ORIGINAL PAPER

URINARY TRACT INFECTIONS

Mulitcenter study on antibiotic prophylaxis, infectious complications and risk assessment in TUR-P

Laila Schneidewind[1*], Jennifer Kranz[2*], Daniel Schlager[3], Dimitri Barski[4], Sandra Mühlsteadt[5], Markus Grabbert[6], Fabian Queissert[7], Tanja Frank[8], Alexandre Egon Pelzer[9]

[1]*University of the Saarland Medical Center, Institute of Virology, Homburg, Germany*
[2]*St.-Antonius-Hospital, Department of Urology and Paediatric Urology, Eschweiler, Germany*
[3]*University of Freiburg Medical Center, Department of Urology, Freiburg (Brsg.), Germany*
[4]*Lukas Hospital Neuss, Department of Urology, Neuss, Germany*
[5]*Martin Luther University Halle-Wittenberg, Department of Urology, Halle, Germany*
[6]*Ludwig Maximilians University, Department of Urology, Munich, Germany*
[7]*University of Muenster Medical Center, Department of Urology, Muenster, Germany*
[8]*RoMed Hospital Rosenheim, Department of Urology, Rosenheim, Germany*
[9]*Hospital Wels-Grieskirchen, Department of Urology, Wels, Austria*
**equal author contribution*

Citation: Schneidewind L, Kranz J, Schlager D, et al. Mulitcenter study on antibiotic prophylaxis, infectious complications and risk assessment in TUR-P. Cent European J Urol. 2017; 70: 112-117.

Article history
Submitted: Oct. 31, 2016
Accepted: Jan. 9, 2017
Published online: Jan. 18, 2017

Corresponding author
Laila Schneidewind
Institution University of the Saarland Medical Center
Institute of Virology
66424 Homburg, Germany
Kirrberger Str. 100
phone: +49 171 321 86 87
laila.schneidewind@uni-greifswald.de

Introduction Transurethral resection of the prostate is one of the most frequent urological procedures. Urinary tract infections represent major sequelae, but data about antibiotic prophylaxis in TUR-P are controversial and outdated.

Material and methods We conducted a retrospective multicentre study of TUR-P in ten German hospitals. Primary endpoints were epidemiological and outcome data of TUR-P. Secondary endpoints were the identification of factors associated with febrile UTIs and sepsis after TUR-P.

Results We included 444 patients with a median age of 71.0 years. Nearly every patient (93.5%) received some kind of antibiotic prophylaxis. Complication rates were 4.9% for febrile UTIs and 2.3% sepsis. Significant risk factors associated with febrile UTIs were pre-existing risk factors for UTIs ($p = 0.035$) and a duration of catheterization of more than three days ($p < 0.0001$). Significant risk factors for sepsis were duration of surgery of more than 60 minutes ($p = 0.030$) and again a duration of catheterization of more than three days ($p < 0.0001$). Interestingly, 50.8% of the cases had evidence of chronic prostatitis in their histological specimen. This evidence of chronic prostatitis was significantly associated with febrile UTIs ($p = 0.019$) and sepsis ($p = 0.018$).

Conclusions Duration of catheterization is one of the major risk factors for infectious complications after TUR-P. Antibiotic prophylaxis in TUR-P needs prospective investigation. These future studies should also address chronic prostatitis a priori.

Key Words: antibiotic prophylaxis ‹› TUR-Prostate ‹› chronic prostatitis ‹› sepsis

INTRODUCTION

Transurethral resection of the prostate (TUR-P) is one of the most frequently performed urological procedures [1]. Urinary tract infections (UTIs) and other infectious complications like sepsis represent major sequelae in 1–26% of cases [1, 2]. TUR-P is a clean contaminated procedure and antibiotic prophylaxis is still controversial [1–6]. On the whole, data about antibiotic prophylaxis in TUR-P are controversial, sparse and out-dated. Additionally, UTIs are a substantial cause of global morbidity and mortality [7, 8] with the severe problem of increasing antibiotic resistance, especially of gram-negative bacte-

ria even to carbapenems, which are considered to be antibiotics of last resort [9].
These challenges require strong data to answer the questions when and how to perform antibiotic prophylaxis in TUR-P patients. Furthermore, epidemiological data about how antibiotic prophylaxis in TUR-P is performed in clinical practice and daily life is inhomogeneous and not up to date.
Therefore, we conducted a multicentre retrospective study of German hospitals (university medical centres and hospitals of tertiary care) with the primary endpoints of epidemiological and outcome data of TUR-P and its antibiotic prophylaxis. Secondary endpoints were the identification of factors associated with febrile UTIs and sepsis as complications of TUR-P.

MATERIAL AND METHODS

Development of the study and study population

The study was designed according to the guidelines in the synthesis of qualitative research (ENTREQ) found on the equatornetwork.org, an international initiative providing robust reporting guidelines [10]. We collected data from TUR-P patients from ten German hospitals with a department of urology including university medical centres (n = 4) and hospitals of tertiary care (n = 6). Patient data were collected retrospectively and consecutively before January 2016. All centres were supposed to document 50 patients or all patients treated in 2015 if less than 50 TUR-Ps are performed per year in the specific department. When conducting the study, we decided not to show a subgroup analysis specific by centre since there should be no threat to competition, especially in terms of complication rates. Palliative TUR-P was not an exclusion criterion. Additionally, we only considered complete records for analysis, and because of this fact 27 cases were excluded from the analysis. On the whole, we included 444 patients in this study.
Data from patients' treatment records included age, volume of the prostate in transrectal sonography in grams, pre-operative prostate specific antigen level (PSA), urine assessment including microbiology, risk factors for UTI (see 2.2), resection technique (mono-/bipolar resection; high or low pressure resection), duration of surgery in minutes, data about antibiotic prophylaxis (frequency, duration and type of antibiotic), data about the type of catheter, complication rates especially including febrile UTIs or sepsis and data about the histological specimen.
The data was documented with the database program Microsoft Excel and then transferred into an SPSS 23.0 data bank for statistical analysis.
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, a formal consent was not required.

Definitions and statistical analysis

We defined pre-existing risk factors for UTIs as antibiotic treatment due to UTI in the last six month prior to TUR-P, pre-operative catheterization of the urinary tract, recurrent UTIs in the past, post void residual urine (>100 ml), diabetes mellitus, abnormalities in the urinary tract (congenital anatomical abnormalities/functional abnormalities/urolithiasis) and immunosuppressive medication.
Febrile UTI was defined as proven UTI in standard microbiology of the urine and fever more than 38.5 degrees Celsius. Additionally, sepsis was defined as proven UTI in the presence of criteria of a systemic inflammatory response syndrome (SIRS). These criteria are fever (≥38.0 degrees Celsius) or hypothermia (≤36.0 degrees Celsius), tachycardia (≥90/min), tachypnea (≥20/min) and leukocytosis (≥12.000/μl) or leukocytopenia (≤4.000/μl). If the blood culture was negative, all four of the SIRS criteria needed to be fulfilled to diagnose sepsis. If the blood culture was positive two of the SIRS criteria were sufficient for a diagnosis of sepsis.
End of catheterisation is defined as the absence of any type of catheter in the urinary tract. Patients who left the hospital with a catheter (transurethral or suprapubic) were excluded for analysis of this measurement (n = 20).
Evidence of infection in the histological specimen was defined as infection/prostatitis mentioned in the final pathology report. We discriminated between fluent and chronic prostatitis.
Other complications meant all adverse events during the inpatient treatment other than febrile UTIs or sepsis.
For each numeric variable, the numeric distribution was preliminarily assessed by the Kolmogorov-Smirnov test. Descriptive statistics were made with median and range for non-parametric data. Since all relevant categorical and continuous variables for statistic testing were non-parametric, we used the Mann-Whitney U test. All reported p-values were based on a two-sided hypothesis, $p < 0.05$ was considered to be significant. All statistical calculations were performed using statistical package for the Social Sciences 23.0 software (SPSS Inc., Chicago, Il, USA).

RESULTS

Demographic characteristics of the study population and outcome data

We included 444 male patients with a median age of 71.0 years (range 45.0–93.0) in our retrospective analysis of TUR-P. Table 1 gives an overview of the basic demographic characteristics of the study population. Relating to the defined pre-existing risk factors for UTI, 135 (30.4%) patients had no risk factor at all, 200 (45.0%) had one risk factor, 87 (19.6%) two, 17 (3.8%) three and 5 (1.2%) even four risk factors for UTI. Due to the retrospective design of the study data about a catheterisation prior to surgery was not available. Antibiotics used for prophylaxis were penicillins with or without beta-lactamase inhibitors in 19 (4.6%) patients, in 272 (65.5%) cephalosporins, in 111 (26.7%) fluoroquinolones and in 17 (3.2%) cases any other groups of antibiotics. The median duration of antibiotic treatment was 1.0 day, whereby single shot treatment was used in 211 (50.8%) cases. Table 2 provides an overview of the outcome data of the study population. Febrile UTIs occurred in 22 (4.9%) of patients while sepsis was found in 10 (2.3%) patients. E.coli was the causative factor of 82.7% of the febrile UTIs and 17.3% were due to Enterococci. Other complications occurred in 67 (15.1%) of the patients, bleeding was the most frequent and occurred in 35 (7.9%) patients. Interestingly, in 176 (39.6%) patients only a post-operative standard microbiology of the urine was performed, of those 154 (87.5%) were negative.

Parameters associated with febrile UTI or sepsis

Levels of significance of the association of clinical parameters with febrile UTI or sepsis are shown in Table 3 including absolute numbers of the clinical parameters. Febrile UTI is significantly associated with the presence of at least one pre-existing risk factor for UTI and most importantly with a duration of catheterisation of more than 3 days. Sepsis, on the other hand, is significantly associated with a higher prostate volume and also a longer duration of the TUR-P, the group of antibiotic used for prophylaxis and a longer duration of catheterisation as well.
Since the group of antibiotic drug used for prophylaxis was significantly associated with sepsis, we performed a subgroup analysis, which is shown in Table 4 including absolute numbers. We found no significant association of the subgroups penicillins with or without beta lactamase inhibitors, cephalosporins, fluoroquinolone or any other antibiotic with febrile UTI and sepsis.

Table 1. *Demographic characterisation of the study population (n = 444)*

	n (%)	Median	Range
Age		71.0	45.0–93.0
Indication for TUR-P: Prostate cancer (palliative)	15 (3.4)		
Indication for TUR-P: Benign prostate hyperplasia	429 (96.6)		
PSA level in ng/ml		2.6	0–594.5
Prostate volume (transrectal sonography) in gram		40.0	10.0–150.0
Pre-surgery UTI	93 (20.9)		
Defined Risk factors for UTI	309 (69.6)		
Monopolar resection	224 (50.5)		
Bipolar resection	220 (49.5)		
Low pressure resection	205 (46.2)		
High pressure resection	239 (53.8)		
Resection volume in gram		20.0	1.0–100.0
Antibiotic prophylaxis	415 (93.5)*		
Duration of surgery in minutes		55.0	10.0–195.0
Duration of antibiotic application in days		1.0	0.0–20.0

*Main reason for not receiving UTI: no risk factors for UTI

Table 2. *Post-operative outcome of the study population (n = 444)*

	n (%)	Median	Range
Only transurethral catheter	275 (61.9)		
Transurethral and suprapubic catheter	169 (38.1)		
Duration of catheterisation		3.0	1.0–24.0
Incidence of febrile UTI	22 (4.9)		
Incidence of sepsis	10 (2.3)		
Incidence of other complications	67 (15.1)		
Duration of inpatient treatment		5.0	2.0–28.0
Carried out post-operative standard microbiology	176 (39.6)		
Evidence of infection in histological specimen	235 (52.9)		

Evidence of infection in histological specimen and its associations

As we mentioned before, in 235 (52.9%) of the patient's resection material the pathologist found evidence of infection indicating fluent or chronic prostatitis. Furthermore, the majority was chronic prostatitis in 230 (50.8%) patients. Table 5 shows an overview of the associations of chronic prostatitis

Table 3. *Clinical parameters associated with febrile UTI or sepsis after TUR-P (n = 444)*

Parameter	n (%) of the Parameter	n (%) of the Parameter in febrile UTI	Association with febrile UTI p value	n (%) of the Parameter in sepsis	Association with sepsis p value
Age >70 years	227 (51.1)	7 (31.8)	0.997	4 (40.0)	0.070
Prostate volume transrectal ultrasonography >40 grams	191 (43.0)	10 (45.5)	0.869	8 (80.0)	0.049
Pre-existing UTI	93 (20.9)	2 (9.1)	0.241	2 (20.0)	0.682
Pre-existing defined risk factors for UTI	309 (69.6)	14 (63.6)	0.035	3 (30.0)	0.265
Defined risk factors >2	109 (24.5)	14 (63.6)	0.004	8 (80.0)	0.004
Monopolar resection	224 (50.5)	12 (54.5)	0.088	6 (60.0)	0.212
High pressure resection	239 (53.8)	7 (31.8)	0.872	2 (20.0)	0.745
Duration of surgery >60 minutes	144 (32.4)	9 (40.9)	0.525	7 (70.0)	0.030
Volume of prostate resection >40 grams	64 (14.4)	5 (22.7)	0.776	4 (40.0)	0.135
Antibiotic prophylaxis	415 (93.5)	21 (95.5)	0.698	9 (90.0)	0.656
Groups of antibiotic drug used for prophylaxis	4 different groups	4 different groups	0.866	4 different groups	0.035
Simultaneous catheterisation: transurethral and suprapubic	169 (38.1)	9 (40.9)	0.778	6 (60.0)	0.149
Duration of catheterization >3 days	198 (44.6)	19 (86.4)	<0.0001	10 (100.0)	<0.0001

Table 4. *Association of antibiotic subgroups used for prophylaxis with febrile UTI or sepsis (n = 415)*

Antibiotic Subgroup	n (%) of the antibiotic subgroup	n (%) of the Parameter in febrile UTI	Association with febrile UTI p value	n (%) of the Parameter in sepsis	Association with sepsis p value
Penicillin with or without beta lactamase inhibitor	19 (4.6%)	0 (0)	Not possible	0 (0)	Not possible
Cephalosporine	272 (65.5%)	15 (71.4)	0.815	9 (100.0)	0.219
Fluorochinolone	111 (26.7%)	5 (23.8)	0.820	0 (0)	Not possible
Any other antibiotic subgroup	17 (3.2%)	1 (4.5)	0.858	0 (0)	Not possible

Table 5. *Association of chronic prostatitis in the resection material with clinical parameters (n = 444)*

Parameter	n (%) of the Parameter	n (%) of the Parameter in chronic prostatitis in histology	Association with chronic prostatitis in histology p value
Age >70 years	227 (51.1)	109 (48.0)	0.151
PSA level >4.0 ng/ml	81 (18.2)	50 (61.7)	0.659
Prostate volume transrectal ultrasonography >40 grams	191 (43.0)	107 (56.0)	0.428
Pre-existing UTI	93 (20.9)	65 (69.9)	0.064
Pre-existing defined risk factors for UTI	309 (69.6)	155 (50.2)	0.957
Febrile UTI	22 (4.9%)	17 (77.3)	0.019
Sepsis	10 (2.3%)	9 (90.0)	0.018

with different clinical parameters and especially post-operative febrile UTI and sepsis. The association of chronic prostatitis with post-operative febrile UTI ($p = 0.019$) and with sepsis ($p = 0.018$) was significant.

DISCUSSION

We conducted a multicentre retrospective study of 444 TUR-P patients and their antibiotic prophylaxis in Germany. Interestingly, the majority of patients (93.5%) received an antibiotic prophylaxis with cephalosporins. The median duration of antibiotic treatment was 1.0 day, whereby single shot treatment was used in 211 (50.8%) cases. In turn, this means nearly 50% of the patients are treated longer than prophylaxis would apply. EAU guidelines recommend single shot prophylaxis and there is little evidence for a longer prophylaxis. Adherence

to EAU guidelines on antibiotic prophylaxis can reduce antibiotic usage without increasing postoperative infection rate and can lower prevalence of resistant uropathogens [11]. In our study population, 69.6% of the patients had one or more risk factors for UTI. This might be the reason for extending the duration of antibiotic prophylaxis in clinical practice. However, there is a danger in doing so; we might do more harm with longer duration of antibiotic prophylaxis and have no evidence for a benefit of this procedure. On the whole, these are key questions which need to be answered on a prospective basis.

In our study population, we found 4.9% febrile UTIs and 2.3% sepsis following TUR-P during inpatient treatment which is little in comparison to published data [1, 2]. This might be due to the fact that nearly every patient received antibiotic prophylaxis. But does every patient require antibiotic prophylaxis? This question is still controversially discussed [1, 3–6]. We did not perform a subgroup analysis considering this question since it did not seem reasonable with 93.5% patients receiving antibiotic prophylaxis. However, this open question should be addressed in prospective studies, especially since reduction of antibiotic use might decrease resistance rates [11].

Interestingly, 15.1% of the patients had other complications than febrile UTIs or sepsis. Bleeding was the most frequent of those adverse events with 7.9% and so the most frequent complication in this study population. This raises the question for patient blood management in TUR-P. Patient blood management is a real up-to-date topic since, especially due to demographic development, there are less and less packed blood products available and there is some evidence that blood transfusion can also lead to negative clinical outcomes [12]. Since this study was conducted for antibiotic prophylaxis we had no data about anticoagulants, blood counts or transfusions available, but urologists should also address this current issue in further investigations.

In our study population, significant factors associated with UTI were the presence of one pre-existing risk factor for UTI, more than two pre-existing risk factors for UTI and most importantly a duration of an indwelling catheter of more than three days. Significant risk factors for sepsis were a volume of the prostate in transrectal ultrasound of more than 40 grams, more than two defined pre-existing risk factors, duration of surgery of more than 60 minutes, the group of antibiotic drugs used for prophylaxis and a duration of an indwelling catheter of more than three days. On the whole, the most important findings were that pre-existing risk factors for UTI seem to summate, the duration of the indwelling catheter seems to be the most important risk factor and, concerning sepsis, duration of the surgery needs to be considered. These results are somewhat self-explanatory, but also difficult to compare to other published studies. Most of the prospective studies use bacteriuria as the end point for risk factor analysis [2, 13, 14, 15]. We could not use bacteriuria as the endpoint due to the retrospective study design, and due to the fact that urine analysis after TUR-P was not mandatory in all included centres. Additionally, one prospective study concluded that postoperative bacteriuria after transurethral surgery is not a risk factor for infectious post-operative complications. Therefore, routine post-operative urine analysis should be advocated only in symptomatic patients [14]. Another study showed that operating time, duration of catheterization, and disconnection of the closed urine drainage system may influence the occurrence of bacteriuria after bipolar TUR-P [15]. This is comparable to our results concerning febrile UTIs and sepsis. Consequently, we must conclude that duration of catheterization is one of the most important risk factors for febrile UTI and sepsis after TUR-P. Clinicians should weigh very carefully how long a catheter after surgery is really necessary.

Since we found the group of antibiotic used for prophylaxis was also significantly associated with febrile UTI and sepsis, we performed a subgroup analysis, which was not conclusive and showed no significant association. However, we think that this fact is confounded by several issues like switching of antibiotic treatment, in some cases long duration of therapy and multiple different antibiotic drugs in the subgroups. Again, this fact along with antibiotic resistance patterns should be addressed in prospective studies.

Surprisingly, 50.8% of the patients had some evidence of chronic prostatitis in their histological specimen and this chronic prostatitis was significantly associated with febrile UTI and sepsis. Furthermore, one study concluded that their findings challenge the commonly held view that urine is the primary source of bacteraemia in TUR-P-associated sepsis and raise the possibility of occult prostatic infection as a cause of bacteraemia. More work is needed to determine the significance of transient bacteraemia in relation to more serious complications like infective endocarditis and malignancy [13]. Our findings support this conclusion. Nevertheless, the clinical problem remains: knowledge about a possible chronic prostatitis is often only available after receiving the pathology report. One solution to this problem might be to specifically ask the patient about symptoms of chronic prostatitis before surgery and perform a microbiology analysis of a 2–4 glass test. Therefore,

a cost-benefit-analysis seems to be reasonable. Furthermore, the chronic inflammation might be linked to the pathogenesis of benign prostate hyperplasia, but for this problem further experimental studies are needed.

Despite its limitations, like selection bias due to retrospective study design, our study also identified some important key points. Additionally, in Germany prospective studies concerning antibiotic prophylaxis in TUR-P are desperately needed, especially due to increasing antibiotic resistance.

CONCLUSIONS

The major risk factor for febrile UTI and sepsis after TUR-P is the duration of catheterization, and this fact should be addressed in daily routine. Additionally, the duration of catheterisation can be easily influenced by urologists. Antibiotic prophylaxis in TUR-P needs prospective investigation. Chronic prostatitis in TUR-P patients is very common and also a risk factor for febrile UTI and sepsis. This fact needs further investigation as well, especially in experimental studies.

CONFLICT OF INTEREST AND COMPLIANCE WITH ETHICAL STANDARDS

This retrospective study received no funding.

No competing financial interests or conflicts of interest exist for all authors.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this kind of study an informed consent was not required. This article does not contain any animal studies performed by any of the authors.

ACKNOWLEDGEMENTS

We would like to thank all participating centres.

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