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
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.[5]

The incidence of multidrug-resistant hospital-acquired urinary tract infection (UTI) and the prevalence of carbapenemase-producing Enterobacteriaceae is rising.[6] 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/mm³. 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 unvariable 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.

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. 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.
It is a water-soluble compound that forms a viable alternative. One of the ideal antiseptic solutions is PI which is already being used extensively for a 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.\[^{[17]}\]
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 intraoperative 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 intraoperative irrigation has been described across a spectrum of medical specialties 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.[11,12] 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.
REFERENCES

1. Fernström I, Johansson B. Percutaneous pyelolithotomy. A new extraction technique. Scand J Urol Nephrol 1976;10:257-9.
2. Shin TS, Cho MJ, Hong SH, Lee YJ, KIm SW, Hwang TK. Complications of percutaneous nephrolithotomy classified by the modified clavien grading system: A single center’s experience over 16 years. Korean J Urol 2011;52:769-75.
3. Rashid AO, Fakhruddin SS. Risk factors for fever and sepsis after percutaneous nephrolithotomy. Asian J Urol 2016;3:82-7.
4. Lojanapiwat B. Infective complication following percutaneous nephrolithotomy. Urol Sci 2016;27:8-12.
5. Wagenlehner F, Tandogdu Z, Bartoletti R, Cai T, Gek M, Kulchavenya E, et al. The global prevalence of infections in urology study: A long-term, worldwide surveillance study on urological infections. Pathogens 2016;5:E10.
6. Exner M, Bhattacharya S, Christiansen B, Gebel J, Goroncy-Bermes P, Hartemann P, et al. Antibiotic resistance: What is so special about multidrug-resistant Gram-negative bacteria? GMS Hg Infect Control 2017;12:Doc05.
7. Rehan HS, Kakkar AK, Goel S. Surgical antibiotic prophylaxis in a tertiary care teaching hospital in India. Int J Infect Control 2010;6:22.
8. Lachapelle JM, Castelo O, Fueyo Casado A. Antiseptics in the era of bacterial resistance. A focus on povidone iodine. Future Med 2013;10:579-92.
9. Dogan HS, Guliyev F, Cetinkaya YS, Sofikerim M, Ozden E, Sahin A. Importance of microbiological evaluation in management of infectious complications following percutaneous nephrolithotomy. Int Urol Nephrol 2007;39:737-42.
10. Leaper DJ, Schultz G, Carville K, Fletcher J, Swanson T, Drake R. Extending the TIME concept: What have we learned in the past 10 years?*. Int Wound J 2012;9 Suppl 2:1-19.
11. Biglardi PL, Alsagoff SA, El-Kafrawi HY, Pyon JK, Wa CT, Villa MA. Povidone iodine in wound healing: A review of current concepts and practices. Int J Surg 2017;44:260-8.
12. Shelanski HA, Shelanski MV. PVP-iodine: History, toxicity and therapeutic uses. J Int Coll Surg 1956;25:727-34.
13. Horn D, Ditter W. Physical-chemical fundamentals of the microbicidal action of povidone-iodine. In: Degenes G, editor. Proceedings of the International Symposium on Povidone. Lexington, KY: University of Kentucky; 1963. p. 120-40.
14. Zamora JL. Chemical and microbiologic characteristics and toxicity of povidone-iodine solutions. Am J Surg 1986;151:400-6.
15. Berkelman RL, Holland BW, Anderson RL. Increased bactericidal activity of dilute preparations of povidone-iodine solutions. J Clin Microbiol 1982;15:635-9.
16. Woodward FE, Hudson A. Reactions of povidone and iodine: Changes in active iodine species with dilution in water. In: Degenes G, editor. Proceedings of the International Symposium on Povidone. Lexington, KY: University of Kentucky; 1983. p. 178-85.
17. Caprioatti K, Pelletier J, Barone S, Caprioatti J. Efficacy of dilute povidone-iodine against multi-drug resistant bacterial biofilms, fungal biofilms and fungal spores. Clin Res Dermatol 2018;5:1-5.
18. Barnes S, Spencer M, Graham D, Johnson HB. Surgical wound irrigation: A call for evidence-based standardization of practice. Am J Infect Control 2014;42:525-9.
19. Bertrós-Torres SI, Umscheid CA, Bratlzer DW, Leas B, Stone EC, Kelz RR, et al. Centers for disease control and prevention guideline for the prevention of surgical site infection, 2017. JAMA Surg 2017;152:784-91.
20. DJ Leaper. Global Guidelines for the Prevention of Surgical site Infection. Geneva: World Health Organization; 2017.
21. Allegrenzi B, Zayed B, Bischoff P, Kubiay NZ, de Jonge S, de Vries F, et al. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: An evidence-based global perspective. Lancet Infect Dis 2016;16:e288-303.
22. Blom A, Cho J, Fleischman A, Goswami K, Ketoson C, Kunutos SK, et al. General assembly, prevention, antiseptic irrigation solution: Proceedings of international consensus on orthopaedic infections. J Arthroplasty 2019;34:S131-8.
23. de Jonge SW, Boldingh QI, Solomkin JS, Allegrenzi B, Egger M, Dellinger EP, et al. Systematic review and meta-analysis of randomized controlled trials evaluating prophylactic intra-operative wound irrigation for the prevention of surgical site infections. Surg Infect (Larchmt) 2017;18:508-19.
24. Goswami K, Austin MS. Intraoperative povidone-iodine irrigation for infection prevention. Arthroplast Today 2019;5:306-8.
25. Biglardi P, Langer S, Cruz JJ, Kim SW, Nair H, Srisawasdi G. An Asian perspective on povidone iodine in wound healing. Dermatology 2017;233:223-33.
26. Chang FY, Chang MC, Wang ST, Yu WK, Liu CL, Chen TH. Can povidone-iodine solution be used safely in a spinal surgery? Eur Spine J 2006;15:1005-14.
27. Langer S, Botteck NM, Bosse B, Reimer K, Vogt PM, Steinau HU, et al. Effect of polyvinylpyrrolidone-iodine liposomal hydrogel on wound microcirculation in SKH1-hr hairless mice. Eur Surg Res 2006;38:27-34.
28. Wang L, Qin W, Zhou Y, Chen B, Zhao X, Zhao H, et al. Transforming growth factor β plays an important role in enhancing wound healing by topical application of Povidone-iodine. Sci Rep 2017;7:991.
29. Morris TW. X-ray contrast media: Where are we now, and where are we going? Radiology 1993;188:11-6.
30. van der Molen AJ, Thomsen HS, Morcos SK; Contrast Media Safety Committee, European Society of Urogenital Radiology (ESUR). Effect of iodinated contrast media on thyroid function in adults. Eur Radiol 2004;14:902-7.
31. Gardner DF, Centor RM, Utiger RD. Effects of low dose oral iodide supplementation on thyroid function in normal men. Clin Endocrinol (Oxf) 1988;28:283-8.
32. Paul T, Meyers B, Witorsch R, Pino S, Chipkin S, Inghar SH, et al. The effect of small increases in dietary iodine on thyroid function in euthyroid subjects. Metabolism 1988;37:121-4.