Clinical Effectiveness of Ertapenem Versus Piperacillin/Tazobactam in Patients With Mild to Moderate Intra-abdominal Infections: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Mehran Pezeshki1, Fatemeh Soleymani1, Meysam Seyedifar1*

1Pharmaceutical Management and Economics Research Center, The Institute of Pharmaceutical Sciences, Tehran University of Medical Sciences, Tehran, Iran.

Abstract

Purpose: This study aimed to search for randomized clinical trials evaluating the clinical effectiveness of ertapenem compared to piperacillin/tazobactam in adult patients with mild to moderate intra-abdominal infections.

Design: A literature review was performed in PubMed, Scopus, Google Scholar, and Cochrane databases in order to find articles published up to April 2019. Then, the pairwise method was used to compare the difference between the mean score of the clinical effectiveness of these two interventions before and after the intervention by the means of a non-direct method (the comparison of drugs with each other).

Results: The analysis of 4 studies involving 767 patients in the ertapenem group and 728 patients in the piperacillin/tazobactam group showed that ertapenem can be 3% more effective than piperacillin/tazobactam (Weighted mean differences = 3.02, confidence interval (0.79-6.84) although the difference was insignificant (I-squared = 0.0%, P = 0.98).

Conclusions: In general, the findings demonstrated that there is no significant difference in the clinical effectiveness of ertapenem in comparison with piperacillin/tazobactam in adult patients with mild to moderate intra-abdominal infections.

Keywords: Ertapenem, Piperacillin/Tazobactam, Intra-abdominal infections

Introduction

The peritoneum is a crucial membrane that lines the abdominal cavity and covers most of the intra-abdominal organs. Unlike uncomplicated intra-abdominal infections, complicated ones extend beyond the site of infection and may cause peritonitis or abscess formation, requiring surgical interventions (1, 2).

Intra-abdominal infections have different classifications such as primary (or spontaneous), secondary (due to the inflammation and infection of intra-abdominal organs), and tertiary (or status and permanent) peritonitis. In another classification, these infections are either localized or generalized, which is consistent with abscess formation and peritonitis, respectively (3-5).

Before the 1930s, the mortality rate of intra-abdominal infections was high (more than 90%). After the introduction and use of surgeries as a common intervention and the advent of novel anesthesia methods, this rate decreased to less than 40%. In the last decade, management and treatment of peritonitis profoundly changed because of an increase in the pathologic and microbiologic knowledge of peritonitis and the introduction of new antibiotics. In addition, the advent of simple abdominal radiography, diagnostic ultrasound, a computerized tomography scan, magnetic resonance imaging, and nuclear medicine helped an accurate diagnosis of the infected site and the etiology of peritonitis. Thus, intra-abdominal infections can now be managed and controlled more feasibly (6, 7).

The predominant bacteria involved in mild to moderate intra-abdominal infections are coliforms including (mainly Escherichia coli, Klebsiella spp., Proteus spp., and Enterobacter spp.) streptococci, enterococci, and anaerobic bacteria. In most series, dominant isolates are Bacteroides fragilis and E. coli (8).

There are various symptoms associated with intra-abdominal infections, including abdominal muscle rigidity, abdominal tenderness, abdominal pain, systemic infection or inflammation symptoms (mild to severe), and septic shock (9,10).

It is noteworthy that the infection source control and timely administration of antibiotic therapy are crucial for the management of patients with intra-abdominal infections (11).

Ertapenem is a carbapenem antibiotic with a narrower spectrum in comparison with imipenem and meropenem thus it can minimize the risk of developing resistance to...
carbapenems and can be used in the Iranian antimicrobial stewardship program. Further, the administration of ertapenem once daily, intravenously or intramuscularly, may be more convenient, safe, economic, and suited for use in the inpatient setting (12,13).

Due to outdated clinical trials and the lack of meta-analyses on the effectiveness of ertapenem and piperacillin/tazobactam in patients with mild to moderate intra-abdominal infections, this systematic review and meta-analysis aimed to investigate information from much more recent studies. The results of this study can help health care policymakers deciding on whether to include ertapenem in the National Medication Formulary of Iran.

Methods
All the outlined procedures in this review were done based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Figure 1) (14).

In this study, the PICO model was used, which stands for the population (adult patients with mild to moderate intra-abdominal infections), intervention (ertapenem regimen), comparison (piperacillin/tazobactam regimen), and outcomes (clinical effectiveness reported in randomized controlled trials).

The study was performed in two steps. First, the related literature was searched with related keywords using the PubMed MeSH tool in order to ensure the lack of similar recent studies. Subsequently, a structured study question was extracted and used to define keywords, possible combinations, and search strategies. Then, the literature was systematically reviewed again in relevant databases.

The clinical effectiveness of ertapenem and piperacillin/tazobactam was reviewed in the second step. In this step, the analysis of effectiveness was run using the data obtained from the systematic review previously conducted in the first step.

Search Strategy
Several databases were systematically searched, including PubMed, Cochrane Library, Scopus, and Google Scholar in order to find articles published from January 2000 to April 2019 using the following keywords:

1. “Intra-abdominal infections [Title/Abstract]” OR “Intraabdominal infections [Title/Abstract]” OR “Complicated intra-abdominal infections [Title/Abstract]” OR “Complicated intra-abdominal infections [Title/Abstract]” OR “IAI [Title/Abstract]” OR “CIai [Title/Abstract]” OR “Peritonitis [Title/Abstract].”

2. “Ertapenem [Title/Abstract]” OR “Invanz [Title/Abstract]” OR “Ertopenem [Title/Abstract]”

3. “Piperacillin and Tazobactam [Title/Abstract]” OR “Piperacillin/Tazobactam [Title/Abstract]” OR “Zosyn [Title/Abstract]” OR “Tazocin [Title/Abstract].”

For each database, appropriate methods were applied, including MeSH keywords. Then, the reference lists of identified clinical trials and review articles were checked to increase sensitivity. A manual search of relevant websites was carried out, and all identified articles were imported.
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into EndNote software (version X8, Thomson Reuters, New York). After the elimination of duplicated studies, the remaining articles were screened by titles, abstracts, and full texts according to our inclusion and exclusion criteria.

Study Selection
The inclusion criteria for including studies were study population (adult patients with mild to moderate intra-abdominal infection), intervention (ertapenem medication), comparator (piperacillin/tazobactam medication), outcome (clinical effectiveness, and study design (parallel and crossover clinical trials).

On the other hand, exclusion criteria included study population (studies on non-human species and diseases other than intra-abdominal infection), intervention (using ertapenem in combination with other medications that can influence the results and using medications other than ertapenem), comparator (using medications other than piperacillin/tazobactam), outcome (studies with no report on the improvement of patients on antibiotics medication and studies reporting other outcomes such as the microbiological effects of antibiotic therapy), and study design (types of studies other than clinical trials and those studies using inappropriate methods and having biases).

Two reviewers separately screened titles and abstracts based on eligibility criteria, and any disagreements were resolved through discussions between the two reviewers.

Data Gathering and Extraction
After assessing the quality of clinical trials, an extraction data form was designed based on previous review articles, and the Cochrane extraction form was also used for data gathering. In addition, two separate authors extracted data from the included articles. Further, the extracted data included study specifications (i.e., design, duration of intervention, and duration of follow-up), participant’s specifications (i.e., numbers, ages, and gender), intervention specifications (i.e., ertapenem and piperacillin/tazobactam doses), and measured outcomes (i.e., clinical effectiveness).

Quality Assessment
Two separate reviewers assessed the quality of randomized clinical trials with the Cochrane Collaboration tool (15). It is a procedure to assess the quality of clinical trials based on the following criteria: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of the outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. Then, each trial was rated as low risk, unclear, or high risk. Any disagreements in scoring were resolved through discussions between the two reviewers. Cochrane risk of the bias of the included studies showed in Table 2.

Results
Study Selection and Data Extraction
The specifications of the included studies in this meta-analysis are presented in Table 1. All 4 studies were published between 2000 and 2019. Furthermore, clinical effectiveness was reported in these studies, and ertapenem and piperacillin/tazobactam were administered with a dose of 1 g every 24 hours and 3.375 g every 6 hours via intravenous infusion, respectively. Moreover, interventions lasted for 7-10 days, and studies were performed in different countries with a sample size of 120-350 participants.

Data Synthesis and Analysis
From 374 identified articles in our search, 100 cases were duplicate. The remaining 274 articles were screened, and five articles were retrieved based on titles and abstracts. According to the inclusion criteria, the full texts of these five studies were reviewed, and only four of them proved to be eligible for the meta-analysis.

Effectiveness Comparison
Based on the analysis of four studies including 767

| Author          | Success of Ertapenem (%) | Success of PT (%) |
|-----------------|---------------------------|-------------------|
| Namias (16)     | 89.6                      | 86.2              |
| Pena (17)       | 98.2                      | 96.4              |
| Solomkin (18)   | 79.3                      | 76.2              |
| Tellado (19)    | 86.4                      | 82.4              |

Note: PT: Piperacillin/Tazobactam.

| First Author     | Sequence Generation | Allocation Concealment | Blinding of Participants and Personnel | Blinding of Outcome Assessment | Incomplete Outcome Data | Selective Outcome Reporting | Other Potential Threats to Validity |
|------------------|---------------------|------------------------|--------------------------------------|-------------------------------|--------------------------|-----------------------------|----------------------------------|
| Namias (16)      | L                   | L                      | L                                    | L                             | L                        | L                          | L                                |
| Dela Pena (17)   | U                   | L                      | U                                    | U                             | L                        | L                          | U                                |
| Solomkin (18)    | L                   | L                      | L                                    | L                             | L                        | L                          | U                                |
| Tellado (19)     | U                   | U                      | L                                    | U                             | L                        | L                          | U                                |

Note: L: Low risk of bias; H: High risk of bias; U: Unknown risk of bias.
patients in the Ertapenem group and 728 patients in the piperacillin/tazobactam group, the observed clinical improvement after the administration of ertapenem was 3% more than that of piperacillin/tazobactam (Weighted mean differences = 3.02, confidence interval = 0.79-6.84). Although no significant heterogeneity was detected (I-square = 0.0%, \( P=0.98 \)), there was no significant difference between the two groups (\( P= 0.12 \)). The results are shown in Figure 2.

**Publication Bias**
Based on the funnel plot, there is no visually detectable bias in studies. In addition, Egger’s test (\( P= 0.86 \)) and Begg’s test provided no evidence for publication bias (Figure 3).

**Sensitivity Analysis**
The sensitivity analysis showed that no individual studies significantly influenced the final results (Figure 4).

**Discussion**
A disruption in a normal mucosal barrier and subsequent leakage of normal bowel flora may lead to intra-abdominal infections (20).

The empiric regimen should cover enteric streptococci, non-resistant Enterobacteriaceae, and anaerobes in patients with mild to moderate community-acquired intra-abdominal infections with no risk factors for antibiotic resistance or treatment failure (21).

Ertapenem is a carbapenem antibiotic that can be used for patients with mild to moderate community-acquired intra-abdominal infections. It targets bacterial membrane proteins and consequently bacterial cell wall synthesis which leads to pathogen killing (22).

Unlike older carbapenems, ertapenem can be administered once daily, which makes it a cost-effective option for patients with mild to moderate intra-abdominal infections. Additionally, this antibiotic drug can be used in the antimicrobial stewardship program due to its narrow spectrum and lower risks of bacterial resistance (23).

This systematic review and meta-analysis was performed to compare the clinical effectiveness of ertapenem and piperacillin/tazobactam medications in patients with mild to moderate intra-abdominal infections. Researchers employ different approaches in reporting clinical trials in terms of effectiveness, including clinical, microbiological, and long-term effectiveness. However, clinical effectiveness is more important in clinical practice because it indicates the alleviation of clinical symptoms during or immediately after the treatment course. Nevertheless, only clinical effectiveness was considered in this study.

Based on the included studies in this meta-analysis, ertapenem was more effective compared to piperacillin/tazobactam although this difference was not statistically significant (\( P=0.211 \)).

In a study by Tellado et al, the effectiveness of ertapenem and piperacillin/tazobactam in patients with mild to moderate intra-abdominal infections was 86.4% and 82.4%, respectively, and no related side effect was reported in this regard (19).

In a randomized, double-blind multicentral study, Solomkin et al reported 79.3% and 76.2% effectiveness for ertapenem and piperacillin/tazobactam, respectively, while finding no medication-related side effects (18).

Additionally, Dela Pena et al evaluated the efficacy and safety of ertapenem versus piperacillin-tazobactam for...
the treatment of intra-abdominal infections requiring surgical intervention and concluded that ertapenem and piperacillin/tazobactam were 98.2% and 96.4% efficacious, respectively (17).

In another study, Namias et al assessed the safety and effectiveness of ertapenem and piperacillin/tazobactam in patients with mild to moderate intra-abdominal infections and found that the effectiveness of ertapenem and piperacillin/tazobactam was 89.6% and 86.2%, respectively (16).

This meta-analysis had some limitations. First, the data, which were defined as cure or improvement of signs and symptoms, were used to analyze the clinical treatment success which may not be accurate compared to complete cure. In addition, ertapenem was not administered for severe cases of intra-abdominal infections. Consequently, the affected patients with resistant pathogens were excluded in most randomized control trials, which may interfere with the finding.

It is hoped that the results of this study help health care policymakers regarding deciding on whether to include Ertapenem in Iran’s National Medication Formulary.

Conclusions

In spite of the limitations, Ertapenem was generally well-tolerated and its effectiveness, when administered 1 gram once daily, was not statistically inferior to that of piperacillin/tazobactam. According to some recent studies, the administration of ertapenem is also associated with lower costs and decreased antimicrobial resistance. Further, no related adverse effects were reported in clinical trials except for nausea and vomiting that was statistically negligible. Therefore, ertapenem is probably a better first-choice treatment in individuals with mild to moderate intra-abdominal infections due to its superior pharmacokinetic properties (e.g., longer half-life and daily regimen) compared to piperacillin/tazobactam and its similar clinical effectiveness profile.

Conflict of Interests

None.

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Ethical Approval

None.

Authors’ Contribution

MP wrote the manuscript and conducted all statistical analyses. All authors reviewed the final manuscript.

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