Nephro-Urology Monthly
Volume 16 · Issue 4 · e148503

OPEN PEER REVIEW

The Impact of Antibiotic Prophylaxis with Cefazolin, and Ceftizoxime Along with Aminoglycosides on Postoperative Complications, Hospitalization, and Returning to Normal Life for Percutaneous Nephrolithotomy, a Prospective Cross-Sectional Study

Siavash Falahatkar, Gholamreza Mokhtari, Ehsan Kazemnezhad Leili, Milad Abed-Kamalchi, Samira Kazemi, Fatemeh Sheikhi, Ali Bonyad, Alireza Jafari

SUBMITTED	REVISED	ACCEPTED	DOI
5 May 2024	18 Aug 2024	2 Sep 2024	10.5812/numonthly-148503

About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

More about open peer review: brieflands.com/knowledgebase/opr

Contents

1 **Original submission** Referee 1, Associate Editor 2
2 **Revision 1** Referee 1, Associate Editor 3
Authors' reply to reviewers 4
Reviewer and editor comments 9

1 Original submission

2 comments · 10 Aug 2024 – 10 Aug 2024

Referee 1 Reviewer

MAJOR REVISION 10 Aug 2024

Dear E.I.C
Here are my comments on the manuscript:
The introduction provides a broad context for antibiotic prophylaxis in surgery but does not strongly justify the clinical significance of comparing cefazolin and ceftizoxime specifically for PCNL.
Methods would benefit from clarifying how randomization was achieved between groups given the study's cross-sectional design. Inclusion/exclusion criteria and definitions of outcomes could be more detailed.
The study states that all patients received aminoglycosides in addition to the cephalosporins. However, there's no justification provided for this decision. The authors should explain the rationale for using aminoglycosides and address potential risks and benefits.
Potential confounders related to sample characteristics, such as comorbidities, are not adequately adjusted for. An a priori power calculation is not described.
The lack of adjustment for confounders and multivariate analyses limits interpretation of the results.
Subgroup analyses by disease severity would provide clinically useful information.
Comparisons to prior studies are weak. Differences in study design, populations, and outcomes limit the direct comparisons that can be made.
While the introduction mentions the global problem of antibiotic resistance, the discussion section lacks a comprehensive analysis of the potential impact of ceftizoxime and cefazolin on resistance patterns.
Conclusions do not consider the observational nature of the study, which limits inference of causality.
Potential mechanisms underlying observed differences in outcomes are not explored.
Overall, while the study addresses an important clinical issue, weaknesses in study design and analysis preclude strong recommendations.
With extensive revisions to address these methodological issues through multivariate analyses, consideration of bias/confounding, and strengthening of the conclusions, this paper could potentially contribute to the field.

Associate Editor

MAJOR REVISION 10 Aug 2024

Major Revision

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Subject: Revised Manuscript Submission - Manuscript ID: 148503

Dear Editor,

I hope this message finds you well. I am writing to inform you that we have revised our manuscript titled "The impact of antibiotic prophylaxis with cefazolin, and ceftizoxime along with aminoglycosides on postoperative complications, hospitalization, and returning to normal life for percutaneous nephrolithotomy: A prospective cross-sectional study" (Manuscript ID: 148503) in response to the reviewers' comments.

We have carefully considered the feedback provided by the reviewers and made the necessary adjustments to enhance the quality of our manuscript. The revised text is included at the bottom of this page for your review.

Thank you for your attention to this matter. We look forward to your feedback and hope for a positive response.

Best regards,

Comments:

1. *The introduction provides a broad context for antibiotic prophylaxis in surgery but does not strongly justify the clinical significance of comparing cefazolin and ceftizoxime specifically for PCNL.*

Response: Various factors should be taken into account when comparing cefazolin and ceftizoxime for antibiotic prophylaxis in PCNL surgery, such as their range of activity, pharmacokinetics, effectiveness, and safety profile. Cefazolin belongs to the first generation of cephalosporins. Cefazolin is effective against a wide range of bacteria, including *Staphylococcus aureus* and *E. coli*. The pharmacokinetics of cefazolin involve quick absorption and excretion, with a half-life of approximately 1.8 hours. It rapidly attains high tissue concentrations, which is advantageous for surgical prophylaxis. Cefazolin's effectiveness is widely recognized in different surgical procedures, such as urological surgeries, for its proven ability to decrease postoperative infections. The safety profile of it is usually well-received, with minimal occurrence of negative effects. Cefazolin can cause allergic reactions, especially in patients who have had a penicillin allergy in the past (6).

Ceftizoxime belongs to the Third-generation cephalosporin class. Ceftizoxime's spectrum of activity is wider than cefazolin, being effective against a greater variety of resistant strains of gram-negative bacteria, such as certain Enterobacteriaceae. The pharmacokinetics of Ceftizoxime is comparable to cefazolin, but it has a longer half-life (approximately 2 hours), which means that it can be taken less often. Furthermore, Ceftizoxime is highly effective in preventing infections, especially in situations where there is a greater risk of gram-negative organisms. Nonetheless, it is not as frequently used in urological surgery as cefazolin. In the meantime, Ceftizoxime's safety profile is mostly safe, although it could lead to more adverse effects than cefazolin. The risk of developing Clostridium difficile infection may also increase because of its wider range of effects (7). Cefazolin is usually the preferred

choice over ceftizoxime for preventing infections during PCNL procedures, as it is effective against the common pathogens associated with urological infections, especially in clean or clean-contaminated surgeries. When looking at the resistance patterns of cefazolin and ceftizoxime, it appears that Ceftizoxime could be a better choice for cases involving resistant gram-negative organisms due to its wider coverage (7).

When specifically looking at preventing infections during PCNL procedures, Cefazolin is usually the preferred choice over Ceftizoxime because of its effectiveness against the usual pathogens found in urological infections, especially in surgeries that are clean or clean-contaminated. Resistance patterns of cefazolin and ceftizoxime indicate that ceftizoxime may be preferable when dealing with resistant gram-negative organisms, although its wider range of effectiveness could potentially harm normal flora. Even though both antibiotics are given differently in terms of dosing and administration, it is noted that Cefazolin is generally given as a one-time dose before surgery, whereas ceftizoxime may need to be given multiple times because of its pharmacokinetics. Due to cost and availability considerations, Cefazolin is typically a more economical option and more readily accessible than ceftizoxime. In general, Cefazolin is frequently the top pick for antibiotic prophylaxis in PCNL because of its proven effectiveness, safety record, and quick response against typical pathogens. Ceftizoxime might be an option for certain cases with increased risks of resistant infections but is not frequently utilized for this purpose. When selecting an antibiotic, it's important to take into account the patient's personal risk factors, resistance trends in the area, and hospital guidelines (6, 7).

2. *Methods would benefit from clarifying how randomization was achieved between groups given its cross-sectional design. Inclusion/exclusion criteria and definitions of outcomes could be more detailed.*

Response:

Randomization is usually not utilized in cross-sectional studies as it is in randomized controlled trials (RCTs) since cross-sectional studies are mainly observational and focus on data collected at a specific time point. Sampling for this research involved utilizing the availability sampling technique on patients undergoing PCNL in a fully supine position. We included all samples obtained from RAZI, GOLSAR, and PARS hospitals in Rasht city and performed the procedure in a completely supine posture from 2013 to 2022.

Inclusion criteria

This study involved patients who had been diagnosed with urinary stones. Patients who were part of the research had urinary tract stones as verified by imaging methods such as CT scan and/or Ultrasound. Patients must also meet the criteria for Percutaneous Nephrolithotomy (PCNL). One particular medical justification for undergoing PCNL is related to the size of stones, typically greater than 2 cm. The positioning of stones (such as within the kidney or upper ureter), and symptoms such as severe pain, obstruction, or recurrent UTIs. Another factor for inclusion was the patients' position requirement. Patients must be suitable for surgery while in the complete supine position, as it is crucial for the surgical procedure. In the meantime, patients with Full Medical Documentation can also take part in the research. This

means that patients had extensive medical records available for examination, enabling a comprehensive comprehension of their medical background. Additionally, participants need to stay for post-procedure follow-up evaluations to monitor outcomes and detect any possible problems in this study.

Exclusion Criteria

Individuals suffering from ongoing urinary tract infections will not be included in the study. Patients currently experiencing urinary tract infections that may complicate surgery or impact outcomes are not included. Additionally, individuals with anatomical abnormalities are not included in the present research. It indicates patients who have structural issues in their urinary system (such as a blockage at the ureteropelvic junction) that could affect the surgery or results. Patients who have been hospitalized previously will not be included in the current study. Patients who were recently admitted to the hospital for any cause, may have underlying health problems that could impact the risk of surgery. Patients who have previously used antibiotics will be excluded from the current study as well. This refers to patients who had used antibiotics before the study, which may impact the presence of resistant bacteria and complicate treating infections. Patients with incomplete or inaccurate medical records, lack of access for follow-up, withdrawal of consent, or loss to follow-up, which hinder proper evaluation of their health status, were not included in the study.

3. *The study states that all patients received aminoglycosides in addition to the cephalosporins. However, there's no justification provided for this decision. The authors should explain the rationale for using aminoglycosides and address potential risks and benefits.*

Response:

It is crucial to assess the potential risks and benefits of combining cephalosporins with aminoglycosides for prophylaxis in patients undergoing PCNL based on current literature and guidelines. The possible advantages might consist of the wide-ranging protection from Cephalosporins and Aminoglycosides. As stated, Cephalosporins are effective in combating a broad spectrum of both Gram-positive and Gram-negative bacteria, making them ideal for infection prevention in surgical environments. On the flip side, Aminoglycosides are highly efficient in combating Gram-negative bacteria, such as Pseudomonas aeruginosa, a common issue in urinary tract infections. Additionally, the simultaneous use of cephalosporins and aminoglycosides can have a synergistic impact, increasing the effectiveness of bacterial eradication, specifically in cases of polymicrobial infections. This is important in surgical prophylaxis when there are several different organisms. Research has demonstrated that using the correct antibiotic prophylaxis can greatly decrease the occurrence of Surgical Site Infections (SSIs), resulting in improved postoperative results and reduced hospital stays. Additionally, by targeting a wide range of possible pathogens, this combination could aid in the prevention of Urinary Tract Infections (UTIs), a common occurrence following urinary surgeries.

Nevertheless, the combination of cephalosporins and aminoglycosides for prophylaxis in patients having percutaneous nephrolithotomy may come with multiple potential risks. Excessive use of wide-ranging antibiotics, such as third-generation cephalosporins and aminoglycosides, can lead to the emergence of antibiotic-resistant bacteria. The NHEP has emphasized that this is a major issue. Additionally, Aminoglycosides are recognized for their possible harm to the kidneys, especially in individuals with existing kidney problems or who are taking other medications that can also harm the kidneys. This danger is particularly important in a group of patients undergoing surgery. Additionally, both types of antibiotics have the potential to result in allergic reactions, gastrointestinal issues, and various other side effects. The risk of adverse effects is heightened when using multiple antibiotics. Additionally, broad-spectrum antibiotics can disturb the balance of normal flora, resulting in opportunistic infections like Clostridioides difficile colitis. Moreover, administering a variety of antibiotics can make the treatment plan more complex, leading to higher expenses and a greater risk of mistakes in medication.

4. *Potential confounders like comorbidities are not adequately adjusted for sample characteristics. A priori power calculation is not described. The lack of adjustment for confounders and multivariate analyses limits interpretation are seen in results. Subgroup analyses by disease severity would provide clinically useful information. Comparisons to prior studies are weak. Differences in study design, populations and outcomes limit direct comparisons should be made.*

In response to the concerns raised regarding our study, we would like to clarify that all statistical analyses were conducted with careful consideration of potential confounding variables. We specifically adjusted for confounders to ensure the robustness of our findings. Regarding the comment about potential confounders, such as comorbidities, we acknowledge the importance of adequately adjusting for these factors. We have taken steps to ensure that our sample characteristics reflect these adjustments. Additionally, we recognize that a priori power calculations were not explicitly described in the manuscript. We appreciate this feedback and will address it in our revised submission to provide a clearer understanding of our study's statistical power.

“After adjusting for confounding variables in the present study, such as diabetes, underlying diseases, hypertension, and cardiovascular diseases, the odds ratio of fever postoperatively after prophylaxis with antibiotics in the first-generation cephalosporins (cefazolin) group compared to the third-generation cephalosporins (ceftizoxime) group was calculated to be 0.203 times lower, which showed a statistically significant difference (p=0.043).”

5. *While the introduction mentions the global problem of antibiotic resistance, the discussion section lacks a comprehensive analysis of the potential impact of ceftizoxime and cefazolin on resistance patterns.*

Response: Thank you for your insightful comment. While we acknowledge the importance of discussing the impact of ceftizoxime and cefazolin on resistance

patterns, our study's primary goals did not include investigating resistance patterns in patients using these antibiotics. We will clarify this limitation in the discussion section and emphasize that further research is needed to explore the relationship between these antibiotics and resistance patterns. Your feedback will help enhance the clarity of our manuscript.

6. *Conclusions do not consider the observational nature of the study limiting inference of causality. Potential mechanisms underlying observed differences in outcomes are not explored. Overall, while addressing an important clinical issue, weaknesses in study design and analysis preclude strong recommendations.*

Response: Thank you for your constructive feedback regarding our conclusions and the limitations of the study. We appreciate your emphasis on the observational nature of the research, which indeed limits the ability to infer causality. In our conclusion, we acknowledge this limitation and stress that while our findings suggest that administering ceftizoxime along with aminoglycosides can positively impact early postoperative outcomes, further studies are necessary to establish a causal relationship. We also recognize the need to explore potential mechanisms underlying the observed differences in outcomes. In our revised manuscript, we will include a discussion on this aspect to provide a more comprehensive understanding of the results. Regarding the weaknesses in study design and analysis, we will address these concerns by incorporating multivariate analyses and a more thorough consideration of bias and confounding factors. This will help strengthen our conclusions and provide a clearer context for our findings. We appreciate your insights and believe that with these revisions, our paper can make a meaningful contribution to the field. Thank you for your guidance in improving the quality of our work.

2 Revision 1

2 comments · 1 Sep 2024 – 1 Sep 2024

Referee 1 Reviewer

ACCEPT 1 Sep 2024

Dear E.I.C
All comments have been carefully and correctly answered, and the manuscript is now ready to go through the next steps for publication.

Associate Editor

ACCEPT 1 Sep 2024

Accept