)	17 (16.3%)	38 (17.4%)	
Primary					
Primary	33 (55%)	31 (57.4%)	61 (58.7%)	125 (57.3%)	0.90**
Recurrent	27 (45%)	23 (42.6%)	43 (41.3%)	93 (42.7%)	
High blood pressure					
Yes	27 (45%)	36 (66.7%)	57 (54.8%)	120 (55%)	0.06**
No	33 (55%)	18 (33.3%)	47 (45.2%)	98 (45%)	
Dyslipidemia					
Yes	32 (52.2%)	20 (37%)	53 (51%)	105 (47.9%)	0.17**
No	29 (47.5%)	34 (63%)	51 (49%)	114 (52.1%)	
Diabetes mellitus					
Yes	13 (21.3%)	12 (22.2%)	32 (31.4%)	57 (26.3%)	0.27**
No	48 (78.7%)	42 (77.8%)	70 (68.6%)	160 (73.7%)	
Neumopathy					
Yes	13 (21.3%)	9 (16.7%)	15 (14.6%)	37 (17%)	0.53**
No	48 (78.7%)	45 (83.3%)	88 (85.4%)	181 (83%)	
Cardiopathy					
Yes	5 (8.2%)	11 (20.4%)	17 (16.3%)	33 (15.1%)	0.16**
No	56 91.8%)	43 (79.6%)	87 (83.7%)	186 (84.9%)	
Neuropathy					
Yes	4 (6.6%)	5 (9.3%)	5 (4.8%)	14 (6.4%)	0.55**
No	57 (93.4%)	49 (90.7%)	99 (95.2%)	205 (93.6%)	
Vasculopathy					
Yes	8 (13.1%)	5 (9.3%)	12 (11.5%)	25 (11.4%)	0.80**
No	53 (86.9%)	49 (90.7%)	92 (88.5%)	194 (88.6%)	
Renal insufficiency					
Yes	6 (9.8%)	5 (9.3%)	11 (10.6%)	22 (10%)	0.96**
No	55 (90.2%)	49 (90.7%)	93 (89.4%)	197 (90%)	
Oncological antecedent	15 (24.6%)	13 (24.1%)	18 (17.3%)	46 (21%)	0.44**
Yes	46 (75.4%)	41 (75.9%)	86 (82.7%)	173 (79%)	
No					
Type of antibiotic					
Cefuroxime	54 (88.5%)	47 (87%)	95 (91.3%)	196 (89.5%)	
Ciprofloxacine	3 (4.9%)	5 (9.3%)	9 (8.7%)	17 (7.8%)	0.12**
Other	4 (6.6%)	2 (3.7%)	0 (0%)	6 (2.7%)	

*Kruskal-Wallis; ** Chi-squared.

differences. Furthermore, none of the patients in either group had symptomatic urinary infections.[12] In the other study, three doses of cephradine the day of the intervention was compared to using no drug.[4] Here, bacteriuria reached 17% of the cases in the no-antibiotic group and 4.5% in the cephradine group, with no significant differences.[6]

The present study, in contrast to the previous ones mentioned, gathered a bigger patient sample and registered variables other than bacteriuria, which may show the benefit of one or another antibiotic protocol. Without a group that did not receive antibiotics in our sample, there are no observable differences in the percentage of positive cultures between the different antibiotic protocols, although these can be seen in the percentage of patients that were re-hospitalized within the first month due to fever. Those with a single preoperative dose were 11.13 times more likely to re-hospitalized for fever than those with a prolonged antibiotic regimen.

The present sample showed that those patients with necrotic tumour characteristics had an augmented risk of temperatures over 37.5 ºC during the hospitalization. The necrosis of the urothelial tumour had been described as a factor that may translate into higher tumour aggressiveness and worse oncological results, but it has not been defined yet as a factor that would predispose for infection independently.[13] In the clinical guidelines of the European Association of Urology, tumour necrosis is referenced as a factor that turns a surgery into a contaminated one. This makes at least a single preoperative antibiotic dose recommended, and a

Table 2. Univariate analysis: Relationship between the variables indicative of infection and each group according to antibiotic protocol

Variable	Group A (preop)	Group B (preop + hospitalization)	Group C (preop + hospitalization + home)	Total	p
At least one positive culture					
Yes	11 (18%)	16 (29.6%)	33 (31.7%)	60 (27.4%)	
No	50 (82%)	38 (70.4%)	71 (68.3%)	159 (72.6%)	0.14*
Temperature ≥37.5 °C					
Yes	6 (10%)	5 (9.4%)	10 (9.8%)	21 (9.8%)	0.99*
No	54 (90%)	48 (90.6%)	92 (90.2%)	194 (90.2%)	
ER 1 month for urinary tract symptoms					
Yes	10 (16.4%)	7 (13%)	9 (8.7%)	26 (11.9%)	0.31*
No	51 (83.6%)	47 (87%)	95 (91.3%)	193 (88.1%)	
Re-hospitalization due to fever					
Yes	6 (9.8%)	1 (1.9%)	1 (1%)	8 (3.7%)	0.01*
No	55 (90.2%)	53 (98.1%)	102 (99%)	210 (96.3%)	

*Chi-squared. ER: emergency room

Table 3. Multivariate analysis: Relationship between the variables indicative of infection and the pre-, intra- and postoperative variables

Variable	p*	OR	95% CI
Dependent variable: Positivity in any of the two cultures			
Over two days of hospitalization	<0.00	4.11	1.87–9.00
Postoperative mmc	0.02	0.35	0.14–0.86
Entering surgery with catheter	0.02	12.35	1.39–109.94
Antibiotic protocol	0.19		
Group A	0.13	0.49	0.20–1.22
Group B	0.15	0.52	0.21–1.26
Group C	(ref)	1	--
Tumour necrosis	0.22	2.38	0.59–9.53
Duration of surgery (minutes)	0.74	1.00	0.98–1.03
Over two days with catheter	0.85	1.26	0.11–14.95
Size of largest tumour	0.91	0.99	0.89–1.11
Number of tumours	0.97	1.00	0.80–1.24
Dependent variable: Temperature ≥37.5 °C during hospitalization			
Tumour necrosis	0.01	7.48	1.76–31.69
Number of tumours	0.01	1.32	1.08–1.62
Entering surgery with catheter	0.04	6.48	1.06–39.62
Over two days of hospitalization	0.13	2.59	0.74–9.04
Antibiotic protocol	0.27		
Group A	0.79	1.18	0.35–3.98
Group B	0.14	0.30	0.06–1.51
Group C	(ref)	1	--
Duration of surgery (minutes)	0.51	0.99	0.94–1.03
Manual washes	0.73	0.79	0.20–3.05
Over two days with catheter	0.75	1.93	0.03–123.15
Postoperative MMC	0.75	0.74	0.12–4.50
Size of largest tumour	0.95	1.01	0.85–1.19
Dependent variable: Re-hospitalization due to fever ≥38 °C			
Antibiotic protocol	0.04		
Group A	0.03	11.13	1.31–94.79
Group B	0.65	1.93	0.12–31.38
Group C	(ref)	1	--
Number of tumours	0.06	1.32	0.99–1.76
Entering surgery with catheter	0.22	5.65	0.35–91.11
Size of largest tumour	0.51	1.07	0.88–1.29

*Logistic binary regression. CI: confidence interval; MMC: mitomycin; OR: odds ratio.

prolonged protocol worth considering. It has been previously described which tissue characteristics of the resected material in TURBT may influence — together with other factors — the appearance of bacteremia.[14] Furthermore, according to the results of the present study, entering surgery with a urinary catheter and the number of tumours were also related to an increased risk of elevated temperature during hospitalization. These variables had not been demonstrated previously as predisposing factors in an independent way with an augmented risk of febricula or fever in this context.

The result obtained from the use of postoperative mitomycin is worth mention. Those patients that received treatment with this cytostatic had a lower risk of having a positive urinary culture. Regarding the relationship between the instillation of mitomycin and infected bladders, there is published data. There is a higher absorption of the drug in the case of an infected bladder.[15] Nonetheless, as far as we know, the data in the present study is the first that shows a possible beneficial effect of the cytostatic on postoperative infection. Despite the typical histological changes in the bladder after the instillation of mitomycin, such as the denudation of the urothelium or the development of inlaid cystitis that might be viewed as predisposing to an infection, its use here presented a lower risk of positive cultures.[16] Even though it is true that a significant bacteriuria in postoperative TURBT does not always translate into infection, it is rather related to the intervention itself; this diminished risk of positive cultures may mean that mitomycin acts upon the microorganisms that cause the infection.[14,17] While it is true that currently there are topical drugs that have been proven effective in the prevention of repetitive cystitis, such as hyaluronic acid, these results may be the basis for future research into new treatments aimed at this.[18] Furthermore, wearing a catheter for over two days during postoperatively or entering surgery with it were also shown as factors that predisposed to having positive cultures.

Table 4A. Univariate analysis: Relationship between the variables indicative of infection and the intra- and postoperative variables

Variable	Entering surgery with catheter		Tumour size	Tumour necrosis		Number of tumours	Duration of surgery (min)	Stenosis of urethra		False urethral pathway	
	Yes	No		Yes	No			Yes	No	Yes	No
At least one positive culture											
Yes	7 (87.5%)	50 (24%)	5.23±4.24	7 (58.3%)	51 (25.1%)	3.39±2.68	38.94±16.75	4 (23.5%)	54 (27.3%)	2 (50%)	56 (26.5%)
No	1 (12.5%)	158 (76%) <0.001*	158 (76%) <0.001*	5 (41.7%)	152 (74.9%) 0.012*	2.15±1.86 0.008**	29.88±13.88 <0.001**	13 (76.5%)	144 (72.7%) 0.73*	2 (50%)	155 (73.5%) 0.29*
Temperature ≥37.5 ºC											
Yes	4 (57.1%)	16 (7.8%)	5.98±4.64	5 (41.7%)	16 (8%)	4.19±2.8	42.11±18.95	1 (5.9%)	19 (9.8%)	1 (25%)	19 (9.2%)
No	3 (42.9%)	189 (92.2%) <0.001*	3.79±3.5 0.019**	7 (58.3%)	183 (92%) <0.001*	2.3±2.03 0.001**	31.47±14.49 0.019**	16 (94.1%)	175 (90.2%) 0.59*	3 (75%)	188 (90.8%) 0.28*
ER 1 month for urinary tract symptoms											
Yes	1 (12.5%)	24 (11.5%)	4.36±3.18	1 (8.3%)	25 (12.3%)	2.84±2.3	30.6±10.34	0	25 (12.6%)	0	25 (11.8%)
No	7 (87.5%)	184 (88.5%) 0.93*	3.92±3.72 0.26**	11 (91.7%	178 (87.7%) 0.68*	2.44±2.17 0.38**	32.53±15.76 0.885**	17 (100%)	173 (87.4%) 0.119*	4 (100%)	186 (88.2%) 0.46*
Re-hospitalization due to fever											
Yes	1 (12.5%)	7 (3.4%)	5.88±3.97	0	8 (4%)	3.75±2.32	32.25±9.05	0	7 (3.6%)	0	7 (3.3%)
No	7 (87.5%)	200 (96.6%) 0.18*	3.91±3.64 0.12**	12 (100%)	194 (96%) 0.48*	2.44±2.18 0.023**	32.38±15.4 0.59**	17 (100%)	190 (96.4%) 0.42*	4 (100%)	203 (96.7%) 0.46*

*Chi-squared; **Mann-Whitney U.

Table 4B. Univariate analysis: Relationship between the variables indicative of infection and the intra- and postoperative variables

Variable	MMC postop		Perforation		Over 2 days hospitalization		Over 2 days catheter		Manual washes		Catheter replacement	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
At least one positive culture												
Yes	9 (10.7%)	48 (37.5%)	16 (32.7%)	41 (25.3%)	44 (44.4%)	16 (13.3%)	43 (43.9%)	17 (14%)	19 (31.1%)	40 (25.5%)	3 (30%)	57 (27.3%)
No	75 (89.3%)	80 (62.5%) <0.001*	33 (67.3%)	121 (74.7%) 0.31*	55 (55.6%)	104 (86.7%) <0.001*	55 (56.1%)	104 (86%) <0.001*	42 (68.9%)	117 (74.5%) 0.39*	7 (70%)	152 (72.7%) 0.85*
Temperature ≥37.5 ºC												
Yes	3 (3.8%)	17 (13.3%)	6 (12.2%)	14 (8.9%)	17 (17.5%)	4 (3.4%)	17 (17.5%)	4 (3.4%)	9 (15%)	12 (7.7%)	1 (10%)	20 (9.8%)
No	77 (96.2%)	111 (86.7%) 0.023*	43 (87.8%)	144 (91.1%) 0.48*	80 (82.5%)	114 (96.6%) 0.001*	80 (82.5%)	114 (96.6%) 0.001*	51 (85%)	143 (92.3%) 0.10*	9 (90%)	185 (90.2%) 0.98*
ER 1 month for IUTS												
Yes	7 (8.3%)	18 (14.1%)	7 (14.3%)	17 (10.5%)	14 (14.1%)	12 (10%)	13 (13.3%)	13 (10.7%)	4 (6.6%)	22 (14%)	1 (10%)	25 (12%)
No	77 (91.7%)	110 (85.9%) 0.206*	42 (85.7%)	145 (89.5%) 0.46*	85 (85.9%)	108 (90%) 0.34*	85 (86.7%)	108 (89.3%) 0.56*	57 (93.4%)	135 (86%) 0.12*	9 (90%)	184 (88%) 0.85*
Re-hospitalization due to fever												
Yes	3 (3.6%)	5 (3.9%)	1 (2%)	6 (3.7%)	5 (5.1%)	3 (2.5%)	5 (5.1%)	3 (2.5%)	3 (4.9%)	5 (3.2%)	1 (10%)	7 (3.4%)
No	81 (96.4%)	122 (96.1%) 0.89*	48 (98%)	155 (96.3%) 0.56*	94 (94.9%)	116 (97.5%) 0.32*	93 (94.9%)	117 (97.5%) 0.30*	58 (95.1%)	151 (96.8) 0.54*	9 (90%)	201 (96.6%) 0.27*

*Chi-squared; **Mann-Whitney U. ER: emergency room; IUTS: inferior urinary tract symptoms. MMC: mitomycin.

Some additional factors related to an augmented risk of infection are currently described in the literature, but the present analysis has not been able to validate these. Matulewicz et al, in a sample of 10 599 cases of TURBT, relate the duration of the intervention to an augmented risk of infection of the urinary tract and sepsis. Furthermore, the study gathers variables that have not been registered in the present study. They conclude that the prolonged duration of the surgical procedure independently increases the risk of deep venous thrombosis, myocardial infarction, and death.[8]

Other analyses performed on TURPT cases have related not only the duration of the intervention, but also the number of days of catheterization or the unplugging of the catheter's closed system as risk factors for bacteriuria.[19,20] No such relationship has been found for age, which might be thought of as an independent factor that increases the infectious complications after surgery. This matches with what is currently published.[21]

Our study presents some limitations. The main one is the lack of randomization because the patients received one antibiotic protocol or another according to the surgeon's criteria. Furthermore, this fact is the one that caused Group C to have a higher number of patients than the other two. The other limitation is that this study has been performed in a single centre. The ideal situation would have been a multicentre design so the results could have been more generalizable. For example, the microorganisms that cause infection may change with the area, and this fact could have been controlled if several centres had participated in the gathering of patients. Despite these limitations, especially given the scarcity of previous studies on the topic, the present one presents a larger sample, a greater number of intra- and postoperative variables recorded, and three different protocols for comparison.

Conclusion

Those patients that receive only one dose of antibiotic before TURBT may have an increased risk of re-hospitalization because of fever compared to those using a prolonged antibiotic protocol. Furthermore, tumour necrosis, the number of tumours, entering surgery with a urinary catheter, and prolonged hospitalizations, may predispose patients to the development of infectious complications. That notwithstanding, the instillation of postoperative mitomycin seems to reduce the risk of positive urinary cultures.

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Supplementary Table 1. Prevalence of different microorganisms in positive cultures within each group

Variable	Group A	Group B	Group C	Total	p
Microorganism					
E. Coli	5 (4.09%)	5 (4.62%)	10 (4.8%)	20 (4.56%)	
E. Faecalis	4 (3.27%)	8 (7.4%)	13 (6.25%)	25 (5.7%)	
Pseudomona	2 (1.63%)	2 (1.85%)	4 (1.92%)	8 (1.82%)	
Klebsiella	3 (2.45%)	0	4 (1.92%)	7 (1.59%)	
Proteus	0	0	1 (0.48%)	1 (0.22%)	
Enterobacter	0	1 (0.92%)	3 (1.44%)	4 (0.91%)	
S. Epidermidis	0	1 (0.92%)	0	1 (0.22%)	0.34*
Candida	0	1 (0.92%)	3 (1.44%)	4 (0.91%)	
Morganella	1 (0.81%)	1 (0.92%)	0	2 (0.45%)	
Citrobacter	0	2 (1.85%)	1 (0.48%)	3 (0.68%)	
Other	1 (0.81%)	0	2 (0.96%)	2 (0.45%)	

The percentages are on the total of cultures within each group. There are twice as many cultures as patients in each group because each subject was asked for two cultures. *Chi-squared test

Supplementary Table 2A. Univariate analysis: Relationship between the variables indicative of infection and histological variables

Variable	T							WHO classification 1973		
	T0	Ta	TIS	T1	T2	T3	T4	G1	G2	G3
At least one positive culture										
Yes	6 (26.1%)	20 (20.6%)	1 (25%)	17 (29.8%)	14 (45.2%)	0	1 (100%)	0 (0%)	22 (25.9%)	31 (30.7%)
No	17 (73.9%)	77 (79.4%)	3 (75%)	40 (70.2%)	17 (54.8%)	0	0 (0%) 0.077*	1 (100%)	63 (74.1%)	70 (69.3%) *0.63
T[a] >37.5 °C										
Yes	3 (13%)	7 (7.4%)	0 (0%)	9 (16.1%)	2 (6.5%)	0	0 (0%)	0 (0%)	6 (7.2%)	12 (12.1%)
No	20 (87%)	87 (92.6%)	4 (100%)	47 (83.9%)	29 (93.5%)	0	1 (100%) 0.52*	1 (100%)	77 (92.8%)	1 (100%) 0.52*
ER 1 month for UTS										
Yes	1 (4.3%)	11 (11.3%)	1 (25%)	7 (12.3%)	4 (12.9%)	0	0 (0%)	0 (0%)	8 (9.4%)	15 (14.9%)
No	22 (95.7%)	86 (88.7%)	3 (75%)	50 (87.7%)	27 (87.1%)	0	1 (100%) 0.83*	1 (100%)	77 (90.6%)	86 (85.9%) 0.49*
Re-hospitalization due to fever										
Yes	0 (0%)	4 (4.1%)	0 (0%)	2 (3.5%)	2 (6.5%)	0	0 (0%)	0 (0%)	3 (3.5%)	5 (5%)
No	23 (100%)	93 (95.9%)	4 (100%)	55 (96.5%)	29 (93.5%)	0	1 (100%) 0.88*	1 (100%)	82 (96.5%)	96 (95%) 0.87*

*Chi-squared test. ER: emergency room; UTS: urinary tract symptoms.

Supplementary Table 2B. Univariate analysis: Relationship between the variables indicative of infection and histological variables

Variable	WHO classification 2016	
	Low-grade	High-grade
At least one positive culture		
Yes	22 (25.6%)	31 (30.7%)
No	64 (74.4%)	70 (69.3%)
		0.43*
Tª >37.5 ºC		
Yes	6 (7.1%)	12 (12.1%)
No	78 (92.9%)	87 (87.9%)
		0.26
ER 1 month for UTS		
Yes	8 (9.3%)	15 (14.9%
No	78 (90.7%)	86 (5.1%)
		0.25*
Re-hospitalization due to fever		
Yes	3 (3.5%)	5 (5%)
No	83 (96.5%)	96 (95%)
		0.62*

*Chi-squared test. ER: emergency room; UTS: urinary tract symptoms.