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의학석사 학위논문

경피적 신절석술의 예방적 항생제 사용과 감염합병증에 대한 무작위 임상 연구

Antibiotic Prophylaxis and Infectious Complication in Percutaneous Nephrolithotomy : A Randomized Clinical Trial

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이 논문을 의학석사 학위 논문으로 제출함

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채한규의 의학석사학위 논문을 인준함

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국문요약

경피적 신절석술은 크기가 큰 신결석의 표준 치료로 시행되고 있다. 상기 수술의 감염 관련 합병증을 예방하기 위해 수술 전후로 사용되는 예방적 항생제는 경피적신절석술 시행 후 감염의 위험을 줄여주는 것으로 알려져 있다. 상기 예방적 항생제의 표준 치료에 대해서 우리 나라에서는 아직 무작위 연구가 없는 상태로, 본 연구에서는 2015 년부터 2017 년까지 본원에서 시행한 경피적 신절석술 환자 58 명 중 40 명을 대상으로 두 가지 용법의 수술 전 예방적 항생제 사용군으로 나누어 수술 후 감염에 의한 발열 및 전신염증반응증후군 발생 여부의 차이를 전향적으로 확인하고자 하였다.

수술 전 무작위 배정에 따라 20 명씩 각각 두 군으로 나눈 후, 1 회 사용군에서는 수술 직전 한차례의 정주 항생제 투입만을 시행하고 3 회 사용군에서는 수술 직전 한 차례의 정주 항생제 투여 시행 후 신루 제거 시까지 경구 항생제를 투여하였였다. 두 군에서 공통적으로 투여될 정맥 항생제는 ceftriaxone sodium 을 수술 시작 30 분전에 예방적 항생제로 한 차례 투여하며, 경구 항생제 추가 투여군에서 술 후 1 일째부터 3 세대 cefpodoxime proexetil 을 하루 2 회 신루를 제거하는 날까지 투여하기로 하였다.

본원에서 시행된 경피적 신절석술 환자 중 연구대상에서 제외된 18 명 중 7 명에서 수술 전 소변 배양 검사상 의미있는 세균뇨를 확인하였고 가장 흔하게 배양된 균은 *E. coli* 였다. 환자의 평균 연령은 55.3 (28-72) 세였고 실험군에서 수술 후 38℃ 이상의 열이 발생한 환자는 없었고 대조군에서 한 명의 발열 환자가 있었다 (P=0.33). 결석 배양 양성은 대조군에서 1 명 있었고 *Proteus mirabilis* 가 배양되었으며 양쪽 그룹에서 유의한 차이는 없었다(P=0.33). 수술 후 전신염증반응증후군은 각 군에서 4 명씩 발생하였고 균혈증은 두 군 모두에서 발생하지 않았으며 유의한 차이는 없었다 (P=1.0).

경피적 신절석술에서 예방적 항생제 사용시 1 회 사용군과 3 회 사용군에서 수술 후 발열 및 전신염증반응증후군의 발생 빈도는 양 군에서 유의한 차이가 없었고 한국에서 항생제 내성균 발생이 증가하는 현재 시점에서 수술 전 1 회의 예방적 항생제 사용이 적절할 것으로 판단된다.

차 례

그림목차

Introduction

Percutaneous nephrolithotomy (PCNL) is the preferred method of removing renal calculi, particularly among the patients with a large or complex stone burden, resulting in stone free rates exceeding 90% (1). Postoperative complications associated with PCNL include fever, bleeding, urinary leakage, and other problems resulting from residual stones (2). Among them, fever is one of the most serious complications associated with PCNL. Although operating upon patients with sterile preoperative urine is considered safe, infectious complications such as fever are encountered in up to 25% of patients after PCNL and severe sepsis occurs in about 1% of patients. More commonly, patients experience less severe symptoms of infection postoperatively, including fever (21%–74%), bacteriuria (10%–37%), and bacteremia (20%–35%). Postoperative fever which is not always related to infections, is one of the most common complications after PCNL. In addition, rates of systemic inflammatory response syndrome (SIRS) can be as high as 23.4%-29% (3). With the current situation,

antibiotic prophylaxis before PCNL is considered important to prevent the infectious complications. Despite the existence of a universal agreement about the need for application of antimicrobial prophylaxis, the optimum administration period of antibiotics for PCNL remains controversial. Varied antibiotic regimens were proposed by the European Association of Urology (EAU) (trimethoprim/ sulfamethoxazole, second- or third-generation cephalosporin, aminopenicillin/ beta-lactamase inhibitors, and fluoroquinolones) and the American Urological Association (AUA) (first- or second-generation cephalosporin, aminoglycoside plus metronidazole or clindamycin, ampicillin/sulbactam, and fluoroquinolones) guidelines (4). However, increasing antimicrobial resistance is a major concern, and resistance patterns vary by region, which are changing secondary to use of different antibiotic regimens in various areas (5).

In this study, we selected third-generation cephalosporins as prophylactic antibiotics and prospectively compared the infectious events and prophylactic efficacy of 2 antibiotic regimens against postoperative infection and infection-

related events such as pyrexia, bacteriuria, and SIRS. Through the study, we attempted to compare the clinical efficacy of a single-dose protocol of a prophylactic antimicrobial agent (2 g intravenous [IV] ceftriaxone) with that of a 3-d protocol in PCNL.

Materials and methods

A total of 58 adult patients with renal stones underwent PCNL at Asan Medical Center between October 2015 and August 2017. Patients having any of the following conditions were excluded from the study: preoperative significant bacteriuria with positive urine culture, indwelling catheter, acute immediate postoperative complication (bleeding that needed angioembolization or pneumothorax requiring chest tube insertion), previous antibiotics use within 2 wk, previous history of infectious stone, allergy to antibiotics, pregnancy, and refusal to participate in the study. Eighteen patients were excluded (Fig 1). A total of 40 patients were randomized into "single-dose group" and "3-d group".

The procedure of this study was approved by the Asan Medical Center Institutional Review Board, and informed consent was obtained from all patients. Enrolled patients underwent laboratory tests, including complete blood count, blood electrolyte and chemistry, routine urinalysis, and midstream urine culture before surgery. During each operation time, pelvic urine samples and fragmented

stone were obtained for culturing and analysis during PCNL. The stone burden was measured by estimating the longest stone diameter on computed tomography analysis of urinary stones. The sum of the largest diameters of all stones was obtained by adding up the maximal length of each stone.

All PCNLs were performed by a single surgeon in the standard aseptic manner and with the patients in the prone position. All patients had the same ureteral catheter and urethral catheter during the operation, and urethral catheters were removed after the patients were mobilized. A nephrostomy tube was inserted in place after the operation.

Patients in the sigle-dose group (n = 20) were administered only a single dose of 2 g ceftriaxone IV during induction of anesthesia 30 min before the operation, whereas the 3-d group (n = 20) was administered ceftriaxone combined with an oral third-generation cephalosporin (Cefpodoxime proxetil) until the day of nephrostomy catheter removal. Vital signs were monitored postoperatively every 2 hours in the first 48 h, then every 8 h thereafter until the patient was

discharged. Fever was reported if the patient presented with a body temperature of >38.0°C at least once. The nephrostomy tube inserted intraoperatively was kept for 48 h, and removed after the patient underwent antegrade pyelography, unless a complication occurred requiring an extended period of drainage. Additional urine and blood cultures were taken from patients in whom fever developed in the postoperative period. Chest radiography was performed in all patients who had supracostal access, to rule out thoracic complications. None of the enrolled patients needed secondary interventions before nephrostomy removal.

The aim of this study was to compare prophylactic efficacy between 2 antibiotic regimens against postoperative infection and infection-related events such as pyrexia, bacteriuria, and SIRS. SIRS was diagnosed when a patient met 2 of the following 4 criteria: body temperature <36°C or >38°C, heart rate >90 beats/min, respiratory rate >20 breaths/min or PCO_2 >32 mmHg, and leukocyte count >12 x 10^3 cells/mm^3 or < 4 x 10^3 cells/mm^3 (Table 1) (6). The SPSS 24.0 program was

used for statistical analysis (SPSS Inc, Chicago, IL, USA). Differences between groups were tested for significance by using the chi-square test, t-test, and Mann-Whitney U-test. The level of statistical significance was defined as $P < 0.05$.

Results

The mean patient age was 55.3 years (range 28-72 years). There were no significant differences between 2 groups with regard to demographics, surgery, or stone characteristics (Table 2). Among the 7 patients excluded because of significant bacteriuria, Escherichia coli was the most commonly isolated microorganism, followed by Proteus mirabilis (Table 3). The mean operation time was 60.9 min in the single dose group and 58.9 min in 3-d group, and there was no difference between the 2 groups (p=0.7). Two patients in the single-dise group and 3 patients in the 3-d group needed postoperative transfusion (Table 4). Table 5 lists the postoperative infections that occurred. Fever (body temperature > 38.0°C) developed in none (0.0%) of the patients in the single-dose group and 1 (5.0%) patient in the 3-d group (p=0.33). In this patient, blood culture result was negative. Analysis of renal pelvic urine samples revealed bacteriuria in none of the patients in both for single-dose and 3-d groups. Positive stone cultures developed in 1 patient (5.0%) in 3-d group, with no

significant difference between the 2 groups (P = 0.33). The specific pathogen colonizing the stones in those patient was Proteus mirabilis. Postoperatively all patients were closely monitored for signs of sepsis. SIRS developed in 8 patients (20.0%): 4 patients in single-dose group and 4 patients in 3-d group (P = 1.0). This result suggests that fever alone does not indicate postoperative SIRS. The incidence of SIRS did not demonstrate any association between 2 groups.

Discussion

The mechanisms for the development of urinary tract infection after PCNL include the release of bacteria from surgical manipulation, fragmentation of renal calculi (struvite or large non-struvite stones), and the introduction of bacteria through the nephrostomy tract, which traverses through skin, retroperitoneum, and renal parenchymal tissues and other urinary tract components. In a case series of 107 patients with preoperative sterile urine who did not receive antibiotic prophylaxis, post-PCNL bacteriuria was found in 35% of the patients, whereas only 10% of the patients developed post-PCNL fever and about 1% developed severe sepsis (7). This result strongly indicates that use of antibiotics before PCNL is mandatory. Meanwhile, appropriate selection of antibiotics appears to be significant in this era of antibiotic stewardship. However, there is a distinct gap between the increasing burden of infections caused by multiresistant bacteria, especially gram-negative bacteria, and the appropriate selection of antibiotics is becoming more difficult. This gap is unlikely to be filled in the near

future (8).

Various studies reported multiple pathogens and antibiotic sensitivities to those pathogens after PCNL. Turck and Stamm mostly isolated E. coli and other microorganisms such as Proteus, Klebsiella, Enterobacter and Pseudomonas in patients after PNL (9). By contrast, Demirtas et al. reported that coagulase-negative Staphylococcus is the most commonly isolated organism from postitive stone culture (10). In a multicenter study performed by Farrell et al., the antibiotic sensitivity rates of E. coli, Klebsiella pneumonia, Pseudomonas aeruginosa, and Proteus mirabilis were reported to be 98%, 94%, 89% and 87%, respectively (11). Medina-Polo et al. reported that urinary stone is one of the risk factors for extended-spectrum β-lactamases(ESBL)-producing bacteria, in addition to previous urinary tract infection and immunosuppression (12). Furthermore, the prevalence of resistance to commonly prescribed antibiotics in primary-care patients with urinary tract infections caused by E. coli is high (13). The resistance rates of uropathogenic E. coli to various antibiotics have been reported as

follows: beta-lactams (57.4%), cotrimoxazole (48.5%), quinolones (74.5%), gentamicin (58.2%), amikacin (33.4%), cefuroxime (56%), nalidixic acid (77.7%) (14). In this current situation, the AUA best-practice statement recommends 24 h or less of antibiotic prophylaxis before percutaneous renal surgery in all patints, even without evidence of infection (15). Meanwhile, the EAU guidelines recommend cephalosporins (second or third generation), cotrimoxazole, fluoroquinolones, or aminopenicillin/beta-lactamase inhibitor combination for prophylaxis without any preference (16).

However, these recommendations were challenged by another study suggesting that extended-duration preoperative antibiotic therapy even in the setting of a negative preoperative urine culture may decrease the risk of infectious complications postoperatively (17). Bag et al. suggested that prophylaxis with nitrofurantoin for a week before PCNL is beneficial in preventing urosepsis and endotoxemia in patients with larger stones and hydronephrosis.

Furthermore, Zowawi et al. clearly showed that the prevalence of antibiotic

resistance in gram-negative pathogens varies considerably worldwide, which implies that the frequency of antibiotic resistance in Asia is relatively higher than in Western countries (18). (Figs. 2, and 3) Edlin et al. analyzed 25,418 urinary isolates, and found that resistance to first- and second-generation cephalosporins (cephalothin, cefazolin, or cefuroxime) was higher than to third-generation cephalosporins (19).

On the other hand, the efficacy of single-dose vs short-course antibiotic prophylaxis has been investigated. Dogan et al. divided 81 patients with preoperative sterile urine who underwent PCNL into 2 groups. The first group (n = 43) received a single intravenous dose of an antibiotic (200 mg ofloxacin) during anesthesia induction, and the second group (n = 38) received treatment doses of antibiotic (400 mg ofloxacin/d) until the nephrostomy catheter was removed. No statistical difference was observed between the 2 groups in terms of bacteriuria, bacteremia, positive stone cultures, or postoperative fever (20).

The other study included 90 patients who had no internal problem, yet had a

negative urine culture and underwent a PCNL operation. The authers compared the infection rates between the ciprofloxacin and ceftriaxone groups and their subgroups. The results also showed no statistical difference between ciprofloxacin and ceftriaxone groups in terms of SIRS (10).

As demonstrated in the 2 previous studies on the use of antibiotic prophylaxis before PCNL, our study also suggests the efficacy of single-dose antibiotic prophylaxis in Asian patients, who tend to carry more numbers of antibiotic-resistant uropathogens than Western patients.

To our knowledge, this is the first prospective randomized trial about the use of antibiotic prophylaxis with PCNL in Asian patients. Several studies have reported that more than 30% of the E. coli isolates from Korean patients are resistant to ciprofloxacin. Considering the high incidence of antibiotic resistance in E. coli isolated from Korea, reducing the overuse of antibiotics is important (21).

Post-PCNL SIRS is common and has the potential to progress to life-threatening sepsis in a minority of patients (22). Furthermore, Cadeddu et al. stated that fever

and bacteremia after PCNL are common, although progression to sepsis is rare (23). The incidence of infectious complications in patients undergoing PCNL is rare under antibiotic prophylaxis. Owing to the relatively small number of enrolled patients, our data revealed only 1 patient with postoperative fever after PCNL, which shows less signiticant difference between the 2 groups. However, in our data, 8 patients (4 patients in each group) satisfied the criteria of SIRS after PCNL. The incidence of postoperative SIRS after PCNL seemed not to differ between single-dose and 3-d groups.

Further studies including larger numbers of patients are needed to reinforce our recommendation.

Conclusions

The 3-d antibiotic prophylaxis regimen was not superior to the single-dose prophylaxis regimen with regard to the rate of postoperative fever or SIRS in patients receiving PCNL for renal stones. Therefore, considering the increasing incidence of antibiotic-resistant microorganisms causing urinary tract infections worldwide, especially in Asia, single-dose prophylaxis may be a better option for patients undergoing PCNL without preoperative bacteriuria.

Figure 1. Flow diagram

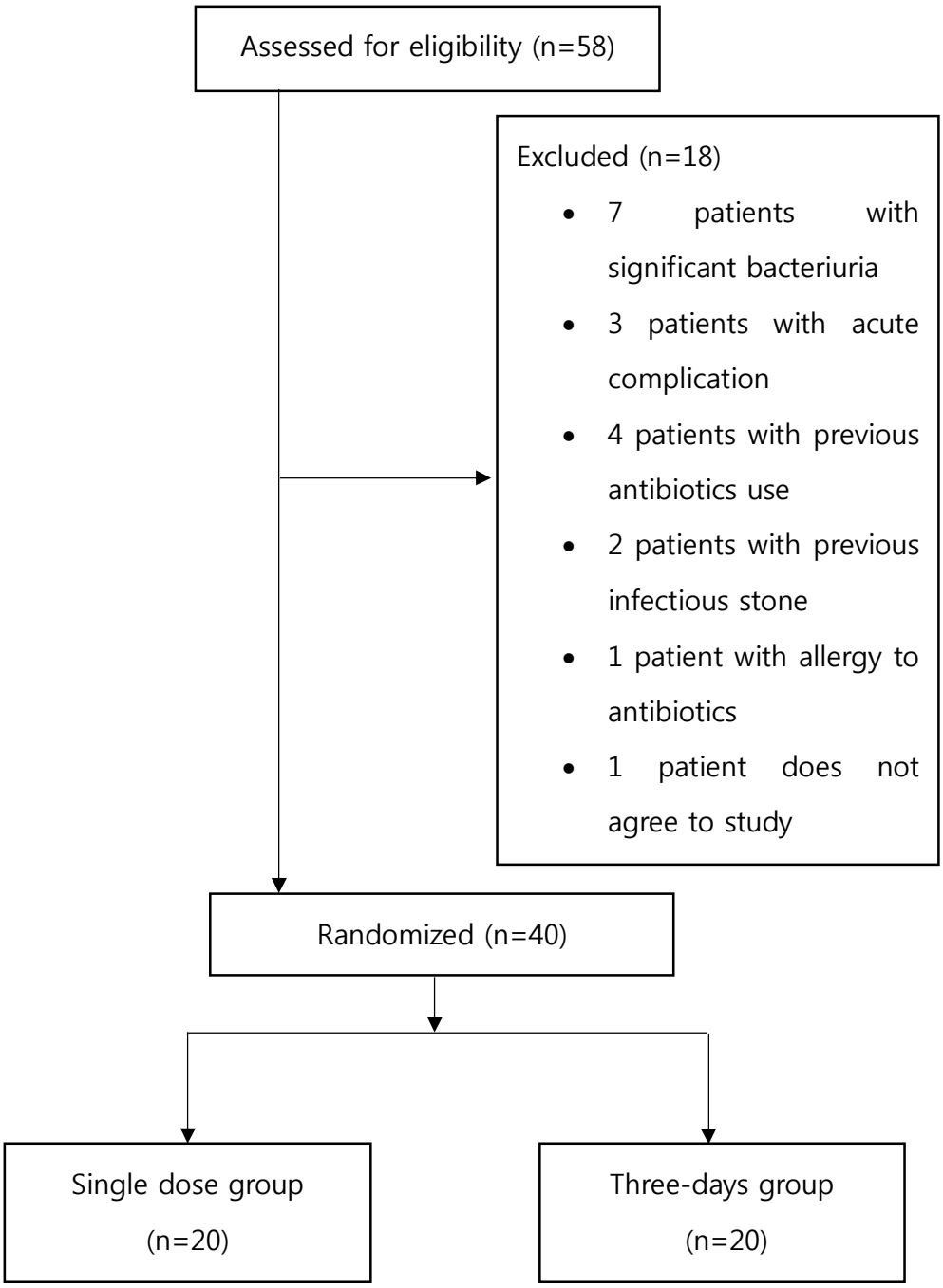

Figure 2. Global epidemiology of resistance in gram-negative uropathogens: fluoroquinolones (18).

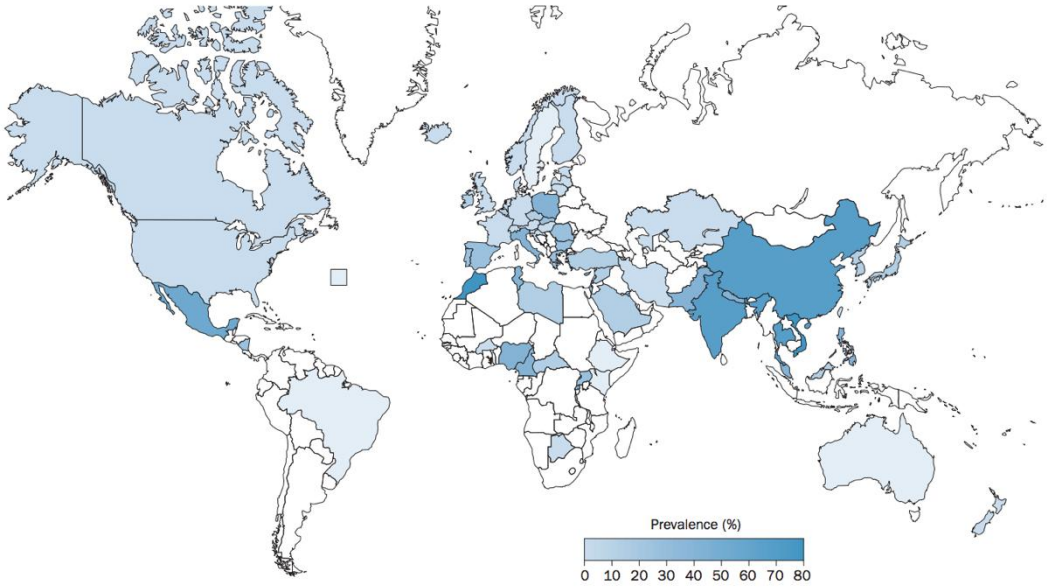

Figure3. Global epidemiology of resistance in gram-negative uropathogens: third-generation cephalosporins (18).

TABLE 1. SIRS, INFECTION, AND SEPSIS DEFINITIONS

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)
TWO OR MORE OF THE FOLLOWING:
BODY TEMPERATURE >38°C OR <36°C
HEART RATE >90 BPM
RESPIRATORY RATE >20 BREATHS/MIN OR $PACO_2$ <32 MMHG
WHITE BLOOD CELL COUNT >12,000 CELLS/ML OR <4,000 CELLS/ML
INFECTION
PATHOLOGICAL PROCESS CAUSED BY INVASION OF NORMALLY STERILE TISSUE OR FLUID OR BODY CAVITY BY PATHOGENIC OR POTENTIALLY PATHOGENIC MICRO-ORGANISMS
SEPSIS
CLINICAL SYNDROME DEFINED BY THE PRESENCE OF BOTH SIRS AND INFECTION
SEVERE SEPSIS
SEPSIS RESULTING IN ORGAN DYSFUNCTION
SEPTIC SHOCK
SEPSIS RESULTING IN ACUTE CIRCULATORY FAILURE CHARACTERIZED BY PERSISTENT ARTERIAL HYPOTENSION

Table 2. Cohort demographics: Single-dose group vs 3-d group

	Single-dose group (n=20)	Three-day group (n=20)	p
Female/male	2/18	6/14	
Mean age ± SD (years)	56.7 ± 10.1	54.0 ± 11.1	0.42
Mean BMI ± SD (kg/m^2)	26.8 ± 3.8	26.4 ± 3.3	0.72
Stone side ± SD (Right/Left)	8/12	10/10	
Mean stone size ± SD (cm)	6.0 ± 2.7	6.3 ± 2.1	0.72
Mean preoperative WBC ± SD (x10^3 /μL)	7.18 ± 1.9	6.7 ± 1.4	0.39
Mean preoperative CRP ± SD (mg/dL)	0.5 ± 1.4	0.3 ± 0.4	0.55

BMI, body mass index; WBC, white blood cell count; CRP, C-reactive protein; SD, standard deviation

Table 3. Distribution of isolated microorganisms in excluded patients (n=7)

	No. of patient (%)	No. of patient resistant to ceftriaxone (%)	No. of patient resistant to ciprofloxacin (%)
Escherichia coli	3 (43%)	0 (0%)	1 (33%)
Proteus mirabilis	2 (29%)	0 (0%)	0 (0%)
Candida albicans	1 (14%)		
Citrobacter baumani	1 (14%)	1 (100%)	0 (0%)

Table 4. Intraoperative and postoperative findings

	Single-dose group (n=20)	Three-day group (n=20)	p
Operation time ± SD (min)	60.9 ± 15.9	58.9 ± 16.7	0.70
No. of puncture location (%)			
Intercostal	14 (70%)	11 (55%)	
Subcostal	6 (30%)	9 (45%)	
Estimated blood loss			
Mild	16 (80%)	17 (75%)	
Moderate	4 (20%)	3 (15%)	
No. of RBC transfusion	2 (10%)	3 (15%)	
Mean duration of nephrostomy placement ± SD (day)	2.7 ± 0.9	2.8 ± 0.5	0.53
Mean hospital stay ± SD (day)	6.2 ± 1.1	6.4 ± 1.5	0.20

RBC, red blood cell; SD, standard deviation

Table 5. Infectious events

	Single-dose group (n=20)	Three-day group (n=20)	p
No. of patient with postoperative fever ≥ 38.0° (%)	0 (0.0%)	1 (5.0%)	0.3
No. of patient with positive renal pelvic urine (%)	0 (0.0%)	0 (0.0%)	1.0
No. of patient with positive stone culture (%)	0 (0.0%)	1 (5.0%)	0.8
No. of patient with SIRS (%)	4 (20%)	4 (20%)	1.0

SIRS, systemic inflammatory response syndrome;

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