Comparison The Effect of Single Daily Dose With 48 Hours Interval of Amikacin With Meropenem in Treatment With Urinary Tract Infection With E. Coli: A Clinical Trial Study

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Abstract

Objective: Urinary tract infection is among the most prevalent infections in humans, and E. coli is the most frequent pathogen causing this disease. The production of Beta lactamase enzymes (ESBL) in this bacterium makes it resistant to many antibiotics. The aim of this study was to evaluate a novel method single daily dose of Amikacin at 48 h intervals in a clinical trial. This was a double-blind clinical trial study.

Material and Methods: The patients were divided into two groups of Intervention (Administration of single daily dose of Amikacin at 48 h intervals) and control (Prescription of Meropenem for 1 Week).

Results: The mean age of the Intervention group was (46.64±3.89) and control group (46.03±2.38). The frequency of E. coli infection was 61(54%), and that of other infections was 52(46%).

Conclusion: The results of our study show the therapeutic effect of single daily dose administration of Amikacin every 48 hours.

Introduction

Urinary tract infection is among the most prevalent infections in humans, and E. coli is the most frequent pathogen causing this disease(1, 2). E.coli is a Gram-negative bacillus of the Enterobacteriaceae family. Today, the treatment of E. coli infections is difficult because of antibiotic-resistant strains. The production of Beta lactamase enzymes(ESBL) in this bacterium makes it resistant to many antibiotics (3, 4). Beta lactamases are produced by Gram-negative bacteria and are widely found in the members of the Enterobacteriaceae family. ESBL-producing bacteria are resistant not only to penicillin, cephalosporins, and aztreonam, but also to other antibiotics, including Co-trimoxazole, tetracycline, and fluoroquinolones. Moreover, the easy transfer of the ESBL-coding plasmid in its species is a major threat to hospitalized patients(5, 6). In recent years, numerous studies have been conducted in different parts of the world on the antibiotic resistance of this bacterium, indicating the resistance of several drugs as well as broad-spectrum ESBL (7-9). In the USA, the level of multidrug resistance was 7.1%, while this value was 10.9% in Iran(10, 11). There are ongoing attempts to find alternative drugs; drugs such as Fosfomycin, carbapenems, Tazocin, and aminoglycosides are currently under study. Carbapenems serve as the treatment of choice for these organisms; recently, Enterobacteriaceae resistant to carbapenems have been produced (12). Since the standard recommended treatment is the use of carbapenems, patients must be hospitalized, and this leads to the consequences of hospitalization and loss of working days, while also increasing the costs and the risk of nosocomial infections. The use of aminoglycoside has been reduced over the past decades. The main obstacles to their use is their side-effects which are higher than those of other antibiotics. However, the side-effects are lower in patients treated with aminoglycosides compared to those receiving beta lactams. The prevalence of microbial resistance to aminoglycosides has been low in recent years. Treatment with aminoglycosides has the same
effectiveness as beta lactames or quinolones in reaching clinical improvement in the case of urinary tract infection (1, 13-15). Therefore, finding an effective alternative method is a therapeutic priority. Accordingly, the present study, the aim of this study was to evaluate a novel method single dose of Amikacin at 48 h intervals in a clinical trial.

Materials And Methods

This was a double-blind clinical trial study. The inclusion criteria were having the following symptoms: burning sensation when urinating, frequent urination and fever; the exclusion criteria were recently taking antibiotics, taking immunosuppressive drugs, septic shock, having a GFR of less than 60 and creatinine level >3. The vital signs of those visiting the hospital with the mentioned symptoms were checked and after doctor visiting, a smear test and urine analysis and culture were performed. If the results of urine analysis indicated the chance of urinary tract infection, all the patients would be included in the study until a positive culture result would be obtained. Subsequently, those with a negative culture were excluded. Patients signed informed consent forms before inclusion. The patients were divided into two groups of intervention and control. The number of patients included in the study in both groups shown as flowchart 1. The study was double-blind since the evaluating doctor, the laboratory, and the patients were blind to the group allocation.

Intervention group received Amikacin 3mg/kg every 48 hours for 7 days then treatment with floxacin 300 mg twice daily for 7 days at the end of the initial injectable treatment. Clinical signs were recorded and urine analysis and culture were performed.

Control group received Meropenem at a dose of 1 gr three times daily for one week, then treatment with floxacin 300 mg twice daily for 7 days at the end of the initial injectable treatment. Clinical signs were recorded and urine analysis and culture were performed.

Data Analysis:

After inputting the data into SPSS 18, quantitative data were described as mean and SD, and qualitative data as frequency and percentage. Independent t test was used for comparing two quantitative variables. Then, using the Fisher exact test, success of treatment was compared between the two groups.

Results

The mean age of the intervention group was (46.64 ± 3.89) and control group (46.03 ± 2.38). The frequency of E. coli infection was 61(54%), and that of other infections was 52(46%). In people with ESBL E.coli infection, the highest antibiotic resistance was Ciprofloxacin 21(70%) and the highest sensitivity was Nitrofurantoin 33(91.7%). Also in individuals with non-ESBL E.coli infection, the highest antibiotic resistance was Ciprofloxacin 9(60%) and the highest sensitivity was Nitrofurantoin& Gentamaicin 13(86.7%). A summary of the results is given in the following tables.
Table 1
Frequency distribution of variables studied before treatment

| Groups | ESBL E.coli (N = 40)) | Non ESBL E.coli (N = 21) | P-Value |
|--------|------------------------|--------------------------|---------|
| Age    |                        |                          |         |
|        | A 4.40 ± 50.63         | 7.32 ± 38.22             | 0.14    |
|        | M 3.17 ± 46.67         | 3.61 ± 44.92             | 0.73    |
| P-Value| 0.46                   | 0.43                     |         |
| Sex    |                        |                          |         |
|        | A Male 3(15.8%)         | 4(44.4%)                 | -       |
|        | Female 16(84.2%)        | 5(55.6%)                 | 0.16    |
|        | M Male 2(9.5%)          | 4(33.3%)                 | 0.15    |
|        | Female 19(90.5%)        | 8(66.7%)                 |         |
| History of urinary tract infection | A 8(42.1%) | 6(66.7%) | 0.42 |
|        | M 11(52.4%)             | 8(66.7%)                 | 0.48    |
| P-Value| 0.54                   | 1                        |         |
| Dysuria |                        |                          |         |
|        | A 16(84.2%)             | 9(100%)                  | 0.53    |
|        | M 19(90.5%)             | 10(83.3%)                | 0.61    |
| P-Value| 0.65                   | 0.48                     |         |
| Frequent urination | A 17(89.5%) | 8(88.9%) | 1 |
|        | M 18(85.7%)             | 11(91.7%)                | 1       |
| P-Value| 1                      | 1                        |         |
| Abdominal pain | A 5(26.3%) | 1(11.1%) | 0.63 |
|        | M 9(42.9%)              | 5(41.7%)                 | 1       |
| P-Value| 0.33                   | 0.17                     |         |
| Flank Pain | A 8(42.1%) | 4(44.4%) | 1 |
|        | M 15(71.4%)             | 7(58.3%)                 | 0.47    |
| P-Value| 0.11                   | 0.67                     |         |

...t test was used
| Groups                        | ESBL E.coli (N = 40) | Non ESBL E.coli (N = 21) | P-Value |
|-------------------------------|----------------------|--------------------------|---------|
| Suprapubic Pain               |                      |                          |         |
| A                             | 12 (63.2%)           | 7 (77.8%)                | 0.67    |
| M                             | 13 (61.9%)           | 6 (50%)                  | 0.71    |
| P-Value                       | 1                    | 0.36                     |         |
| Costovertebral angle tenderness (CVAT)) |                      |                          |         |
| A                             | 9 (47.4%)            | 4 (44.4%)                | 1       |
| M                             | 15 (71.4%)           | 7 (58.3%)                | 0.47    |
| P-Value                       | 0.19                 | 0.67                     |         |

...t test was used

Fisher exact test was used for other comparisons.
**Table 2**
Frequency distribution of clinical symptoms after 48 hours of treatment

| Groups      | ESBL E.coli (N = 40) | Non ESBL E.coli (N = 21) | P-Value |
|-------------|----------------------|--------------------------|---------|
| Dysuria     |                      |                          |         |
| A           | 3 (15.8%)            | 1 (11.1%)                | 1       |
| M           | 4 (19%)              | 1 (8.3%)                 | 0.63    |
| P-Value     | 1                    | 1                        |         |
| Frequent urination | 2 (10.5%)          | 1 (11.1%)                | 1       |
| M           | 3 (14.3%)            | 2 (16.7%)                | 1       |
| P-Value     | 1                    | 1                        |         |
| Abdominal pain | 1 (5.6%)           | 0 (0%)                   | 1       |
| M           | 3 (15%)              | 2 (16.7%)                | 1       |
| P-Value     | 0.6                  | 0.48                     |         |
| Flank Pain  | 2 (11.8%)            | 1 (11.1%)                | 1       |
| M           | 7 (33.3%)            | 1 (8.3%)                 | 0.21    |
| P-Value     | 0.15                 | 1                        |         |
| Suprapubic Pain | 4 (21.2%)        | 2 (22.2%)                | 1       |
| M           | 3 (15%)              | 1 (8.3%)                 | 1       |
| P-Value     | 0.69                 | 0.55                     |         |

Fisher exact test was used.
Table 3
Frequency distribution of the studied variables after one week of treatment

| Groups   | ESBL E.coli (N = 40)) | Non ESBL E.coli (N = 21) | P-Value |
|----------|-----------------------|--------------------------|---------|
| Dysuria  | A 2(10.5%) 0(0%)      | 1                        |
|          | M 1(4.8%) 0(0%)       | 1                        |
| P-Value  | 0.59                  | -                        |
| Frequent urination | A 2(11.1%) 0(0%) 0.53 |                        |
|          | M 0(0%) 0(0%)         | -                        |
| P-Value  | 0.21                  | -                        |
| Abdominal pain | A 1(5.3%) 0(0%) 1    |                        |
|          | M 1(4.8%) 0(0%)       | 1                        |
| P-Value  | 1                     | -                        |
| Flank Pain | A 2(10.5%) 0(0%) 1    |                        |
|          | M 1(4.8%) 0(0%)       | 1                        |
| P-Value  | 0.59                  | -                        |
| Suprapubic Pain | A 2(10.5%) 0(0%) 1   |                        |
|          | M 1(4.8%) 0(0%)       | 1                        |
| P-Value  | 0.59                  | -                        |
| UC       | A 5(12.5%) 0(0%)      | 0.14                     |
|          | M 0(0%) 0(0%)         | -                        |
| P-Value  | 0.01                  | -                        |

Fisher exact test was used.
| Antibiotics                  | Sensitive | Intermediate | Resistant  |
|------------------------------|-----------|--------------|------------|
| Ampicillin                   | 1 (2.5%) | 2 (5%)       | 12 (30%)   |
| Gentamicin                   | 18 (45%) | 2 (5%)       | 9 (22.5%)  |
| Piperacillin                 | 3 (7.5%) | 3 (7.5%)     | 14 (35%)   |
| Tazobactam                   | 1 (2.5%) | 6 (15%)      | 2 (5%)     |
| Cefepime                     | 5 (12.5%)| 1 (2.5%)     | 15 (37.5%) |
| Cefotaxime                   | 5 (12.5%)| 3 (7.5%)     | 15 (37.5%) |
| Ceftazidime                  | 7 (17.5%)| 3 (7.5%)     | 12 (30%)   |
| Ciprofloxacin                | 6 (15%)  | 3 (7.5%)     | 2 (5%)     |
| Meropenem                    | 19 (47.5%)| 3 (7.5%)    | 1 (2.5%)   |
| SXT                          | 4 (10%)  | 3 (7.5%)     | 2 (5%)     |
| Nitrofurantoin               | 33 (82.5%)| 3 (7.5%)    | 0 (0%)     |
| Clavulanic acid + Ceftazidime| 3 (7.5%) | 0 (0%)       | 1 (2.5%)   |
| Clavunic acid + Cefotaxime   | 3 (7.5%) | 0 (0%)       | 1 (2.5%)   |
| AmyKacin                     | 10 (25%) | 1 (2.5%)     | 0 (0%)     |
| Oxacillin                    | 0 (0%)   | 0 (0%)       | 0 (0%)     |
| Norfloxacin                  | 1 (2.5%) | 1 (2.5%)     | 4 (10%)    |
| Clindamycin                  | 1 (2.5%) | 0 (0%)       | 2 (5%)     |
Table 5
Antibiotic Resistance in NonESBL E.coli E.coli

| Antibiotics           | Sensitive | Intermediate | Resistant |
|-----------------------|-----------|--------------|-----------|
| Ampicillin            | 2(9.5%)   | 0(0%)        | 5(23.8%)  |
| Gentamicin            | 13(61.9%) | 1(4.8%)      | 3(14.3%)  |
| Piperacillin           | 7(33.3%)  | 1(4.8%)      | 4(19%)    |
| Tazobactam            | 3(14.3%)  | 1(4.8%)      | 1(4.8%)   |
| Cefepime              | 4(19%)    | 0(0%)        | 5(23.8%)  |
| Cefotaxime            | 3(14.3%)  | 0(0%)        | 7(33.3%)  |
| Ceftazidime           | 2(9.5%)   | 1(4.8%)      | 6(28.6%)  |
| Ciprofloxacin         | 6(28.6%)  | 0(0%)        | 9(42.9%)  |
| Meropenem             | 12(57.1%) | 0(0%)        | 2(9.5%)   |
| SXT                   | 5(23.8%)  | 0(0%)        | 8(38.1%)  |
| Nitrofurantoin        | 13(61.9%) | 0(0%)        | 2(9.5%)   |
| Clavulanic acid + Ceftazidime | 0(0%) | 0(0%) | 0(0%) |
| Clavunic acid + Cefotaxime | 1(4.8%) | 0(0%) | 0(0%) |
| AmyKacin              | 6(28.6%)  | 0(0%)        | 0(0%)     |
| Oxacillin             | 3(14.3%)  | 0(0%)        | 0(0%)     |
| Norfloxacin           | 2(9.5%)   | 0(0%)        | 2(9.5%)   |
| Clindamycin           | 1(4.8%)   | 0(0%)        | 0(0%)     |

Discussion

The results revealed that a treatment regimen with monotherapy and single daily dose Amikacin with two-day intervals act as the standard treatment of urinary tract infection in 48 hours since the onset of treatment, and one week after the onset of treatment, significantly reducing clinical symptoms; after two weeks of treatment, the clinical symptoms of urinary tract infection is resolved in both groups. These findings were the same in terms of a reduced E. coli urinary tract infection. Although this reduction was more prominent in the control group after a week, after two weeks of treatment, E. coli infections was zero in both groups. As mentioned in the Introduction, the side-effects in patients treated with aminoglycosides are less compared to those receiving beta lactams. The standard recommended treatment is the use of Carbapenems, and patients must be hospitalized; this leads to consequences of hospitalization, increases the costs, ends in loss of working days, and increases the risk of nosocomial
infections\textsuperscript{(1, 13–15)}. Based on our results, it seems that monotracy and single daily dose Amikacin can be a good alternative for treatment of E. coli urine.

A clinical trial study was conducted by SY Cho et al. in 2011–2012 in South Korea, entitled “Treatment of ESBL E. coli urinary tract infection with Amykacin”. In this study, 9 episodes of urinary tract infection caused by ESBL E. coli were examined in 8 women under outpatient intravenous treatment with Amykacin. The mean duration of treatment was 10 days. The results showed clinical and laboratory improvement at the end of treatment with Amykacin in all episodes. Finally, one untreated case, and one case of relapse were observed\textsuperscript{(1)}. Results of this study are in line with our results, with the difference being that, in this study, Amykacin was taken on a daily basis. A clinical trial was conducted by SH Wie et al. (2011) in South Korea, entitled “Effects of gentamicin monotherapy for the initial treatment of community-onset complicated non-obstructive acute pyelonephritis due to Enterobacteriaceae in elderly and non-elderly women”. Out of 275 cases included in the study, 43 cases were gentamicin-resistant, and 232 cases were gentamicin-sensitive Enterobacteriaceae\textsuperscript{(16)}. Although, in this study, sensitivity to gentamicin was 83.3%, which is higher than our study, both studies report the high sensitivity of this antibiotic. Another clinical trial study was conducted by SB Han et al. in 2010–2014 in South Korea, entitled “Aminoglycoside therapy for childhood urinary tract infection due to extended-spectrum β-lactamase-producing Escherichia coli or Klebsiella pneumoniae”. In this study, 211 children aged < 14 years diagnosed with urinary tract infection due to E. coli with Klebsiella pneumoniae who visited clinics inside or outside the hospitals were included. The level of antibiotic sensitivity was 100% for Imipenem and Meropenem in both groups of ESBL and non-ESBL. This was followed by gentamicin with the sensitivity of 99.5% in the non-ESBL group and 100% in the ESBL group, showing the highest sensitivity to Cephalosporins, Fluoroquinolones, and other antibiotics (15). Results of this study are consistent with our study, demonstrating the sensitivity of Amykacin in both ESBL and non-ESBL groups.

A study entitled “Escherichia coli and Klebsiella pneumoniae Sensitivity/Resistance Pattern Towards Antimicrobial Agents in Primary and Simple Urinary Tract Infection Patients Visiting University Hospital of Jamia Hamdard New Delhi” was conducted by M Rizwan (2018), in which 14 patients with urinary tract infection were examined. Results showed that E. coli, followed by Klebsiella pneumoniae, were the most prevalent strains. E. coli had the highest antibiotic resistance to ampicillin, followed by Co-Trimoxazole, Norfloxacin, ciprofloxacin, gentamicin, tetracycline, and Ceftazidime, and the least antibiotic resistance to amikacin and nitrofurantoin (17). The results of our study show the therapeutic effect of single dose administration of Amikacin every 48 hours. The main concern with regard to the use of aminoglycosides is their toxicity; the nephrotoxicity of these drugs is 8–14%, which is increased by increasing drug dosage, having a treatment period of 10 days or longer, or simultaneous prescription of nephrotoxic agents (1). Nevertheless, in our study, the renal function of the patients was examined by serum creatinine measurement repeatedly before, during, and after treatment. Moreover, to examine the ototoxicity of patients before and after treatment with Amikacin, they were followed-up in terms of clinical symptoms, e.g. Hearing loss, balance disorder, and vertigo, during and at the end of treatment, and the results showed no nephrotoxicity or ototoxicity in any patient.
Conclusion

The results of our study show the therapeutic effect of single daily dose administration of Amikacin every 48 hours

Declarations

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Ethics approval and consent to participate: Informed consent was documented by the use of a written consent form approved by the Ethics Committee Kurdistan University of Medical Sciences(IR.MUK.REC.1395/197).

Competing interests: “The authors declare that there is no conflict of interests regarding the publication of this article”.

Authors’ contributions: BM &HA and AM carried out the study and collected data. BM and AA supervised the study, participated in designing and conducting it, and prepared the original version of the manuscript. EG conducted research and performed the statistical analysis. All authors studied and approved the content of the present manuscript and participated in revising the paper. Availability of data and materials: 199 Only publicly available data were used as specified in the manuscripts.

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