ORIGINAL RESEARCH

Efficacy of Single Dose Intravenous Antibiotic Prophylaxis for the Prevention of Postoperative Systemic Inflammatory Response Syndrome in Patients Undergoing Percutaneous Nephrolithotomy: A Randomized Controlled Study

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Introduction: Despite universal agreement on the application of antimicrobial prophylaxis, the optimum administration period of antibiotics for percutaneous nephrolithotomy (PCNL) remains controversial and the risk for antimicrobial resistance due to prolonged antibiotic use as well as financial burden that may prove to be challenging for both the patient and the physician. This study therefore aims to determine the safety and effectiveness of a single dose antibiotic prophylaxis in patients undergoing PCNL.

Methods: A randomized controlled trial was conducted in PCNL patients between 2021-2023. The patients were randomly assigned to three groups: single dose prophylaxis 30 minutes before surgery arm (Group A), 30 minutes before and 12 hours after surgery arm (Group B), and continued antibiotics until removal of nephrostomy tube arm (Group C), respectively.

Results: A total of 81 patients were included (Group A=27, Group B=28, and Group C=26). The rate of comorbidities did not differ significantly in the three groups: HTN (p=0.166), DM (p=0.121), and Others (p=0.405). The presence of hydronephrosis was seen in 70.4% of patients. About half had solitary stone type (54.3%) and had left area affected (51.8%). Also, 14.8% had history of UTI. The patient groups did not differ in clinical and operative characteristics (all p>0.05) except in history of previous stone surgeries. Significantly more patients had previous history of stone surgeries in Group A (37.0%) than in Group B (3.6%) and Group C (15.4%) (p=0.006). The following proportion of no growth in preoperative urine culture was observed: Group A (92.6%), Group B (89.3%), and Group C (80.8%) (p=0.174). The estimated blood loss was significantly lower in Group A (130.7ml) than in Group B (235.7ml) and Group C (261.5ml) (p=0.032). Significantly less patients in Group A were free from stone (74.1%) compared to Group B (92.9%) and Group C (96.2%) (p=0.030). After surgery, only two patients (2.5%) had criteria consistent with SIRS and both belonged in Group C. No significant difference in incidence of SIRS was observed among the three groups (p=0.067).

Conclusion: Single dose antibiotic prophylaxis for the prevention of post-operative bacterial infection in patients undergoing PCNL is as effective as multiple dose antibiotic prophylaxis. Consistent with existing guidelines on PCNL, single dose antibiotic prophylaxis is highly recommended as it is more cost-effective and may lower the risk for antibiotic resistance in the future. More RCTs with larger sample size which can determine the effectiveness of single dose antibiotic prophylaxis in patients at high-risk for post-operative PCNL infections are recommended.

Key words: Percutaneous nephrolithotomy prophylactic antibiotic regimen, Systemic Inflammatory Response Syndrome

Introduction

Percutaneous Nephrolithotomy (PCNL) is widely used in the surgical treatment of patients with kidney stones larger than 2 cm in diameter with success rates exceeding 90%.[1,2] Although PCNL is preferred because of its minimally invasive nature, minor and major complications are reported in up to 83% of cases. The postoperative complications of PCNL include bleeding, infection, urine leakage, and residual pain. Infectious complications are among the most common.[1] The signs of infections, including fever (21-74%), transient bacteremia (20-35%), systemic inflammatory response syndrome (SIRS; 23.4- 29.0%), and bacteriuria (10-37%), are reported more commonly, sepsis rates have been reported to vary from 0.25 to 1.5%. Because of high infectious complication rates, antibiotic prophylaxis is highly recommended.[2,3]

Percutaneous nephrolithotomy (PCNL) involves the opening or manipulating of the upper urinary tract and thus is categorized as a ''clean-contaminated'' complex endourologic surgical procedure.[4] Both European Association of Urology (EAU) and American Urological Association (AUA) guidelines recommend antibiotic prophylaxis for PCNL.[1] Despite universal agreement on the application of antimicrobial prophylaxis, the optimum administration period of antibiotics for PCNL remains controversial and the risk for antimicrobial resistance due to prolonged antibiotic use as well as financial burden that may prove to be challenging for both the patient and the physician.

The study aimed to determine the safety and effectiveness of a single dose antibiotic prophylaxis for the prevention of developing post-operative bacterial infection in patients undergoing PCNL.

Methods

Research Design

Double-Blind, Prospective, Three arm, Randomized Controlled Study

Patient Selection

A total of 81 patients underwent PCNL for renal calculi between 2021 to 2023 were included. The exclusion criteria are as follows: 1) significant preoperative bacteriuria or a positive urine culture, a significant bacteruria will be considered if count is $\geq 10^5$ cfu/ml, 2) indwelling catheter (Double J Stents, Nephrostomy Catheters, Urethral Catheters), 3) prior history of infectious stones, 4) allergy to preoperative antibiotics, 5) presence of purulent urine from the access needle, 6) significant comorbidities that would predispose to SIRS (chronic renal failure, uncontrolled diabetes mellitus, severe heart failure, recent onset myocardial infarction or stroke, hepatic or hematologic diseases, etc.), 7) patients aged less than 18 years old and 8) refusal to enroll in the study. This study was approved by the Institutional Review Board of the National Kidney and Transplant Institute (NKTIREC 2021-04) and informed consent was obtained from all patients on the day they were hospitalized for surgery.

Randomization

Patients who underwent PCNL received Ceftriaxone in three different regimens based on the mentioned arms and were selected using simple random sampling technique by computer-generated random numbers. A computer-generated random numbers 0-15 was used to assign the treatment, Group A was assigned to numbers multiple of 3, Group B was assigned to even numbers that is not a multiple of 3 (0 is regarded as even) and Group C was assigned to odd numbers not multiple of 3. Blocking design was used to ensure the equal allocation of treatment. Consecutive sampling was done until the minimum sample size in all groups is met.

Perioperative Assessment

The approximate stone surface area was calculated from the length, width and height of the stone in terms of centimeters (cm) using plain computed tomography (CT) of the kidneys, ureters, and bladder. Stones were classified as solitary (isolated pelvic or calyceal) or multiple (stone in more than one calyceal system, partial or complete staghorn stones). Stone complexity was computed using the Guy's Stone Complexity Scoring.

Preoperatively, all patients underwent laboratory tests including complete blood cell count, blood chemistry, serum creatinine measurement, bleeding and coagulation profile, and urine cultures were performed in all patients. Patients with positive urine cultures were treated accordingly until sterile urine was obtained. Perioperative urine samples were obtained for culturing. SIRS criteria is defined as, namely tachycardia (heart rate >90 beats/min), tachypnea (respiratory rate >20 breaths/min) or arterial carbon dioxide tension ($PaCO_2$) lower than 32 mm Hg, fever or hypothermia (temperature >38 or <36°C), and leukocytosis, leukopenia or bandemia (white blood cells >1,200/mm^3, <4,000/mm^3 or bandemia ≥10%).[5]

Intervention

The patients were randomly assigned to three groups according to the regimen of antibiotic used single dose prophylaxis 30 minutes before surgery (Group A), 30 minutes before and 12 hours after surgery (Group B), and continued antibiotics until removal of nephrostomy tube (Group C), respectively.

Surgical Procedure

The surgery started when patient was inducted under general anesthesia. A ureteral catheter under C-arm fluoroscopy was placed cystoscopically at the beginning of each procedure. Approach was either standard prone or supine position. After a percutaneous access was established, serial dilation of the nephrostomy tract carried up sizes up to 30 Fr under fluoroscopic guidance to insert a 24 Fr Nephroscope. Lithoclast (pneumatic, ultrasonic or laser) was used for stone fragmentation and some stones were retrieved with stone forceps. A double J stent and a nephrostomy catheter (size is upon surgeon's preference) was placed at the end of the operation. Number of access, operative time, and other auxiliary procedures were recorded.

Post-operative follow up

Vital signs were monitored postoperatively every 1 hour then every 4 hours once transferred back to the room from Post Anesthesia Care Unit (PACU). Transfusion performed, infection related events and hospitalization time were documented. Complete blood cell count and serum creatinine measurement were performed for all patients during the hospitalization period. The nephrostomy tube inserted intraoperatively was kept for up to 48 hours, then clamped and subsequently removed, unless a complication occurred necessitating an extended period of drainage. Presence of SIRS criteria was monitored for all patients. Blood and urine cultures were obtained for patients with fever >38.5°C. Patients with positive SIRS criteria and clinical suspicion of urosepsis were managed accordingly. Oral antibiotics were not prescribed upon discharge.

Statistical Analysis

All demographic and clinical characteristics were summarized using mean and standard deviation for continuous variables, frequency and percentage for categorical variables to describe patient profile. Chi-square analysis was used to compare urine culture positivity and SIRS incidence among the 3 groups. ANOVA and chi square were used to compare intra-operative and post-operative characteristics among the 3 groups.

Stata 14 was used for data analysis and p-value<0.05 was considered statistically significant

Ethical Considerations

The protocol of this study adheres to the ethical considerations and ethical principles set out in relevant guidelines, including the Declaration of Helsinki, WHO guidelines, International Conference on Harmonization-Good Clinical Practice, Data Privacy Act of 2012, and National Ethics Guidelines for Health Research 2017.

Conflicts of Interest

No potential conflicts of interest have been identified. The principal investigators and co-investigators had nothing to disclose.

Data Safety, Privacy and Confidentiality

Subject information was kept secured, with access available only to members of the research team. Computerized study information was stored

on a secured network with password access. All identifiable information and data were given a code number. A master list linking the code number and subject identity was kept separately from the research data. Only members of the research team will have access to the list. The research records shall be stored for at least 5 years following completion of the study. Individually identifiable research data shall not be shared with other individuals outside of the research and analysis team.

The investigator and all key personnel have completed the Good Clinical Practice (GCP) training on the responsible conduct of research with human data. Monitoring and reporting of adverse events were the responsibility of the primary investigator. Data monitoring included the proper attainment of informed consent and monitoring of adverse events. This information was reviewed on throughout the study.

Results

A total of 81 patients were included (Group A=27, Group B=28, and Group C=26). The mean age of the participants was 27.0 years old and majority were males (65.4%). The mean stone size was 3.0 cm^2. Significantly, more patients had previous history of stone surgeries in Group A (37.0%) than in Group B (3.6%) and Group C (15.4%) (p=0.006). The rate of comorbidities did not differ significantly in the three groups: HTN (p=0.166), DM (p=0.121), and Others (p=0.405). The presence of hydronephrosis was seen in 70.4% of patients. About half had solitary stone type (54.3%) and affected left area (51.8%). The mean stone opacity was 1040 and 14.8% had history of UTI. The mean preoperative white blood cell was 7.5. The mean creatinine was 1.07 and mean hemoglobin was 13.6. The patient groups did not differ in clinical and operative characteristics (all p>0.05) except in history of previous stone surgeries. (Table 1)

The following proportion of no growth in preoperative urine culture was observed: Group A (92.6%), Group B (89.3%), and Group C (80.8%) (p=0.174). The most common isolated microorganism was Diphtheroids (6.2%).

The mean operation time was 88.7 min. About half had level of access above the 12th rib (50.6%). Almost all only had one access (95.1%). The estimated blood loss was significantly lower in Group A (130.7ml) than in Group B (235.7ml) and Group C (261.5ml) (p=0.032). The mean stone clearance rate was 99.5. Significantly less patients in Group A were stone-free (74.1%) compared to Group B (92.9%) and Group C (96.2%) (p=0.030). Only two patients needed blood transfusion (2.5%) and 8.8% had auxiliary procedures done. None had pelvic perforation. Nephrostomy withdrawal day was significantly shorter in Group A (1.5) than in Group B (2.1) and Group C (2.3) (p<0.0003). Hospital length of stay did not differ significantly in the three groups (Group A=4.5, Group B=5.6, Group C=5.2, p=0.058).

Only two patients (2.5%) had criteria consistent with SIRS and both were from Group C. No significant difference in incidence of SIRS was observed among the three groups (p=0.067).

Discussion

Following PCNL, studies reported a 10.8% and 0.5% incidence rate of infection-related complications, such as fever and sepsis, respectively. The European Association of Urology (EAU) Guidelines on Urolithiasis recommend using a single-dose prophylactic antibiotic to lower the risk of these consequences. According to the American Urological Association (AUA) policy, PCNL patients should receive antibiotic prophylaxis and perioperative antibiotic therapy within 60 minutes following the surgery.[5] No current guideline stated if nephrostomy tube placement during the end of the PCNL procedure is routine, and is only upon discretion of the attending surgeon. The same holds true for when to remove the nephrostomy tube. The average time between removal of nephrostomy tube placement and removal was 2 days after the procedure.

In the current study, it was observed that a single dose of preventive antibiotics is sufficient to prevent infection-related complications in percutaneous nephrolithotomy (PCNL).[6] The overall incidence of SIRS was 2.5% with 0 incidence in patients given single dose prophylaxis 30 minutes before surgery.

Table 1. Clinical and operative characteristics of patients (n=81).

	Total (n=81)	**Group A (n=27)**	**Group B (n=28)**	**Group C (n=26)**	***p***
	Frequency (%); Mean ± SD; Median (Range)				
Patient age, years	53.7±3.5	56.0±1.5	54.2±2.6	50.9±2.0	0.231
Body mass index, kg/m^2	27.0±0.8	27.4±0.8	56.4±0.7	26.9±0.8	0.680
Sex					
Male	53 (65.4)	17 (63.0)	18 (64.3)	18 (69.2)	0.880
Female	28 (34.6)	10 (37.0)	10 (35.7)	8 (30.8)	
Stone size, cm^2	3.0±0.2	2.5±0.2	3.2±0.3	3.1±0.3	0.164
Comorbidities					
HTN	35 (43.2)	13 (48.2)	15 (53.6)	7 (26.9)	0.116
DM	21 (25.9)	11 (40.7)	5 (17.9)	5 (19.2)	0.121
Others	17 (21.0)	8 (29.6)	4 (14.3)	5 (19.2)	0.405
History of previous stone surgery	15 (18.5)	10 (37.0)	1 (3.6)	4 (15.4)	**0.006**
Presence of hydronephrosis	57 (70.4)	19 (70.4)	21 (75.0)	17 (65.4)	0.742
Stone type					
Solitary	44 (54.3)	12 (44.4)	19 (67.9)	13 (50.0)	0.190
Multiple	37 (45.7)	15 (55.6)	9 (32.1)	13 (50.0)	
Opacity of stone	1040±250.1	955.2±68.4	1137.9±191.7	1025±76.4	0.594
Laterality					
Left	42 (51.8)	17 (63.0)	13 (46.4)	12 (46.2)	0.367
Right	39 (48.2)	10 (37.0)	15 (53.6)	14 (53.8)	
History of UTI	12 (14.8)	6 (22.2)	4 (14.3)	2 (7.7)	0.329
Preoperative white blood cell, x10^3/uL	7.5±0.5	7.2±0.3	7.6±0.4	7.8±0.4	0.515
Mean creatinine, mg/dL	1.07±0.03	1.12±0.07	1.0±0.04	1.1±0.07	0.490
Mean hemoglobin	13.6±0.4	13.6±0.3	13.7±0.3	13.5±0.6	0.812

Table 2. Distribution of commonly isolated microorganisms in preoperative urine (n=81).

	Preoperative urine culture			
	Total (n=81)	**Group A (n=27)**	**Group B (n=28)**	**Group C (n=26)**
No growth	71 (87.6)	25 (92.6)	25 (89.3)	21 (80.8)
Diphtheroids	5 (6.2)	2 (7.4)	2 (7.1)	2 (7.6)
Staphylococcus spp	4 (4.9)	2 (7.4)	1 (3.6)	1 (3.8)
Enterobacter clocease	1 (1.2)	0 (0.0)	0 (0.0)	1 (3.8)
Proteus	1 (1.2)	0 (0.0)	0 (0.0)	1 (3.8)
Streptococcus spp	1 (1.2)	0 (0.0)	0 (0.0)	1 (3.8)

Table 3. Intraoperative and postoperative characteristics of patients (n=81).

	Total (n=81)	**Group A (n=27)**	**Group B (n=28)**	**Group C (n=26)**	***p***
	Frequency (%); Mean ± SD; Median (Range)				
Operation time, min	88.7±9.2	80.5±7.1	91.7±8.2	94.0±8.5	0.449
Level of access					
Below the 12th rib	40 (49.4)	15 (55.6)	13 (46.4)	12 (46.2)	0.734
Above the 12th rib	41 (50.6)	12 (44.4)	15 (53.6)	14 (53.8)	
Number of access					
1	77 (95.1)	27 (100.0)	26 (92.9)	24 (92.3)	0.348
≥2	4 (4.9)	0 (0.0)	2 (7.1)	2 (7.7)	
Estimated blood loss	209.0±152.0	130.7±95.7	235.7±141.2	261.5±189.1	**0.032**
Stone free rates	99.5±0.5	99.6±0.4	99.0±0.7	99.8±0.2	0.485
Stone composition					
None	71 (87.6)	20 (74.1)	26 (92.9)	25 (96.2)	**0.030**
Calcium oxalate	1 (1.2)	1 (3.7)	0 (0.0)	0 (0.0)	
Mixed	9 (11.1)	6 (22.2)	2 (7.1)	1 (3.8)	
Red blood cell transfusion	2 (2.5)	0 (0.0)	1 (3.6)	1 (3.9)	0.598
Auxiliary procedures	7 (8.8)	1 (3.7)	3 (10.7)	3 (12.0)	0.515
Pelvic perforation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	n/a
Nephrostomy withdrawal day	2.0±0.8	1.5±0.1	2.1±0.1	2.3±0.1	**0.0003**
Hospital stay	5.1±0.5	4.5±0.3	5.6±0.4	5.2±0.2	0.058

Table 4. Incidence of SIRS in patients (n=81).

	Total (n=81)	Group A (n=27)	Group B (n=28)	Group C (n=26)	*p*
	Frequency (%)				
Temperature ≥38ºC or ≤36ºC	2 (2.5)	0 (0.0)	0 (0.0)	2 (7.7)	0.067
Heart rate >100 beats/min	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	n/a
Respiratory rate >20 breaths/min	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	n/a
White blood cell count >12,000/uL or <4,000/uL	2 (2.5)	0 (0.0)	0 (0.0)	2 (7.7)	0.067
Met SIRS criteria (2 or more)	2 (2.5)	0 (0.0)	0 (0.0)	2 (7.7)	0.067

Consistent with the findings of the current study, Chae et al. (2018) observed that when compared to a single-dose prophylactic antibiotic regimen, the three-day regimen did not show superior efficacy in preventing bacterial infections in PCNL. In their RCT, they randomly assigned patients in the single-dose group (n=20) who received single dose of 2 g ceftriaxone 30 minutes before PCNL, whereas those in the three-days regimen group (n=20) received preoperative single dose of 2 g ceftriaxone and an additional postoperative oral cefpodoxime proxetil (100 mg twice a day) for three days. Their results showed that fever did not develop in any of the patients in the single-dose group but developed in one patient (5.0%) in the three-day regimen group due to pneumonia (p=0.3). SIRS developed in four patients from each group but none developed sepsis after PCNL.[7]

Also related to the current study, a meta-analysis was conducted by Jung et al. (2022) to explore the efficacy of single dose antibiotic prophylaxis in perioperative period of PCNL. In ten included studies, the authors observed no significant differences between single dose and extended dose in the rate of fever [p = 0.93, OR = 0.96, 95% confidence interval (CI) 0.44–2.13, I^2 = 64%].[8] In contrast to the current study's findings, extended dose showed lower rate of SIRS compared to single dose (p = 0.0005, OR = 1.81, 95% CI 1.30–2.53, I^2 = 53%). The authors concluded that sepsis in post-operative PCNL can be effectively prevented with a single dosage of antibiotics, but in high-risk individuals, longer-term antibiotic treatment may be necessary to prevent PCNL infections.

Using as little antibiotics as feasible is crucial to reducing antibiotic resistance. There is a clear link between the misuse of antibiotics and the emergence of resistance.[9] Bacteria may become resistant to a particular antibiotic if it is used excessively. An empirical antibiotic's potential for failure surpasses its benefits when the global population becomes more resistant to specific antibiotics. An increased need for antibiotics may arise from such a failure due to postoperative infections.[10] As a result, administering antibiotics only once can save healthcare costs. However, further studies should be done if the same findings on the effectiveness of single dose antibiotic prophylaxis is applicable in high-risk individuals who are prone to post-PCNL infections.

Trials usually ensure comparability of baseline characteristics of the three study groups in terms of history of previous stone surgery, estimated blood loss, and stone clearance in treatment groups by doing randomized allocation. However, in the current study, significant differences were still observed despite randomization, and these can affect patient outcomes. The impact of these differences on the outcomes cannot be further explored since only two patients had SIRS in the

overall study sample. Nonetheless, other baseline clinical and intraoperative factors are comparable in the three groups. Nephrostomy withdrawal day was also significantly highest in patients who had continuous antibiotic prophylaxis compared to other groups. The decision of the clinician to remove nephrostomy tube later in the patients with continuous prophylaxis, could partially explain the increased SIRS incidence.

The current limitation of the study is the small sample size (only 88 of 126 were included) which could have lowered the power of the statistical test to observe significant differences among groups.

Conclusion

Single dose antibiotic prophylaxis for the prevention of post-operative bacterial infection in patients undergoing PCNL is as effective as multiple dose antibiotic prophylaxis. Consistent with existing guidelines on PCNL, single dose antibiotic prophylaxis is highly recommended as it is cheaper and may lower the risk for antibiotic resistance in the future. More RCTs with larger sample size which can determine the effectiveness of single dose antibiotic prophylaxis in patients at high-risk for post-operative PCNL infections are recommended.

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