Original Article

Comparing Efficacy and Safety of Piperacillin/tazobactam and Amoxicillin/clavulanic acid in the Treatment of Complicated Urinary Tract Infections

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Abstract

Background: There has been an increasing concern regarding high morbidity and mortality rate among patients with severe and complicated urinary tract infections (UTIs) and their related complications. Hence, there is a great demand for choosing the best treatment protocol. In the study, we evaluated and compared the efficacy of piperacillin/tazobactam and amoxicillin/clavulanic acid for treating complicated urinary tract infections.

Materials and Methods: This study enrolled 42 patients suffering from UTIs referred to Labbafinezhad hospital, Tehran, Iran. Subjects were randomly assigned to receive intravenous piperacillin/tazobactam or intravenous amoxicillin/clavulanic acid. Clinical manifestations, vital signs, laboratory parameters, and drug side effects within three days of completing the treatment protocols were evaluated and compared between the two groups. Data analysis was performed using SPSS version 16.0. A P-value of less than 0.05 was considered significant.

Results: There was no significant difference in the frequency of pyuria and hematuria between the two groups before and after the intervention. The frequency of positive urine cultures for extended-spectrum beta-lactamase bacteria, *Escherichia coli,* was also similar between patient groups before intervention. However, a statistically significant difference in the rate of positive urine cultures for Klebsiella was found between the two groups. There was no significant difference between the two groups in terms of clinical signs and symptoms, including fever, dysuria, frequency, pain intensity, supra-pubic pain, or nausea and vomiting before the intervention, as well as within 72 hours after treatment. The vital signs were also similar between these two groups. No drug side effect was found among patients.

Conclusion: Using piperacillin/tazobactam or intravenous amoxicillin/clavulanic acid was effective and safe for treating complicated UTIs. Clinicians should consider the cost and availability of these drugs to choose the most appropriate treatment for the patients.

Keywords: Urinary tract infection, Antibiotic, Efficacy, Safety

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Introduction

Due to the high recurrence rate, complications, and increased antibiotic resistance, urinary tract infections (UTIs) have become a significant health concern[1,2]. Complicated UTIs can occur in both sexes and all age groups and are often associated with anatomical or functional abnormalities of the urinary tract[3,4]. Complicated UTIs make the treatment more difficult. Furthermore, the recurrence rate is significantly higher among patients with complicated UTIs. On the other hand, bacterial resistance to drugs is growing due to excessive use of antibiotics, especially wide-spectrum antibiotics. Together, these factors may decrease the treatment success rate for patients suffering from complicated UTIs.

Improper use of antibiotics can lead to microbial resistance development[5, 6], which is associated with higher rates of treatment failure. Failure in treatment increases the rate of morbidity and mortality among patients. Therefore, the appropriate use of antibiotics may help to prevent and minimize microbial resistance to these drugs. Infection with drug-resistant microorganisms makes the treatment more complicated. The most common resistant organisms are *Escherichia coli* (*E. coli*) and extended-spectrum beta-lactamase (Extended-spectrum beta-lactamases are a type of enzyme in some bacteria used for deactivating antibiotics, such as cephalosporins and penicillins) (ESBL) bacteria[7,8]. Piperacillin/tazobactam and penicillin are commonly used to treat UTIs caused by these organisms[9,10].

On the other hand, these antibiotics effectively treat infections caused by Pseudomonas aeruginosa, a multi-drug resistant organism. Therefore, excessive use of piperacillin/tazobactam may increase *P. aeruginosa* resistance to these drugs, leading to increased infections caused by this microorganism[11, 12]. Therefore, clinicians need to use antibiotics properly to decrease the risk of microorganism resistance development. Amoxicillin/clavulanic acid, another antibiotic regimen, is used frequently to treat complicated UTIs. However, it is still unclear which type of antibiotic protocol is more effective for these patients suffering from complicated UTIs.

To the best of our knowledge, this is the first randomized clinical trial study evaluating the efficiency, safety, and efficacy of treatment with piperacillin/tazobactam or amoxicillin/clavulanic acid among Iranian patients with complicated UTIs who were admitted to Labbafinezhad hospital.

Methods

Study population: The study enrolled 42 patients suffering from complicated UTIs hospitalized in Labbafinejad Hospital, Tehran, Iran, in 2018. The eligible patients had a history of urinary manipulation during the last three months, using the third generation of cephalosporin antibiotics during the last three months, a history of previous urinary tract infection or urinary cloning with ESBL bacteria, and had clinical symptoms at the time of diagnosis. Exclusion criteria included any signs of severe sepsis, hypotension, loss of consciousness, or metabolic acidosis, positive urinary cultures for microorganisms resistant to Piperacillin+Tazobactam, Amoxicillin+Clavulanic acid, and carbapenem, pregnancy or breastfeeding, a history of severe sensitivity to these drugs, intra-renal or perinephric abscess, complete obstruction of the urinary tract, prostatitis, underlying immunosuppressive diseases or treatment with immunosuppressive medications, acute liver failure, and undergoing peritoneal dialysis or hemodialysis.

Data collection and study interventions: Patients' baseline characteristics, including demographic data, medical history, clinical signs and symptoms, and vital signs, were all collected using hospital records and documents. Urine analysis and urine culture were performed on admission. A random number table was used to divide patients into two different groups. The first group (21 patients, including 14 males and seven females) received piperacillin/tazobactam (100mg/kg piperacillin plus l2.5 mg/kg tazobactam, administered over 30 to 60 minutes every 8 hours), and the second group (21 patients including 11 males and ten females) intravenous amoxicillin/clavulanic acid (NORMON pharmaceutical company) (40 mg/kg per day)was treated with amoxicillin/clavulanic acid. Doses of drugs were adjusted based on Glomerular filtration rate (GFR). On the second day of hospitalization, the patients' response to treatment was checked by evaluating clinical signs and symptoms, including fever, pain severity, urinary incontinence, nausea, and

vomiting. Vital signs including blood pressure, heart rate, respiratory rate, and oral temperature were recorded. On the third day of treatment (48 hours after the treatment initiation), the patients were evaluated regarding their clinical manifestations. Urine analysis and urine culture were performed on the third day of the treatment period. At the time of discharge, the patients were examined for drug side effects, including diarrhea, skin rash, and abdominal pain. Patients and researchers were blinded as to which treatment each patient received.

Statistical analysis: Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. The normality of data was analyzed using the Kolmogorov-Smirnoff test. Categorical variables were compared using the chi-square or Fisher's exact test when more than 20% of cells with an expected count of less than five were observed. Quantitative variables were also compared with the t-test or Mann U test. The statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used for the statistical analysis. P values of 0.05 or less were considered statistically significant.

Ethical considerations: Written consent was obtained from patients, and they were given sufficient information about the study. The research subjects were given the right to quit anytime they wanted. The ethical committee approved the study protocols at Shahid Beheshti University of Medical Sciences (Ethical code: IR.SBMU.MSP.REC.1398.121).

Results

There was no significant difference in mean age between the two groups (56.47±16.62 in the first group VS 53.76±16.39 in the second group; p value>0.05). No statistically significant difference in the prevalence of comorbidities was found between these two groups (Table 1). There was no significant difference in history of urinary stones (p value=0.74), urinary manipulations (p value=0.54), previous UTI (p value=0.17) or previous hospitalization due to UTI (p value=0.18) (Table 1).

Results of urine analysis performed before and after intervention were similar between the two groups (Table 2). The prevalence of positive urine culture for Klebsiella ESBL was significantly higher among the first group before intervention (p value=0.01). However, no statistically significant difference in positive urine cultures for *E. coli* was found between the two groups before and after treatment (Table 3).

According to Table 4, there was no significant difference between the two groups in terms of clinical signs and symptoms before the intervention and within 72 hours after treatment initiation. Vital signs, including blood pressure, heart rate, and respiratory rate, were also similar between these two groups (Details are shown in Table 5). Finally, no drug side effect was found among patients at discharge (Data not shown).

Discussion

We chose the best antibiotic treatment protocol for patients with severe and complicated UTIs associated with high morbidity and mortality rates. Improper use of antibiotics increases microbial drug resistance and deteriorates the patient clinical condition. Furthermore, it is important to choose safe antibiotic regimens to decrease the risk of drug side effects development. Although several studies are conducted to determine the most efficient antibiotic regimens to treat complicated UTIs, the results are inconclusive. In the present study, we evaluated and compared the efficacy and safety of two antibiotic treatment protocols, including piperacillin/tazobactam and amoxicillin/clavulanic acid, to treat complications of UTIs. Our results showed no significant difference between these two protocols regarding efficiency or safety. Furthermore, the prevalence of signs and symptoms was similar between these two groups during treatment. Finally, none of the treatment protocols was associated with severe side effects.

Both groups observed improvements in laboratory parameters, including a decrease in the prevalence of pyuria (51.6% in the first group and 43.3% in the second group). In addition, urine culture was reported negative in both patient groups after treatment. Moreover, most of the vital and clinical signs and symptoms improved during treatment in both groups. However, the differences were not significant between the intervention groups. Therefore, the present study's results showed that piperacillin/tazobactam and

Table 1: Frequency of patient baseline characteristics in piperacillin/tazobactam and amoxicillin/clavulanate groups (p valu<0.05 is considered significant).

Patient Characteristic	Piperacillin/tazobactam group N (%)	Amoxicillin/clavulanate group N (%)	p value
Sex			
Male gender	14 (66.7)	11 (52.4)	
Female	7(33.3)	10(47.6)	0.34
Mean age, year	56.47±16.62	53.76±16.39	0.59
Comorbidity			
Diabetes	4 (19.0)	5 (23.8)	0.71
Hypertension	7 (23.3)	7 (23.3)	1.000
Heart disease	3 (14.3)	4 (19.0)	0.67
Renal disease	4 (19)	3 (14.3)	0.67
Hypothyroidism	2 (9.5)	1 (4.8)	0.54
Renal grafting	1 (3.3)	2 (6.7)	0.999
Cancer	5 (16.7)	5 (16.7)	1.000
Renal disorders			
Renal stone	8 (38.1)	7 (33.3)	0.74
Renal manipulation	9 (42.9)	11 (52.4)	0.54
Previous urinary infection	13 (61.9)	17 (81.0)	0.17
Previous hospitalization due to urinary tract infection	4 (19)	8 (38.1)	0.18

amoxicillin/clavulanic acid effectively treat complicated UTIs. Furthermore, dramatic clinical response to treatment with these antibiotics indicated that common microorganisms responsible for UTI development are still sensitive to these effective drugs. To the best of our knowledge, this is the first study evaluating and comparing the efficacy and safety of piperacillin/tazobactam and amoxicillin/clavulanic acid regimens among patients suffering from complicated UTIs. Furthermore, the results of studies evaluating the effectiveness of these drug regimens are inconclusive. Verzasconi et al. showed that after the treatment with amoxicillin/clavulanic acid, bacteriuria and fever were continued among 15% and 2.2% of patients, respectively[13]. However, our results revealed that no patient had bacteriuria or fever after treatment with amoxicillin/clavulanic acid. It indicates that the microorganism sensitivity and resistance patterns are different among countries. Another study by Liu et al. showed that 34.2% of children with complicated UTIs were resistant to treatment with amoxicillin/clavulanic acid[14]. In contrast, in the present study, most subjects treated with amoxicillin/clavulanic acid showed a dramatic response to the regimen, and clinical signs and symptoms gradually improved during the treatment period. Like our findings, Beytur et al.

Table 2: Frequency distribution of laboratory parameters in piperacillin/tazobactam and amoxicillin/clavulanate groups before and after interventions (P valu<0.05 is considered significant).

Laboratory Parameter	Piperacillin/tazobactam group N (%)	Amoxicillin/clavulanate group N (%)	p value
Pyuria			
Before intervention	15 (71.4)	16 (76.2)	0.72
After intervention	4 (19)	7 (33.3)	0.29
Hematuria			
Before intervention	6 (28.6)	9 (42.9)	0.33
After intervention	4 (19)	2 (9.5)	0.37

Table 3: Frequency distribution of positive urine cultures for different microorganisms in piperacillin/tazobactam and amoxicillin/clavulanate groups before interventions (p valu<0.05 is considered significant).

Microorganism	Piperacillin/tazobactam group N (%)	Amoxicillin/clavulanate group N (%)	p value
ESBL *E. coli*	5 (23.8)	6 (28.6)	0.72
ESBL *Klebsiella*	7 (33.3)	1 (4.8)	0.01
Klebsiella pneumoniae (Sensitive to all antibiotics)	1 (4.8)	1 (4.8)	1.000
Enterococcus (Sensitive to all antibiotics)	0 (0)	1 (4.8)	0.31
E. coli (Sensitive to all antibiotics)	2(9.5)	0 (0)	0.14
E. coli KPC *	1(4.8)	0 (0)	0.31

* Klebsiella pneumoniae carbapenemase (KPC)-producing *E. coli* are a group bacteria with high antibiotic resistance

reported that treatment with an amoxicillin/clavulanic acid regimen was successful among 84.7% of patients who suffered from UTI[15].

Similarly, several studies that evaluated the efficacy of the piperacillin/tazobactam regimen in patients with UTIs reported different results. Dizbay et al. reported that 29.4% of patients with UTI who received piperacillin/tazobactam developed superinfection[16], in contrast to our study in which most of the patients in the piperacillin/tazobactam group improved gradually. Similar to our results, a study by Naber et al. showed that treatment with a piperacillin/tazobactam regimen was successful among 83% of patients[17]. The differences in organism resistance and sensitivity patterns to antibiotics may be due to two reasons: First, the prevalence of microorganisms developing UTI is different among countries. Second, various antibiotics are used in other countries. The availability and cost of antibiotics affect the use of these drugs in different societies.

Table 4: Frequency distribution of Clinical signs and symptoms in piperacillin/tazobactam and amoxicillin/clavulanate groups before interventions (p valu<0.05 is considered significant)

Sign/Symptom	Piperacillin/tazobactam group N (%)	Amoxicillin/clavulanate group N (%)	p value
Fever			
Before intervention	16 (76.2)	14 (66.7)	0.49
24 hours after intervention	3 (14.3)	4 (.19)	0.67
48 hours after intervention	1 (4.8)	1 (4.8)	1.000
72 hours after intervention	1 (4.8)	2 (9.5)	0.54
Dysuria			
Before intervention	13 (61.9)	15 (71.4)	0.51
24 hours after intervention	8 (38.1)	6 (28.6)	0.53
48 hours after intervention	2 (9.5)	0 (0)	0.14
72 hours after intervention	1 (4.8)	1 (4.8)	1.000
Frequency			
Before intervention	12 (57.1)	14 (66.7)	0.52
24 hours after intervention	4 (19)	5 (23.8)	0.7
48 hours after intervention	1 (4.8)	1 (4.8)	1.000
72 hours after intervention	1 (4.8)	1 (4.8)	1.000
Flank pain			
Before intervention	16 (76.2)	13 (61.9)	0.31
24 hours after intervention	6 (28.6)	3 (14.3)	0.25
48 hours after intervention	3 (14.3)	0 (0)	0.08
72 hours after intervention	1 (4.8)	0 (0)	0.31
Nausea			
Before intervention	12 (57.1)	15 (71.4)	0.33
24 hours after intervention	3 (14.3)	1 (4.8)	0.29
48 hours after intervention	0 (0.0)	1 (4.8)	0.31
72 hours after intervention	0 (0.0)	1 (4.8)	0.31

Vomiting			
Before intervention	11 (52.4)	10 (47.6)	0.75
24 hours after intervention	0 (0.0)	1 (4.8)	0.33
48 hours after intervention	0 (0.0)	0 (0.0)	1.000
72 hours after intervention	0 (0.0)	0 (0.0)	1.000
Suprapubic pain			
Before intervention	3 (14.3)	4 (19)	0.67
24 hours after intervention	1 (0.0)	3 (14.3)	0.29
48 hours after intervention	0 (0.0)	2 (9.5)	0.14
72 hours after intervention	0 (0.0)	1 (4.8)	0.31

Table 5: Frequency distribution of vital signs in piperacillin/tazobactam and amoxicillin/clavulanate groups before interventions (p valu<0.05 is considered significant).

Vital sign	**Piperacillin/tazobactam group Mean ± SD**	**Amoxicillin/clavulanate group Mean ± SD**	**p value**
Systolic blood pressure	122.38±19.66	117.61±15.86	0.29
Diastolic blood pressure	71.19±9.8	77.10±8.45	0.07
Heart rate	79.57±5.88	86.14±21.38	0.18
Oral temperature	37.55±.9	37.10±0.77	0.08
Respiratory rate	14.30±2.34	15.13±3.36	0.269

The present study had several limitations. First, the sample size was small, which affected the generalization of the results. Second, the follow-up period was short, which means that late side effects of the drug are missed. Third, the study was carried out in just one center. This is the first study that evaluated and compared the efficacy and safety of piperacillin/tazobactam and amoxicillin/clavulanic acid among patients with UTIs. Second, the study was double-blinded, which decreased the risk of bias. Finally, we evaluated both the efficacy and safety of these drug regimens. Further multicentric studies with larger sample sizes and longer follow-up periods are needed.

Conclusion

Both piperacillin/tazobactam and amoxicillin/clavulanic acid regimens are effective and safe in treating complicated UTIs. These drug regimens are associated with significant improvement in patient clinical conditions. Therefore, one of the above antibiotic regimens is recommended for treating patients suffering from complicated UTIs. They live in countries where microorganism resistance to these drugs is low. Clinicians should consider the cost and availability of these drugs to choose the most appropriate treatment for the patients. Further researchers must determine and compare late side

effects and other characteristics of these two antibiotic regimens.

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