Comparison of the effectiveness of two combinations of antibiotic used for perioperative prophylactic therapy during radical cystectomy: A retrospective cohort study

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Abstract

Introduction: This retrospective cohort study aimed to compare primary and secondary outcomes of patients undergoing radical cystectomy according to two different perioperative antimicrobial therapy protocols in 2016.
Methods: In this single-center, retrospective cohort study, we investigated data of 104 patients undergoing radical cystectomy due to bladder cancer from January 1, 2016, to December 31, 2016. According to perioperative antimicrobial prophylaxis, patients were divided into two groups: 48 patients received piperacillin/tazobactam 3x4.5 g intravenously (IV) combined with metronidazole 3x500 mg IV, and 56 patients received ceftriaxone 1x2 g IV combined with metronidazole 3x500 mg IV. All patients received the first dose of antibiotics 24 hours prior to the operative procedure, and it continued over the next 48 hours after the procedure. We analyzed and compared data from various primary and secondary outcomes for both groups of patients.
Results: In the group of patients receiving the combination of the piperacillin/tazobactam with metronidazole, the length of postoperative hospitalization was shorter (14 vs. 16 days, Z=2.24957 p=0.02383), leukocyte blood count on the first postoperative day was lower (9.80 vs. 11.15, p=0.01384), and hospital-acquired pneumonia was less common (2.08% vs. 12.5%, p=0.04688) than in the group receiving a combination of ceftriaxone and metronidazole.

Conclusions: In radical cystectomy, perioperative antimicrobial prophylaxis protocol using piperacillin/tazobactam combined with metronidazole proved to be more effective than the combination of ceftriaxone with metronidazole.

Introduction

Urinary bladder cancer is the 10th most frequently diagnosed cancer worldwide, approximately with 549, 000 new cases and 200,000 deaths every year[1,2]. The age-standardized incidence rate of bladder cancer in The European Union is 19.1 for men and 4.0 for women[3]. The main risk factor for developing invasive urinary bladder cancer is cigarette smoking, with worse outcomes in females than males [1,2,3].

Radical cystectomy is the standard treatment for invasive urinary bladder cancer. The operation includes resection of the distal ureters, lymph nodes, prostate gland, and seminal vesicles in men and the resection of the urethra, adjacent vagina, and uterus in women with dissection of lymph nodes in both men and women[3]. Three standard types of urine diversion are performed: the abdominal wall diversions (ureterocutaneostomy, ileal or colonic conduit, continent pouches); the orthotopic diversion or neobladders, and the rectosigmoid diversions (Mainz Pouch II)[3,4]. In the first postoperative month, relative survival of patients with invasive bladder cancer who underwent cystectomy ranged from 97.1% to 98.8% while the range from 72.9% to 91.3% was noticed after five to six postoperative months depending on tumor stage[5].

Perioperative antibiotic prophylaxis is a part of the routine procedure in the surgical treatment of patients with invasive bladder cancer. However, worldwide, there is significant heterogeneity in the recommended antibiotic prophylaxis and duration. According to data available on the internet, a few medical centers recommend the use of 1st or 2nd generation of cephalosporins in a combination with metronidazole (MDZ), while other centers recommended a combination of penicillin with a beta-lactamase inhibitor, and a combination of aminoglycosides, MDZ, and ampicillin. According to available guidelines, the combination of piperacillin and tazobactam (TZP) is most often recommended as alternative antimicrobial prophylaxis without the additional use of MDZ. The duration of antibiotic prophylaxis also shows significant variation and ranges from a single-dose administration to administration in the course of 24 hours and up to 72 hours[6,7,8,9,10,11,12,13,14].

The Department of Urology of the Clinical Hospital Sveti Duh in Zagreb has a long tradition of successful treatment of invasive bladder cancer, with more than a hundred patients undergoing radical cystectomy annually. During radical cystectomy, two combinations of antibiotics were used for all surgical procedures (with and without intestinal penetration). The first combination comprises ceftriaxone (CRO) at a dose of 1x2 grams together with MDZ 3 x 500 mg over 3 days, while the second combination comprises TZP 3x4.5 grams with MDZ 3x500mg over 3 days. The routine practice included administration of the first dose of antibiotics 24 hours prior to the operative procedure, which continued up to 48 hours after the procedure. Continuous and

systematic monitoring of postoperative courses and complications related to the procedure itself was done routinely. With this retrospective study, we wanted to compare the effectiveness of these two antibiotic combinations and contribute to the uniformity of recommended antibiotic prophylaxis and a better surgical outcome.

Methods

Study participants

We retrospectively analyzed the medical records of 125 patients with bladder cancer undergoing radical cystectomy at Clinical Hospital Sveti Duh in the period from January 1. 2016 to December 31. 2016. Based on the preoperative antibiotic prophylaxis, patients were divided into two groups. The first group received a combination of CRO 1x2g and MDZ 3x500mg over 3 days (CRO+MDZ group), as already described. The second group received a combination of TZP 3x4.5 grams in combination with MDZ 3x500 mg also for 3 days (TZP+MDZ group).

Study design

A total of 21 patients were excluded from the study: 13 patients due to preoperative urinary tract infection that required antibiotic treatment, four patients due to a recorded primary tumor originating outside the bladder affecting the urothelium, two patients underwent radical cystectomy due to a non-malignant disease (vesica contracta and neurogenic bladder) and two patients due to incomplete documentation. All male patients underwent a radical cystectomy. Female patients underwent anterior pelvic exenteration including regional extended lymphadenectomy, with aiming for a complete oncological local eradication of the disease. The urine derivatives used were continental orthotopic small intestinal derivation according to Hautmann, and urethral ileo-cutaneous derivation according to Bricker and uretero-cutaneous stoma (incontinent forms). Operation Mainz Pouch II (rectosigmoid diversions) was performed on two patients. The indication for surgery was determined based on the oncology patient's physical condition, biopsy results after the resection of bladder tumors performed transurethrally in previous surgery, and also on the willingness of the patient for the orthotopic pouch. Contraindications to Hautman derivation were: older age (80 years and older), neurological complications that prevent frequent urination according to instructions, or possible postoperative self-catheterization needs, further patients with renal failure (patients with renal clearance below 60 ml/minute), or other severe metabolic disorders, with chronic intestinal disease, or after abdominal and/or pelvic radiotherapy.

In both patients` groups, standard demographically, analytically, and clinically relevant parameters were analyzed: age, gender, concomitant chronic diseases such as diabetes mellitus, arterial hypertension, renal failure, chronic obstructive pulmonary disease (COPD), the existence of hydronephrosis, vascular heart disease, stage of tumor disease, length of preoperative hospital stay, duration of surgery and type of surgery. During the treatment, the following parameters were monitored: the C-reactive protein values (CRP) and the leukocytes blood count (L) on the 1st, 2nd, and 3rd postoperative day, the onset of the first postoperative urinary tract infection, the onset of the second postoperative urinary tract infection, postoperative infection of the surgical site, hospital-

acquired pneumonia, systemic infection, length of hospital treatment in the intensive care unit (ICU), the total length of postoperative treatment and colonization with multidrug-resistant organisms (MRO) at the end of hospital treatment. Superficial, deep, and organ surgical site infection (SSI) were counted as one entity.

Study outcome measures

The primary outcomes of the study were as follows: duration of total postoperative hospitalization in days, duration of ICU hospitalization in days, number of patients with one UTI, number of patients with two UTI, number of patients with HAP, number of patients with SSI, number of patients with BSI, number of patients colonized with MRO, and number of deaths.
The secondary outcomes of the study were the level of L and CRP measured on the 1st, 2nd, and 3rd postoperative days.

Statistical analysis and definitions

Data storage and processing for statistical analysis were performed using Microsoft Excel 2013 (Microsoft, USA). Continuous variables were presented as mean and standard deviation (SD) if they had normal distribution, or median and interquartile range (IQR) if they did not. Comparisons between groups were made using a Student's t-test for normally distributed variables or Mann Whitney test for non-normally distributed ones and using chi^2-test or Fisher exact test for categorical variables. The data were analyzed using STATISTICA version 10 (StatSoft, Inc. Tulsa, OK). Statistical significance was set to $p<0,05$ for all tests.

Bacteriuria is defined as the presence of bacteria in the urine[15]. Febrile urinary tract infection (UTI) was defined as bacteriuria with fever[8]. SSI was defined following criteria for superficial SSI, deep incisional SSI, and organ/space SSI set by the National Health Safety Network, Center For Disease Control and Prevention, Surgical Site infection event[16]. The clinical stage of the tumor is defined by the 2015 NCCN guidelines[17]. Assessment of the clinical stage of invasive bladder cancer was based on routine examinations that included: general urological examination, cystoscopy, partial resection of the primary tumor with pathohistological diagnosis, intravenous urography, pelvic and abdominal CT, and chest X-ray.
MRO was defined as follows: carbapenem-resistant Enterobacterales (CRE), methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* species (VRE). *Clostridioides difficile* (CD) associated diarrhea was defined as the detection of CD toxins production in the diarrheal stool[18]. Bloodstream infection (BSI) was defined as bacteremia with fever (>38°C) or hypothermia (<36°C), tachypnea (respiratory rate>20), tachycardia (heart rate>90), and inflammatory response (elevated CRP and L)[19]. Hospital-acquired pneumonia (HAP) was defined as pneumonia that occurs 48 hours or more after hospital admission if not presented at the time of admission[20].

Results

In both patient groups, standard demographically, analytically, and clinically relevant parameters were analyzed: age; gender; concomitant chronic diseases such as diabetes mellitus; arterial

hypertension; renal failure; COPD; hydronephrosis; vascular heart disease; stage of tumor disease; length of preoperative hospital stay; duration of surgery and type of surgery. Except for hydronephrosis which was more common in the TZP+MDZ group (39.6% vs 19.6%, p=0,02524) no other significant differences were found between the two groups (Table 1). None of the patients included in this study were treated with neoadjuvant chemotherapy before the surgical procedure.

Primary outcomes such as hospitalization in the ICU, a total hospital stay, infectious complications such as UTI, HAP, SSSI, and BSI, are summarized in Table 2. The median duration of total postoperative hospital stay was significantly longer in the CRO+MDZ group than in the TZP+MDZ group (16 days vs 14 days, p=0,02383). HAP after surgical treatment appeared statistically more often in the CRO+MDZ group than in the TZP+MDZ group (12.5% vs 2.08%, p= 0,04688).

Secondary outcomes such as level of CRP and L on 1st, 2nd, and 3rd postoperative days and results of statistical evaluation are summarized in Table 3. The median level of L on the 1st postoperative day was significantly higher in the CRO+MDZ group compared to the TZP+MDZ group (11.145 vs. 9.8; Z=2,46149, p=0,01384).

Although there were no statistically significant differences between two groups in the levels of CRP and L on the 2nd and 3rd days it is worth noticing that the patients in the TZP+MDZ group had lower levels of both parameters in the observed period (Figures 1 and 2).

Discussion

In this retrospective study we compared two different protocols for antibiotic prophylaxis used for radical cystectomy. Based on our results the protocol using TZP+MDZ was superior to the one using CRO+MDZ. The shorter duration of postoperative hospitalization, a lower incidence of HAP, and a lower median L on the first postoperative day was recorded in the TZP+MDZ group. Although the higher number of patients with hydronephrosis before surgical treatment in the TZP+MDZ group was statistically significant, those patients had better outcomes compared to the patients in the CRO+MDZ group. Available protocols for the perioperative antimicrobial prophylaxis recommend the different antibiotic combinations as well as the different duration of antibiotic administration[6,7,8,9,10,11,12,13,14]. In the study done by Ross et al., two different prophylactic, antibiotic protocols during radical cystectomy were compared and no association between different regimens and the incidence of postoperative infections has been detected[23]. The spectrum of antimicrobial activity of the prophylactic antibiotics used in radical cystectomy must include intestinal microbiota, mainly gram-negative bacteria, anaerobes, and *Enterococcus* spp. TZP, due to the spectrum of antibacterial activity, is an excellent drug for the treatment of anaerobic infections. The combination of CRO+MDZ shows a similar spectrum of antimicrobial activity with no efficacy on the genus *Enterococcus*. The combined therapy consisting of MDZ with TZP should not be considered superior to the TZP monotherapy in the treatment and prevention of anaerobic infections. Current guidelines recommend the administration of the first dose of antibiotics during the induction of anesthesia with the completion of the first dose of antibiotics before the incision[19,21]. Recent work also indicates the possibility of short-term antibiotic usage,

over 24-hours, showing superiority to long-term antibiotic administration[22]. Most of the available guidelines recommend a single dose or a 24-hour treatment[6,7,8,9,10,11,12,12,14].

The study showed some limitations. This was retrospective study and some cases of SSI, UTI, HAP, or BSI may not have been recorded. Although this was a single-center study, the number of patients included was not negligible (N=104). The TZP + MDZ group had statistically significant shorter postoperative stay, but there was no significant difference in the incidence of UTI, SSI, or BSI between both groups. Also, monotherapy with TZP is sufficient for the anaerobic microbiota, therefore no need for combination therapy with MDZ during radical cystectomy. Further, available studies have shown that female gender is associated with a poorer outcome of radical cystectomy in bladder cancer treatment[3,24]. Although the percentage of women in the CRO + MDZ group is higher than in the TZP + MDZ group, statistical analysis of baseline demographic data did not reveal a significant difference between groups (p=0,36994), and data for both genders were processed together. We suggest that future studies should be multicenter studies in order to achieve a higher rate of patient enrolment and perhaps the results of incidence of postoperative infections would show a different pattern.

Conclusions

Our study suggests that the antibiotic prophylaxis with combination of TZP + MDZ is better than the CRO + MDZ combination in the perioperative prophylaxis of radical cystectomy. Future studies should investigate the effect of short-term antibiotic prophylaxis in radical cystectomy and compare the antibiotic prophylaxis with TZP alone with CRO + MDZ combination. The short-term usage of antimicrobial prophylaxis should result with a lower antibiotic pressure on the gut microbiota, lower selection of multidrug-resistant bacterial strains and health-care associated infections.

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Figures and Tables

Figure 1. Comparison of median C-reactive protein (CRP) levels on 1st, 2nd, and 3rdpostoperative day. CRO: ceftriaxone; MDZ: metronidazole; TZP: tazobactam.

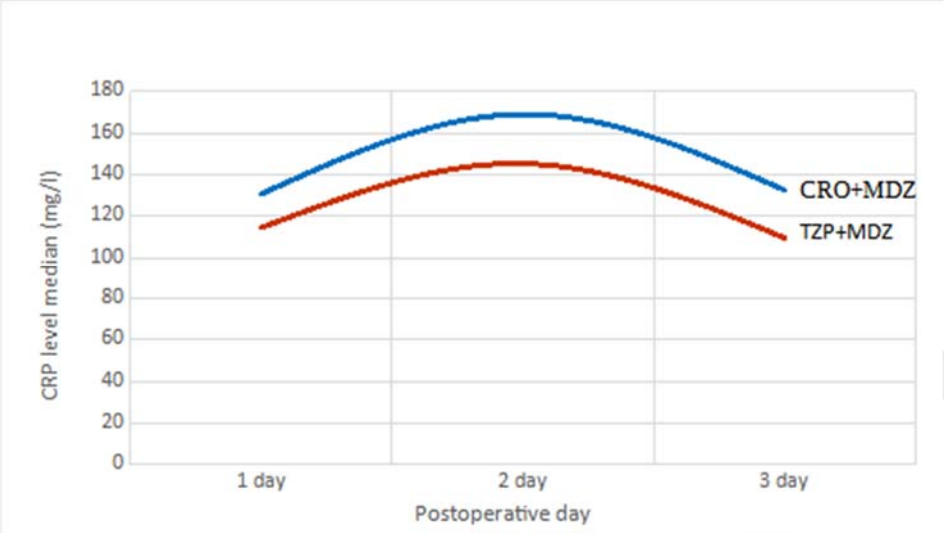

Figure 2. Comparison of median leukocyte blood count on 1st, 2nd, and 3rd postoperative day. CRO: ceftriaxone; MDZ: metronidazole; TZP: tazobactam.

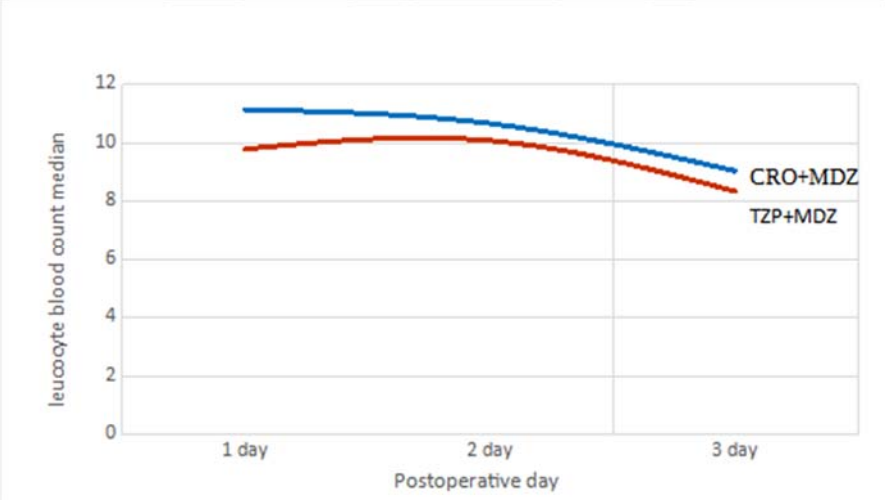

Table 1. Baseline demographic and clinical characteristic of two compared groups			
	TZP+MDZ	**CRO+MDZ**	**Statistical significance**
N	48	56	
Male/female, n (%)	34/14 (70.8%/19.2%)	35/21 (62.05%/37.95%)	p=0.36994*
Age, mean (SD)	65.38 (8.64)	65.86 (9.48)	p=0.78822*** t=0.26934***
Diabetes mellitus, n (%)	8 (16.7%)	10 (17.9%)	p= 0.87290*
Renal insufficiency, n (%)	3 (6.3%)	5 (8.9%)	p=0.60932*
Arterial hypertension, n (%)	27 (56.3%)	32 (57.1%)	p=0.92700*
COPD, n (%)	1 (2.1%)	6 /10.7%)	p=0.07990*
Coronary heart disease, n (%)	5 (10.4%)	5 (8.9%)	p=0.79747*
Another malignant disease, , n (%)	5 (10.4%)	7 (12.5%)	p=0.74025*
T1, n (%)	7 (14.6%)	6 (10.7%)	p=0.55200*
T2, n (%)	12 (25.0%)	19 (33.9%)	p=0.32102*
T3, n (%)	10 (20.8%)	7 (12.5%)	p=0.25193*
T4, n (%)	19 (39.6%)	24 (42.9%)	p=0.73538*
Hydronephrosis, n (%)	19 (39.6%)	11 (19.6%)	**p=0.02524***
Bricker, n (%)	22 (45.8%)	21 (37.5%)	p=0.38962*
Hautman, n (%)	18 (37.5%)	24 (42.9%)	p=0.57885*
Mainz pouch II, n (%)	0 (0.0%)	2 (3.6%)	p=0.18620*
Urethrorocutaneous stoma, , n (%)	8 (16.7%)	9 (16.1%)	p=0.93478*
Duration of operative procedure in minutes, mean, (SD)	286.34 (40.93)	282.08 (43.02)	t=0.51633** p=0.60674**
Duration of preoperative hospitalization in days, median (IQR)	5 (3)	5 (2)	t=-0.97598** p= 0.33139**

*Chi-square test, df=1. **Mann Whitney test. ***Student t-test. The clinical stage of the tumor is defined by the 2015 NCCN guidelines as T1, T2, T3, and T4. COPD: chronic obstructive pulmonary disease; CRO: ceftriaxone; IQR: interquartile range; MDZ: metronidazole; SD: standard deviation; TZP: tazobactam.

Table 2. Primary outcome measures of the patients included in the study			
Primary outcome measures	**CRO+MDZ (56)**	**TZP+MDZ (48)**	**Statistical significance**
Duration of hospitalization in ICU in days, median (IQR)	13 (7.5)	10.5 (6)	Z=1.32366 p=0.18562**
Duration of total postoperative hospitalization in days, median (IQR)	16 (6.5)	14 (7.5)	Z=2.24957 p=0.02383**
Patients with 1 postoperative UTI, n (%)	29 (51.8%)	21 (43.75%)	p=0.41355*
Patients with 2 postoperative UTI, n (%)	10 (17.86%)	7 (14.58%)	p=0.65265*
Patients with HAP, n (%)	7 (12.5%)	1 (2.08)	p=0.04688*
Patients with SSI, n (%)	4 (7.14%)	3 (6.25%)	p= 0.85624*
Patients with bloodstream infection, n (%)	3 (5.36%)	3 (6.25%)	p=0.84564*
Patients colonized with MRO, n (%)	17 (30.36%)	16 (33.33%)	p=0.74511*
Exitus, n (%)	1 (1.79%)	1 (2.08%)	p=0.91227*

*Chi-square test, df=1. **Mann Whitney test. CRO: ceftriaxone; HAP: hospital-acquired pneumonia; ICU: intensive care unit; IQR: interquartile range; MDZ: metronidazole; MRO: multidrug-resistant organism; SSI: surgical site infection; TZP: tazobactam; UTI: urinary tract infection.

Table 3. Secondary outcomes measures in two compared groups with results of statistical evaluation											
CRP blood level										**Student t-test**	
Post-operative day	**Group**	**N**	**Mean**	**Median**	**Min**	**Max**	**Lower QR**	**Upper QR**	**SD**	**t**	**p**
1st day	CRO+ MDZ	56	135.5107	130.7	60.9	289.2	106.85	154.85	44.56026	1.93115	0.05624
	TZP+ MDZ	48	120.1458	114.45	36	217.5	96.5	145.1	35.03143		
2nd day	CRO+ MDZ	56	169.7804	169.05	61.4	371	120.5	209.6	63.31779	1.11139	0.26901
	TZP+ MDZ	48	155.3854	145.3	55	405.6	109.15	173.35	68.69033		
3rd day	CRO+ MDZ	56	133.1196	132.55	36.2	264.7	91.9	183.35	56.17899	0.66640	0.50666
	TZP+ MDZ	48	124.8208	109.55	25.2	360.7	78.9	145.4	70.74966		
Leukocyte blood level										**Mann Whitney test**	
Post-operative day	**Group**	**N**	**Mean**	**Median**	**Min**	**Max**	**Lower QR**	**Upper QR**	**SD**	**Z**	**p**
1st day	CRO+ MDZ	56	12.0374	11.145	7.2	22.6	9.69	13.8	3.21584	**2.46149**	**0.01384**
	TZP+ MDZ	48	10.9877	9.8	4.95	33.6	8.48	12.28	4.72443		

2nd day	CRO+ MDZ	56	13.4025	10.67	5.8	90	9.12	13.65	11.76591	1.42799	0.15330
	TZP+ MDZ	48	12.4058	10.085	5.1	110.4	7.755	12.325	14.83038		
3rd day	CRO+ MDZ	56	10.9064	9.05	5.58	46.4	7.42	11.55	7.01671	0.98134	0.32643

CRO: ceftriaxone; MDZ: metronidazole; SD: standard deviation; TZP: tazobactam.