Original Article

Dilute povidone-iodine irrigation during percutaneous nephrolithotomy to reduce postoperative infective complications – Is there any benefit?

Kalyanaram Kone, Naveen Thimiri Mallikarjun, Joseph Philipraj

Department of Urology, Mahatma Gandhi Medical College, Puducherry, India

Abstract

Background and Objective: Infectious complications following stone lithotripsy is a significant source of patient morbidity and mortality. Post percutaneous nephrolithotomy fever is reported in 37% of patients undergoing PCNL and sepsis is the most common cause of mortality following PCNL. Thus, there is an urgent need to tackle lithotripsy-associated bacteremia occurring intraoperatively, keeping in mind the threat of emerging global antibiotic resistance. The aim of our study was to study the efficacy of using intermittent 0.35% dilute Povidone-Iodine (PI) irrigation during PCNL in reducing postoperative infection rate.

Materials and Methods: This is a prospective observational study done in 24 patients diagnosed with Staghorn and matrix calculi requiring PCNL. All patients were taken up for the procedure with sterile urine culture or after treating them with culture-specific antibiotic with initial positive urine culture. Intraoperative pelvic urine was sent for culture and sensitivity. 0.35% dilute PI irrigation was used intermittently during the procedure. Patients were monitored and assessed for signs of post-PCNL infection and PI-related side effects. The results were compared with similar group of patients with similar stone characteristics who underwent PCNL before adopting the dilute PI irrigation protocol (non-PI irrigation group).

Results: Among 24 patients, 18 patients had partial or complete Staghorn and 6 had matrix calculi. Five patients with Staghorn and three patients with matrix calculi had positive renal pelvic urine culture. In the non-PI irrigation group, 19 patients had Staghorn stones and 5 had matrix calculi. Three patients with Staghorn and two patients with matrix calculi had positive renal pelvic urine culture. Three patients (12.5%) had postoperative fever in the dilute PI irrigation group, compared to 11 patients (45.8%) in the non-PI irrigation group. No patient had PI-related complications.

Conclusion: Our prospective study highlights that the use of 0.35% dilute PI irrigation intermittently during PCNL reduces the postoperative infection rate significantly.

Keywords: Dilute betadine irrigation, percutaneous nephrolithotomy, polyvinylpyrrolidone-iodine, post percutaneous nephrolithotomy fever, povidone-iodine

Address for correspondence: Dr. Naveen Thimiri Mallikarjun, 7/77, AH Block, 5th Street, Anna Nagar, Chennai - 600 040, Tamil Nadu, India.
E-mail: tm.naveen1992@gmail.com

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INTRODUCTION

Infection following stone lithotripsy is a significant source of morbidity and mortality leading to the consumption of health-care resources. Percutaneous nephrolithotomy (PCNL) is a commonly performed procedure in the management of renal stones and was first described by Fernstrom and Johansson in 1976.[1] The most common complications encountered in our clinical practice following PCNL are fever and bleeding.[2] Post-PCNL fever is reported in up to 37% of patients undergoing PCNL and in one-third of patients, fever occurs despite preoperative sterile urine culture.[3] The incidence of septic shock after PCNL is 1%, but the mortality rate is as high as 66%–80%.[4] Fever and postoperative sepsis commonly occur as a result of stone manipulation resulting in bacterial translocation from stone or release of lipopolysaccharide as endotoxin from the bacteria colonized in stone, which enters into bloodstream through pyelovenous, pyelolymphatic, and pyelotubular backflow.[4]

The incidence of multidrug-resistant hospital-acquired urinary tract infection (UTI) and the prevalence of carbapenemase-producing *Enterobacteriaceae* is rising.[5] Inappropriate administration of antibiotics postsurgery and failure to adhere to surgical prophylaxis guidelines are the reasons for emergence of multi-drug resistant strains. Many times, operating surgeons in the apprehension of postoperative urosepsis prescribe higher antibiotics, disregarding antibiotic prophylaxis guidelines.[6,7] Thus, we have two goals here for undertaking this study – first one is to reduce the incidence of post-PCNL infective complication and the second one is to respond to the threat of emerging antibiotic resistance with antibiotic stewardship program by extending the use of antiseptics in the form of intermittent irrigation before and during stone fragmentation in PCNL.

Out of all antiseptics, povidone-iodine (PI) or betadine is the most commonly used. PI has a broad-spectrum antimicrobial effect, has ability to break biofilms and also does not possess the risk of developing anti-microbial resistance.[8] So far, PI irrigation was not tried as a way of bringing down the infection rate in PCNL. This study was done to study the feasibility, safety, and efficacy of using 0.35% dilute PI irrigation intermittently during PCNL in reducing post-PCNL infection.

MATERIALS AND METHODS

This is a prospective observational study done in a tertiary care center after obtaining Institutional Ethical Committee clearance (IRC/01/2020/50/IHEC/196). Twenty-four patients who presented to urology outpatient unit with partial or complete staghorn and matrix renal calculi requiring PCNL were included in our study (Dilute PI irrigation Group-Group 2). The results were compared with similar group of patients with similar stone characteristics who underwent PCNL before adopting the dilute PI irrigation protocol from June 2019 to September 2020 (Non-PI irrigation Group-Group 1). Patients with age less than 18 years or more than 65 years, pregnant women, previous history of any allergy, deranged thyroid function parameters, those with altered renal function parameters and solitary kidney were excluded from our study. Patients who had significant intraoperative bleeding were also excluded as dilute PI irrigation was not continued during PCNL. Similar selection criteria were used in patients requiring PCNL in the comparison group. All patients were taken up for PCNL with sterile urine culture or after treating with appropriate antibiotic according to urine culture and sensitivity.

Prior written informed consent was taken. Preoperative skin prick test was done to rule out allergy to PI solution. On the procedural day, standard preoperative antibiotic prophylaxis (injection cefaperazone sulfbactum 1.5 g) was given intravenously after induction of anesthesia. Standard PCNL procedure was carried out, except with regard to pelvicalyceal irrigation during PCNL in Group 2. 0.35% diluted betadine solution was prepared aseptically by diluting 17.5 ml of sterile 10% betadine solution in 500 ml of normal saline. Ureteric catheter was passed into the renal pelvis during cystoscopy and urine from the renal pelvis was collected and sent for culture and sensitivity. 5–15 ml of 0.35% diluted betadine solution was instilled into the renal pelvis through ureteric catheter depending upon an individual's renal pelvis capacity and after 3 min of contact time, the renal pelvis was irrigated with normal saline. After establishing percutaneous access into the pelvicalyceal system, 20 ml of 0.35% diluted betadine solution was instilled slowly over 3 min through ureteric catheter which exited from the secured Amplatz sheath. 60–80 ml of 0.35% diluted betadine solution was used intermittently during stone lithotripsy. Following stone clearance, nephrostomy tube was placed *in situ* for 24–48 h and was then removed if there was no evidence of fever. Culture-specific antibiotic or a broad-spectrum antibiotic (Cefaperazone sulfbactum) was continued for 3 days. All these patients were monitored for signs of postoperative infection: Temperature <36°C or >38°C, heart rate >100/min, respiratory rate >20/min and white blood cells >15 × 10^9/mm^3. The presence of any 2 or more of these criteria was considered as infection. Complete hemogram and renal function parameters were

done on postoperative day 1. Thyroid function tests were done on postoperative day 2. If any patient developed fever, higher level antibiotics were initiated. Post-PCNL fever, sepsis, higher level antibiotic requirement, and length of hospital stay were recorded, and the data were compared with the non-PI irrigation group. Intraoperative and postoperative complications were assessed according to the modified Clavien–Dindo classification. The two groups were compared in terms of baseline patient characteristics, stone characteristics, operative outcomes, and overall complications.

RESULTS

A total of 24 patients underwent PCNL in each group for renal stones from September 2020 to April 2021. Group 1 (non-PI irrigation group) was compared to Group 2 (dilute PI irrigation group). For continuous data, variables were presented as mean ± standard deviation. For variables with non-normal distribution, the groups were compared using Mann–Whitney U-test. The categorical variables were compared using the Chi-squared test, using, where possible, the Yates correction or the Fisher's exact test. To assess the effect of continuous variables on the dichotomous variable "overall complications," an univariable and multivariable logistic regression model was performed. Statistical analysis was done using the IBM SPSS software version 17.0. The mean age of Group 1 was 44 ± 14.65 years, whereas the mean age of Group 2 was 46 ± 14.36 years. The demographics of the two study groups are shown in Table 1. Group 2 patients had an overall higher percentage of positive initial urine culture as compared to Group 1 patients (50% vs. 37.5%). There was no statistically significant difference between the two groups. Stone and preoperative data of the two groups are shown in Table 2. Stone characteristics were not significantly different between the two groups. Preoperative decompression was done in eight patients in Group 1 and 12 patients in Group 2.

Perioperative outcomes are shown in Table 3. Out of 24 patients in whom 0.35% dilute PI irrigation was used intermittently during PCNL, only four patients (16.7%) had postoperative signs of infection (fever >100°F) compared to 45.8% infection rate (11 patients) in the non-PI irrigation group. This was statistically significant. Among four patients who had developed postoperative febrile UTI in the dilute PI irrigation group, two patients had Matrix stones. These patients recovered well after starting on injection meropenam without any undue complications. The other parameters: duration of surgery, hematuria, additional procedures (cystoscopy for clot retention and chest tube placement), hospital stay, and stone free status were similar between the groups. The comparison of complications between Group 1 and Group 2 by Clavien – Dindo grading is shown in Table 4.

Table 1: Demographic data of the two study groups

Variables	Group 1 (Non-PI group), *n* (%)	Group 2 (Dilute PI group), *n* (%)	*P*
Number of patients	24 (100)	24 (100)	
Gender			
Male	14 (58.24)	13 (54.08)	0.386
Female	10 (41.6)	11 (45.76)	
Age (mean±SD)	44±14.655	45.67±14.361	0.693
ASA score (≥3)	3 (12.48)	4 (16.64)	0.682
Diabetes mellitus	8 (33.2)	10 (41.7)	0.551
Hypertension	12 (50.0)	15 (62.5)	0.383
Coronary artery disease	4 (16.6)	6 (25)	0.477
Positive initial urine culture	9 (37.5)	12 (50)	0.383

PI: Povidone iodine, ASA: American Society of Anaesthesiologists

Table 2: Stone and preoperative data of the two study groups

Variables	Group 1 (Non-PI group), *n* (%)	Group 2 (Dilute-PI group), *n* (%)	*P*
Stone characteristics			
Partial staghorn	14 (58.3)	15 (62.5)	0.767
Complete staghorn	3 (12.5)	5 (20.8)	0.438
Matrix calculi	5 (20.8)	6 (25)	0.731
Laterality (right:left)	14:10	12:12	
Presence of perioperative DJ stent	6 (25)	8 (33.3)	0.241
Presence of perioperative PCN	2 (8.3)	4 (16.64)	

DJ stent: Double J stent, PCN: Percutaneous nephrostomy, PI: Povidone iodine

No patient had positive skin prick test preoperatively. No patient had PI related allergic or systemic complications intraoperatively. There was no problem with visibility during the procedure as instilled povidone iodine was quickly washed away with saline irrigation. The renal pelvis did not seem inflamed at the end of the procedure and looked the same as before the procedure with PI irrigation. No patient developed iodine toxicity. Postoperative TSH levels varied between 0.4 and 1.8 pg/ml. No patient had significantly elevated or depressed T3 and T4 levels.

DISCUSSION

Postoperative infection is the most common complication of PCNL and few patients may also develop postoperative urosepsis leading to mortality. Extreme age, female gender, infection stones, staghorn calculi, prolonged operative time, indwelling catheters, urinary tract obstruction, immunocompromised status, renal failure, positive pelvic urine, and positive stone culture are risk factors that contribute to post-PCNL urosepsis.[4] Some of these factors can be addressed effectively during preoperative work-up by adequate preoperative preparation, decompression of the infected system, and treatment of the infected system

Table 3: Peri-operative outcomes of the two study groups

Variables	Group 1 (non-PI group), *n* (%)	Group 2 (dilute-PI group), *n* (%)	*P*
Renal pelvis urine culture	5 (20.8)	8 (33.3)	0.329
OT (min) (mean±SD)	148.8±24.179	154.6±26.181	0.428
Postoperative fever >100°F	11 (45.8)	4 (16.7)	0.029
Initiation of higher end antibiotic	13 (54.1)	6 (25)	0.038
Postoperative stay (days) (mean±SD)	4.13 (1.513)	3.13 (1.191)	0.014
Stone-free status, *n* (%)	21 (87.5)	22 (91.7)	0.637

OT: Operative time, PI: Povidone iodine, SD: Standard deviation

Table 4: Comparison of complications between Group 1 and Group 2

Overall complications*	Group 1 (non-PI group)	Group 2 (dilute-PI group)	*P*
Grade I			
Creatinine elevation >0.5 mg %	5 (20.8)	8 (33.3)	0.329
Grade II			
Blood transfusion	2	4	0.382
Postoperative fever >100°F	11	4	0.029
Initiation of higher end antibiotic	13	6	0.038
Grade III			
Clot retention	1	2	0.550
Chest tube insertion	1	0	-
Grade IV			
Myocardial infarction	0	1	-
Acute renal failure	1	1	-
Sepsis	3	1	0.296

*Based on Clavien-Dindo classification. PI: Povidone iodine

with culture specific antibiotics. Despite administration of proper antibiotics, many times renal pelvic urine and stone cultures turn out to be positive. Dogan *et al.* stressed the role of intraoperative renal pelvic urine culture in treating postoperative infection according to culture and sensitivity as preoperative urine culture may be sterile due to obstruction of the urinary system.[9] Even though antibiotics are given intraoperatively to tackle the bacteremia arising out of stone fragmentation, sometimes this measure is not enough during overwhelming bacteremia.[4,9] Thus, an effective intra-operative strategy preventing the cascading effect of bacterial translocation from the stone during lithotripsy is needed at the source. At the same time, urologic community should also shy away from indiscriminate use of antibiotics and promote antibiotic stewardship to tackle an emerging trend of increasing multidrug-resistant organisms. In this respect, antiseptics, with a broader spectrum of antimicrobial activity and lack of acquired or cross resistance provide a viable alternative. One of the ideal antiseptic solutions is PI which is already being used extensively for intraoperative wound irrigation by urologists and other surgical specialties.[8,10] Many times, dilute PI is injected through ureteric catheter during PCNL to find the Calyceal opening, passage or lost track but was not tried exclusively as an anti-infective agent. PI has a lasting and broad spectrum of antimicrobial effect, ability to break biofilms, and also does not possess the risk of developing anti-microbial resistance.[10,11]

In our study, Betadine instillation reduced the number of patients developing infective complications and the need for higher antibiotics was also reduced. These two factors were statistically significant. However, there was no difference in the operative time, bleeding complications, hospital stay, and stone free status between the two groups. Most of the patients were discharged on postoperative day 2 or day 3. Antibiotics were stepped up in 13 patients of Group 1 and six patients of Group 2. They were discharged if they were afebrile for 24 h. 3 patients in Group 1 and one patient in Group 2 required admission in the intensive care unit for sepsis and recovered without any undue complications with supportive care.

Polyvinylpyrrolidone-iodine (PVP-I) is a widely used antiseptic introduced by Shelanski and Shelanski in 1956.[12] It is a water-soluble compound that forms from the combination of molecular iodine and polyvinylpyrrolidone. The 10% PVP-I solution generally contains 90% water, 8.5% polyvinylpyrrolidone, 1% available iodine, and iodide. The free iodine concentration in this is typically 1 part/million (ppm) or 0.0001%.[13,14] Iodine is complexed by polyvinylpyrrolidone and iodide through hydrogen bond and a small amount of free iodine is constantly released, maintaining the dynamic equilibrium with the complex. The PVP-I complex in PI delivers free iodine directly to the microbial cell surface by virtue of its affinity to cell membrane, which then penetrates through the cell wall and disrupts the protein synthesis, the function of respiratory chain enzymes and nucleic acid activity resulting in cell death.[14] This microbial cytotoxicity effect of PVP-I is directly dependent on the local bioavailability of free iodine. The free iodine availability increases with increasing dilution of PVP-I as dilution weakens the iodine linkage to the carrier [Table 5]. This paradoxically increases the anti-microbial effect with increasing degree of PI dilution.[15,16] Moreover, dilute PVP-I formulation is an effective anti-biofilm and anti-fungal agent.[17]

Table 5: Various concentrations of Betadine and its free iodine content

Name	Total iodine/100 ml	Free iodine	Free iodine/100 ml
10% betadine 1% iodine	10000 ppm	1 ppm	100 µg
5% betadine 0.5% iodine	5000 ppm	2.5 ppm	250 µg
1% betadine 0.1% iodine	1000 ppm	12 ppm	1200 µg
0.7% betadine 0.07% iodine	700 ppm	24 ppm	2400 µg
0.35% betadine 0.035% iodine	350 ppm 35000 µg/100 ml	16 ppm	1600 µg
0.1% betadine 0.01% iodine	100 ppm	20 ppm	2000 µg
0.01% betadine 0.001% iodine	10 ppm (aqueous solution)	10 ppm	1000 µg
Contrast media	300,000 ppm (300 mg/ml)	35 ppm	3500 µg

A 2014 focus group which was convened to discuss evidence for standardization of surgical wound irrigation protocols decided to eliminate the use of antibiotic solutions for surgical irrigation, as there is no risk reduction benefit.[18] Instead of antibiotic solutions, the World Health Organization (WHO) and Centers for Disease Control recommended intra-operative irrigation of deep or subcutaneous tissues with aqueous iodophor solution for the prevention of SSI.[19-21] The WHO guidelines committee evaluated available evidence from seven randomized controlled trials in abdominal surgery and spinal surgery which signified that irrigation with aqueous PI solution is beneficial compared to saline solution alone. Furthermore, experts at the second International Consensus Meeting on Musculoskeletal Infection voted in favor of dilute PI use for the irrigation of wounds during surgical procedures.[22] Hence, based on these recommendations, we initiated a pilot study to see whether extrapolating the use of 0.35% diluted betadine irrigation during PCNL is safe and effective in negating the lithotripsy-bacteremia cycle.

There have been concerns with regard to the intrapelvic instillation of diluted betadine leading to allergic reactions, cytotoxic effect on normal cells, iodine toxicity and systemic absorption with attendant complications. However, no patient had PVP-I related allergic or systemic complications in our study. Sceptics of PI frequently cite sporadic *in vitro* studies that reported an adverse effect of PI on tissue regeneration and historical case studies that described systemic serum iodine toxicity. However, none of these aforementioned adverse effects have ever been substantiated in the clinical trials. The use of PVP-I solution for intra-operative irrigation has been described across a spectrum of medical specialties and found to be safe.[23-25] No allergic reactions were reported from any of these studies. Regarding cytotoxicity, Chang *et al*. did not find any unforeseen complications with the use of dilute betadine lavage in spine surgery with respect to fusion rates and wound healing.[26] Cytotoxic studies on isolated cells significantly differ from three dimensional biologic systems and *in vitro* studies may not necessarily be clinically relevant to the wound-healing process. *In vivo* studies done on wounds in male SKH1-hr hairless mice, PVP-I showed a positive effect on dermal wound healing and wound microcirculation.[11,27] Remarkably, a recent study showed that povidone iodine can enhance wound healing through transforming growth factorβ, not only by increasing granulation but also enhancing neovascularization.[28]

Regarding iodine toxicity, we are all familiar with intravascular contrast agents, which deliver much higher iodine load than PI. For renal imaging, a common dose of intravenous iodinated contrast exposes the patient to 25–50 g of bound iodine, which is approximately 400,000 times the daily turnover rate in the human body, but this dose rarely causes any toxicity.[29] On an average, each ml of contrast agent contains 35 µg/mL free iodine. A 100 ml dose of contrast agent containing 35 µg/mL free iodine provides 3500 µg free iodine, equivalent to 45 times the recommended daily intake.[30] There were also studies revealing that the lowest observed adverse effect level was 1700 mcg/day to alter serum TSH level.[31,32] Our study used 100 ml of 0.35% diluted betadine solution which contains 1600 mcg of free iodine only.

There are some limitations in our study. Our study used up to 100 ml of 0.35% solution for intermittent irrigation which was not enough in some cases where the stone burden was high, and when the duration was prolonged. However, our study established some facts - 100 ml of 0.35% solution can be given safely and does not cause any allergic or systemic complication and did not pose any problems during the procedure regarding visibility or excessive bleeding. Another problem with our study is the limited number of patients and nonrandomized nature of the study. Multi-center randomized studies recruiting larger number of patients should be carried out for validating the safety and efficacy of using 0.35% diluted PI irrigation intermittently during PCNL.

CONCLUSION

Our study highlights that the use of 0.35% dilute PI irrigation intermittently during PCNL is safe and seems to reduce the postoperative infection rate significantly. However, there was no significant difference among other parameters.

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Conflicts of interest
There are no conflicts of interest.

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