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Original Article

Amikacin once every other day versus Daily Meropenem for Treatment of Urinary Tract Infection with *Escherichia Coli*

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ABSTRACT

Background and Aim: Urinary tract infection (UTI) is a common medical challenge, especially in the light of increased antibiotic resistance. This work aimed to compare between amikacin (3 doses, once each other day) with a daily dose of meropenem (once daily for seven days) for the treatment of urinary tract infection caused by *Escherichia Coli*.

Patients and Methods: 70 patients with confirmed UTI infection by E. Coli were included and divided for two groups. The first was treated by amikacin 15mg/kg once every 48 hours for seven days. The second group was treated by meropenem 1 g three times daily for one week. Then, urinary culture and sensitivity was re-performed and tested against the commonest panel of antibiotics. The clinical manifestations were documented before treatment and one week after treatment.

Results: There was no significant difference between groups regarding patient demographics or manifestations of UTI. 54.3% in amikacin and 65.7% in meropenem groups reported previous UTI. The clinical manifestations of UTI include dysuria, frequent urination, flank pain, abdominal pain, fever and suprapubic pain. The treatment was associated with eradication of E. Coli in 60.0% and 54.3% in Amikacin and meropenem respectively, with no significant differences between groups at the end of the first week and at that time, the most sensitive drugs were nitrofurantoin (34.3%) followed by meropenem (22.9%) and amikacin (18.6%). However, the highest resistance was registered for cefepime and cefotaxime (41.4%) followed by ceftazidime-clavulanic acid (40.0%). Clinical manifestations of UTI were significantly reduced in both groups one week after treatment with no significant differences between groups.

Conclusion: Amikacin could be considered as is an effective and safe alternative to meropenem for treatment of UTI due to *E. Coli*.

Keywords: **Extended spectrum beta-lactamase; *E. Coli*; Urinary Tract Infection; Antibiotic resistance**.

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INTRODUCTION

Urinary tract infections (UTIs) are the commonest infections among humans, and usually due to infection by *Escherichia coli* (*E. coli*) [1-3]. The treatment of *E.Coli* infection is challenging due to higher incidence of antibiotic resistance for several antibiotics [4,5]. Extended spectrum beta-lactamase (ESBL)-producing bacteria are resistant to different antibiotics (e.g., cephalosporins, penicillin, tazobactam/ piperacillin, co-trimoxazole, tetracyclines and fluoroquinolones) [6,7].

Other alternative antibiotics are examined to deal with the antibiotic resistance (e.g., Fosfomycin). Carbapenems are considered the treatment of choice to ESBl. However, *E. Coli* resistance was reported [8]. The accepted regimen is using these carbapenems in a hospitalized patient. However, hospitalization is not free of risks (e.g., hospital acquired infections and lost working days) [9].

The use of aminoglycosides showed progressive decrease in the last decades due to associated side effects [10]. However, its use is reported to yield fewer side effects than meropenem [11,12]. In addition, the use of amino-glycosides is effective as beta-lactams or quinolones for clinical improvement of urinary tract infection [13-15]. Thus, searching for an effective and safe effective substances and methods of treatment is crucial.

The current work aimed to compare between amikacin (3 doses, once each other day) with a daily dose of meropenem (once daily for seven days) for the treatment of urinary tract infection with E. Coli.

PATIENTS AND METHODS

Th This was a prospective comparative study conducted at the department of urology, Al-Azhar University hospital (New Damietta) who presented with clinical manifestations of upper or lower urinary tract (UTI) infection. *E. Coli* as a causative agent was confirmed by the culture. The suggestive clinical manifestations include burning micturition, frequent urination, right upper abdominal quadrant pain and fever. Patients were excluded if they reported recent use of antibiotics, had septic shock, renal affection (creatinine > 3 or GFR < 60 ml/minute), using immunosuppressive medications, or their culture showed non-*E Coli* infection or identification of other bacteria in addition to *E. Coli*.

At initial visit, patients were submitted to full clinical examination and urine culture was performed. The positivity of culture was determined on the basis of gram staining, chemical reactions and selective media (e.g., blood Agar, Eosin methylene blue, Sulfide indol motility, Triple sugar iron agar and Simmon citrate agar, as described elsewhere [16-19].

All eligible patients were randomly (closed envelope for randomly generated numbers) assigned to one of the two groups (1:1). The final analysis was performed for 35 patients in each group. The first group was treated by amikacin 15mg/kg (maximum 1 gm) once every 48 hours for seven days (a total of three doses were used). Then a second sample for urinary culture and sensitivity was collected, and tested against the commonest panel of antibiotics. The treatment was continued by oral ofloxacin 300 mg, two times daily for the next week regardless the results of the culture. The second group was treated by meropenem 1 g three times daily for one week. Then completed by ofloxacin as in the first group for the next week. Clinical manifestations of UTI were recorded before- and after- one week of treatment. For concealment, all patients received the same frequencies of injections (drugs or normal saline) and a micro-infusion set was used for injection.

Statistical analysis

The collected data was coded, fed to a statistical computer software package (statistical package for social sciences), version 18 for windows. The qualitative data were presented as frequencies and percentages. However, quantitative data were expressed as mean and standard deviation (SD). Both groups were compared by independent samples student "*t*" and Chi square tests (or their equivalents) for quantitative and qualitative data, respectively. The clinical manifestations of UTI were compared before and one week after treatment were compared by the Wilcoxon signed rank. P value < 0.05 was considered significant.

RESULTS

The current study included 70 patients with confirmed E. Coli Urinary tract infection. They were assigned for amikacin (once every other day) or meropenem. The patients were mainly in their forties, with female predominance in both groups. More than 50% in both groups reported positive history of UTI (54.3% versus 65.7% in amikacin and meropenem groups respectively). The clinical manifestations of UTI include dysuria, frequent urination, flank pain, abdominal pain, fever and suprapubic pain. No significant differences were recorded for patient characteristics, history of UTI or clinical manifestations of UTI (Table 1).

The urine culture after the first week of treatment revealed that, treatment was associated with eradication of E. Coli in 60.0% and 54.3% in Amikacin and meropenem respectively, with no significant differences between groups (Table 2). The antibiotic sensitivity tests were performed for positive cultures.

One week after treatment, the sensitivity tests revealed that, the most sensitive drugs were nitrofurantoin (34.3%) followed by meropenem (22.9%) and amikacin (18.6%). However, the highest resistance was registered for cefepime and cefotaxime (41.4%) followed by ceftazidime-clavulanic acid (40.0%) (Table 3).

The clinical manifestations of UTI were significantly reduced in both groups one week after treatment with no significant differences between groups (Tables 4 and 5).

Table (1): Patient characteristics and clinical manifestation of UTI before treatment

Variable		Amikacin (n=35)	Meropenem (n=35)	Test	p
Age (year)	Mean±SD	41.63±9.45	43.94±10.31	0.97	0.33
	Min. – Max.	28-59	26-60		
Gender (n, %)	Male	13(37.1%)	11(31.4%)	0.25	0.61
	Female	22 (62.9%)	24(68.6%)		
History of UTI		19(54.3%)	23(65.7%)	0.95	0.32
Manifestations of UTI (n, %)	Dysuria	32(91.4%)	31(88.6%)	0.16	0.69
	Frequent urination	34(97.1%)	33(94.3%)	FE	1.00
	Flank pain	19(54.3%)	22(62.9%)	0.53	0.46
	Abdominal pain	14(40.0%)	17(48.6%)	0.52	0.47
	Suprapubic pain	25(71.4%)	22(62.9%)	0.58	0.44
	Fever	35(100.0%)	35(100.0%)	0.001	1.0

Table (2): Results of culture one week after treatment

		Amikacin	Meropenem	Total	Test	p
Culture	Positive	14(40.0%)	16(45.7%)	30(42.9%)	0.23	0.62
	Negative	21 (60.0%)	19 (54.3%)	40(57.1%)		

Table (3): Results of sensitivity one week after treatment

	Sensitive	Intermediate	Resistant
Amikacin	**13 (18.6%)**	**17(24.3%)**	**0(0.0%)**
Meropenem	**16(22.9%)**	**3 (4.3%)**	**11 (15.7%)**
Ampicillin	4(5.7%)	1 (1.4%)	25(35.7%)
Gentamicin	5(7.1%)	2(2.9%)	23(32.9%)
Cefepime	1(1.4%)	0 (0.0%)	**29(41.4%)**
Cefotaxime	1(1.4%)	0 (0.0%)	**29(41.4%)**
Ciprofloxacin	3(4.3%)	3(4.3%)	24(34.3%)
Ceftazidime	6 (8.6%)	2 (2.9%)	22(31.4%)
Sulphamethoxazole-trimethoprim	6 (8.6%)	4(5.7%)	20(28.6%)
Nitrofurantoin	**24(34.3%)**	**4(5.7%)**	**2(2.9%)**
Oxacillin	1(1.4%)	3(4.3%)	26(37.1%)
Norfloxacin	3(4.3%)	4(5.7%)	23(32.9%)
Clindamycin	2(2.9%)	1(1.4%)	27(38.6%)
Ceftazidime - clavulanic acid	1(1.4%)	1(1.4%)	28(40.0%)
Cefotaxime- clavulanic acid	4(5.7%)	4(5.7%)	22(31.4%)
Piperacillin	6(8.6%)	7(10.0%)	17(24.3%)

NB: Percentages were calculated from the who study subjects

Table (4): Clinical manifestations one week after initiation of treatment

Variable		Amikacin	Meropenem	Test	p
Clinical Manifestations of UTI (n, %)	Dysuria	4(11.4%)	1(2.9%)	1.93	0.16
	Frequent urination	1(2.9%)	2(5.7%)	0.34	0.55
	Flank pain	2(5.7%)	3(8.6%)	0.21	0.64
	Abdominal pain	3(8.6%)	1(2.9%)	1.06	0.30
	Suprapubic pain	1(2.9%)	0(0.0%)	1.01	0.31
	Fever	0(0.0%)	0(0.0%)	-	

Table (5): Paired comparison of clinical manifestations in each group

Variable		Pre-treatment	After-treatment	Test	p
Amikacin	Dysuria	32(91.4%)	4(11.4%)	5.29	<0.001*
	Frequent urination	34(97.1%)	1(2.9%)	5.74	<0.001*
	Flank pain	19(54.3%)	2(5.7%)	3.71	<0.001*
	Abdominal pain	14(40.0%)	3(8.6%)	2.84	0.005*
	Suprapubic pain	25(71.4%)	1(2.9%)	4.89	<0.001*
	Fever	35(100.0%)	0(0.0%)	5.92	<0.001*
Meropenem	Dysuria	31(88.6%)	1(2.9%)	5.47	<0.001*
	Frequent urination	33(94.3%)	2(5.7%)	5.56	<0.001*
	Flank pain	22(62.9%)	3(8.6%)	4.35	<0.001*
	Abdominal pain	17(48.6%)	1(2.9%)	4.00	<0.001*
	Suprapubic pain	22(62.9%)	0(0.0%)	4.96	<0.001*
	Fever	35(100.0%)	0(0.0%)	5.92	<0.001*

DISCUSSION

The results of the current work showed that, a single dose of Amikacin injected each 48 hours is as effective as daily use of three doses of Meropenem. The clinical manifestations of UTI were significantly reduced. Amikacin is associated with higher eradiation rate for E. Coli. However, the difference than meropenem did not reach statistical significance. After one week of treatment, the most sensitive drug was nitrofurantoin followed by the drugs of the study (amikacin and meropenem). The highest resistance was recorded with cefepime, cefotaxime and ceftazidime-clavulanic acid. Thus, amikacin with this regimen seems to be reasonable alternative for reported regimens (aminoglycosides or beta-lactams).

In line with our results, **Cho *et al.*** [9] investigated nine episodes of UTIs due to *E. coli* in eight women receiving outpatient intravenous (IV) treatment with amikacin. They reported 10 days as the average length of treatment. There was laboratory and clinical improvement of UTI manifestations after amikacin treatment. Infection was re-emerged in one female and treatment. These results are in line with the current work.

Iakovlev *et al.* [20] conducted a multicenter study to examine the effect of meropenem (1 g every 8 hours for 3-14 days; average 9 days) compared to amikacin (0.5 g every 12 hours for 2-14 days; average 9 days) combined with ceftazidime (1 g every 8 hours) for treatment of different infections (respiratory, abdominal, skin, soft tissues and urinary). At the end of treatment, the clinical effect (defined by recovery and improvement) was 97.9% for meropenem and 89.1% for combined treatment. These results explained by the results or microbial isolates (133 strains were isolated; 121 were susceptible to meropenem and 111 to amikacin and 90 (67.7%) to ceftazidime). The side effects profile was mild. These results are in line with ours regarding the efficacy of both drugs even when used with infections include UTI and others.

Zacharias *et al.* [21] investigated the effect of amikacin sulfate bladder wash for prevention of catheter-associated urinary tract infection in neurosurgical patients admitted to intensive care unit. None of patients received amikacin bladder wash developed catheter associated UTI. However, 40% of those who did not receive amikacin developed UTI. These results reflected the amikacin in prevention of UTI irrespective of the causative organism

(as the most common cause in the infected patients was *Pseudomonas aeruginosa* followed by *E. Coli*).

Ipekci *et al*. [22] conducted a retrospective study of adult 36 outpatients' subjects with confirmed UTI with E Coli or Klebsiella Pneumoniae- resistant to nitrofurantoin, quinolones, trimethoprim-sulfamethoxazole and Fosfomycin. Patients were treated by intramuscular (IM) amikacin 15 mg/kg/day for 10 days. The clinical success rate (disappearance of symptoms) on the third day of treatment was 97.1%. They concluded that, amikacin is an efficient and safe alternative option before the carbapenem treatment especially in patients with lower UTIs caused by E Coli or *Klebsiella Pneumoniae* that are resistant to all oral antibiotics. These results are consistent with the current work.

Polat and Tapisiz [23] conducted a study to investigate the effectiveness of amikacin in treatment of febrile urinary tract infection due to infection by Extended-Spectrum β-Lactamase-producing *Escherichia coli* in Children. They reported clinical improvement in 96.0% of patients with no need for further treatment or urinary culture after 3 days of treatment. The efficacy of amikacin in treatment of UTI was explained by its high urinary excretion as reported by **Vidal *et al*.** [24].

Polat and Tapisiz [23] concluded that, in the era of increasing resistance to antibiotics, it is crucial to investigate alternative carbapenem-sparing agents for UTI treatment. Carbapenems should be only used for patients with severe infection with ESBL-producing organisms. They added, their results revealed that amikacin might be a reasonable alternative for treatment of such infections in children with normal renal function. These results are in accordance with ours.

Finally, **Nguyen *et al*.** [25] conducted a systematic review and meta-analysis to determine the clinical cure rate of carbapenem-sparing beta-lactams (combination of drugs) versus meropenem for gram-negative infections. They reached to the conclusion that different carbapenem -sparing beta-lactams combinations can be considered as viable alternatives for the treatment of UTIs.

In short, our study proved the effectiveness of amikacin with a special regimen (once daily for one week) is effective and safe alternative to meropenem. The strength points include the prospective nature of the study. However, the small sample size representing a limiting step of the work. Thus, future studies are recommended.

Conflict of interest: None

Financial disclosure: None

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