Original Article

A Randomized Controlled Trial: Colistin Alone or Colistin and Meropenem: Which Is More Effective for the Management of Urinary Tract Infections?

Davood Yadegarynia[1], Shabnam Tehrani[1], Amirreza Keyvanfar[1], Latif Gachkar[1], Behnaz Najafi[1*]

[1]Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Received: 19 April, 2022; Accepted: 24 July, 2022

Abstract

Background: Colistin is a common antibiotic used to treat urinary tract infections (UTIs) caused by gram-negative bacteria. In recent years, due to the increasing resistance, consumption of colistin alone could lead to treatment failures. This study aimed to compare the effectiveness of colistin alone with colistin and meropenem to treat patients with urinary tract infections.

Materials and Methods: In this randomized, open-label, parallel groups controlled trial, hospitalized patients with urinary tract infections were included. Patients were randomly allocated to the control group (n=35) that received colistin (1 mIU every 12 hours) and the intervention group (n=35) that received colistin (1 mIU every 12 hours) with meropenem (1gr every 8 hours). An infectious disease specialist evaluated the therapeutic responses 48-72 hours after admission. Cessation of fever, improvement of symptoms and signs, and negative urine culture within 48 hours were considered successful therapeutic responses.

Results: The mean length of hospitalization was longer in the control group (4.74±0.78 days) compared with the intervention group (4.26±0.56 days) (P=0.004). The prevalence of fever cessation had no significant difference between the two groups at any time (P>0.05). Also, there was no significant difference between the two groups at any time, considering vital signs, irritative urinary symptoms, nausea and vomiting, and flank pain (P>0.05).

Conclusion: The administration of colistin and meropenem to treat UTIs was associated with a shorter length of hospital stay. However, regarding response to treatment, it did not matter if they were treated with colistin alone or with combination therapy (colistin and meropenem).

Keywords: Colistin, Drug resistance, Gram-negative bacteria, Meropenem, Urinary Tract Infections

***Corresponding Author:** Behnaz Najafi, Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, Email: Behnaznajafi1386@gmail.com

Please cite this article as: Yadegarynia D, Tehrani Sh, Keyvanfar A, Gachkar L, Najafi B. A randomized controlled trial: Colistin alone or Colistin and Meropenem: Which is more effective for the Management of Urinary Tract Infections? Novel Biomed. 2022;10(4):213-8.

Introduction

One of the most common infections worldwide is Urinary tract infection. Previous epidemiological studies have reported them as the second most common bacterial infections after respiratory ones[1,2]. These infections are estimated to affect approximately 150 million people annually[3]. UTIs can occur from childhood to adulthood and, if left untreated, lead to more severe complications such as pyelonephritis, sepsis, pre-term birth, and renal damage[4]. Additionally, improper antibiotic consumption

increases the prevalence of drug resistance, which is indirectly considered another complication of UTIs.

Authorities classified UTIs into the following categories: uncomplicated or complicated[5]. The uncomplicated type usually affects healthy individuals with no structural or functional urinary tract abnormality. Complicated type is demarcated as UTIs related to agents compromising the urinary tract, such as urinary retention, immunosuppression, urinary obstruction, renal transplantation or rejection, pregnancy, and insertion of foreign bodies[5,6].

UTIs are caused by both gram-positive and gram-negative bacteria[7]. The most common agent causing both types of UTIs is uropathogenic *Escherichia coli* (UPEC)[8]. The basis of appropriate treatment for UTIs is the choice of a high-performance and inexpensive antibiotic. Besides, urinary tract infections caused by *Escherichia coli* (*E.coli*) are often resistant to many common antibiotics, which is a therapeutic challenge[9]. On the other hand, the development of antibiotic resistance is almost always accompanied by increased antibiotic consumption. Up to now, colistin has been commonly used to treat UTIs caused by gram-negative bacteria[10]. However, due to increased resistance to colistin, its consumption alone could lead to treatment failures. This study aimed to compare the effectiveness of colistin alone with colistin and meropenem to treat patients with UTIs.

Methods

Study design and setting: This randomized, open-label, parallel groups controlled trial was conducted from April 2019 to March 2020 at Labbafinejad Hospital in Tehran, Iran.

Patients: The study population included all hospitalized patients with severe UTIs. The inclusion criteria were: patient willingness to participate in the research and definite diagnosis of severe UTIs caused by gram-negative bacteria based on laboratory evidence, carbapenem resistance (Minimum inhibitory concentrations (MIC)> 4-8 mg/L), sensitivity to colistin (MIC ≤2 mg/L). Exclusion criteria were: taking a drug other than carbapenem and colistin to treat UTIs, multiple microbial infections containing carbapenem-sensitive bacteria, receiving colistin to treat this clinical course, pregnancy, and hypersensitivity to colistin or carbapenems.

Randomization and blinding: First, eligible patients completed the written informed consent form. Then, using the random number table and simple randomization method, they were randomized into two groups of control and intervention (1:1 ratio). Random concealment was performed using sequentially numbered sealed opaque envelopes (SNOSE). Also, this was an open-label study without blinding.

Interventions: Patients were randomly allocated to the control group, which received colistin (1 mIU every 12 hours intravenously), and the intervention group, which received colistin (1 mIU every 12 hours intravenously) with meropenem (1gr every 8 hours intravenously).

Outcomes: An infectious disease specialist evaluated the therapeutic responses 48-72 hours after the initiation of treatment. In addition, 48 hours after the initiation of treatment, secondary urine culture samples were taken from patients. Cessation of fever, improvement of symptoms and signs (irritative urinary symptoms, instability of vital signs, nausea, vomiting, flank pain), and negative urine culture within 48 hours were considered successful treatments. Also, patients who did not meet the above response criteria were considered treatment failures.

Detection of isolates and assessment of drug resistance pattern: Samples were cultured on Blood Agar, EMB, and MacConkey agar medium (MAC; Becton Dickinson, Germany) and kept at 37°C for 24 hours. After incubation, direct slides were prepared from the colonies. If gram-negative bacilli were seen, the following diagnostic tests were performed: oxidase test, culture in TSI, SIM, MR, VP media, lysine decarboxylase, citrate, and urea were used. The minimum inhibitory concentration (MIC) of imipenem, meropenem, aztreonam, and colistin was determined by the agar dilution method (116275/Anaerocult® C Merck, Germany) using Clinical and Laboratory Standards Institute (CLSI) instructions [(11)]. Additionally, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as standard strains.

Statistical analysis: Data were processed by SPSS statistical software (SPSS Inc., Chicago, IL, USA) version 19.0. We reported variables by frequency,

percentage, mean, and standard deviation. Also, student *t*-test and chi-square were performed to analyze data. A P-value of less than 0.05 was considered statistically significant.

Ethical considerations: The ethics committee of the School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran approved this study (ID: IR.SBMU.MSP.REC.1398.181). All the participants completed the written informed consent form, and the patient information was confidential.

Results

In this study, 70 patients were recruited into the following groups: the control group received colistin alone (n=35), and the intervention group received colistin and meropenem (n=35). The mean age of the patients was 50.89±10.83, and 50% were male. There was no difference between the two groups in terms of the baseline characteristics, except for nausea and vomiting, which was more in the intervention group than the control group (P<0.001). Table 1 shows the baseline characteristics of the patients in detail.

The prevalence of fever cessation 24 hours after the initiation of treatment was higher in the intervention group (51.53%) compared with the control group (25.71%). Also, the fever cessation during 48 and 72 hours after treatment in the control group was 54.29% and 20%, respectively, while these values for the intervention group were 40% and 8.57%, respectively. Based on further analysis, there was no association between the study group and the time of fever cessation (P= 0.07).

At baseline, the prevalence of irritative urinary symptoms was higher in the intervention group (80.0%) compared with the control group (65.71%) (P = 0.18). On the second day, the prevalence of these symptoms in the intervention and control groups was 37.14% and 45.71%, respectively (P = 0.46). Also, on the third day, it was 2.86% in the intervention group and 8.57% in the control group (P = 0.30).

Moreover, the mean length of hospitalization of patients in the control group (4.74±0.78 days) was longer than the intervention group (4.26±0.56 days) (P= 0.004). Table 2 shows the symptoms and vital signs of the patients over time (admission, second day, and third day). There was no difference between the two groups considering the prevalence of the symptoms and vital signs at any time.

The results of the urine culture of the patients (on admission and 48 hours later) represent in Table 3. The negative urine cultures of the control and intervention groups were 28.57% and 45.71%, respectively (P= 0.14). Additionally, the prevalence of

Table 1: Baseline characteristics of the patients.

Variables		Control	Intervention	Total	P-value
Age		50.43±10.05	51.34±11.69	50.89±10.83	0.72
Gender	**Male**	20(57.14)	15(42.86)	35(50.0)	0.23
	Female	15(42.86)	20(57.14)	35(50.0)	
Diabetes mellitus		9(25.71)	9(25.71)	18(25.71)	1.00
Hypertension		8(22.86)	11(31.43)	19(27.14)	0.42
Anatomic anomalies		6(17.14)	7(20.0)	13(18.57)	0.75
History of renal stones		10(28.57)	14(40.0)	24(34.29)	0.31
History of UTIs		14(40.0)	16(45.71)	30(42.86)	0.63
Fever		32(91.43)	35(100)	67(95.71)	0.07
Irritative urinary symptoms		23(65.71)	28(80.0)	51(72.86)	0.18
Instability of vital signs		7(20.0)	9(25.71)	16(22.86)	0.57
Nausea and vomiting		11(31.43)	26(74.29)	37(57.86)	<0.001
Flank pain		14(40.0)	16(45.71)	30(42.86)	0.63

Variables are expressed as frequency (%) or mean±SD.

Table 2: Symptoms and vital signs of the patients over time.

Variables	Day	Control	Intervention	Total	P-value
Instability of vital signs	1st	7(20.0)	9(25.71)	16(22.86)	0.57
	2nd	4(11.43)	2(5.71)	6(8.57)	0.40
	3rd	0(0)	0(0)	0(0)	-
Nausea and vomiting	1st	11(31.43)	26(74.29)	37(47.14)	<0.001
	2nd	6(17.14)	9(25.71)	15(21.43)	0.38
	3rd	3(8.57)	2(5.71)	5(7.14)	0.64
Flank pain	1st	14(40.0)	16(45.71)	30(42.86)	0.63
	2nd	8(22.86)	8(22.86)	16(22.86)	1.00
	3rd	0(0)	0(0)	0(0)	-

Variables are expressed as frequency (%).

Table 3: The results of urine cultures on admission and 48 hours later.

Time	Results	Control	Intervention	Total	P-value
Admission	Negative	10(28.57)	16(45.71)	26(37.14)	0.31
	Escherchia coli	9(25.71)	7(20.0)	16(22.86)	
	Klebsiella spp.	7(20.0)	2(5.71)	9(12.86)	
	Pseudomonas spp.	4(11.43)	3(8.57)	7(10.0)	
	Acinetobacter spp.	3(8.57)	6(17.14)	9(12.86)	
	Proteus spp.	2(5.71)	1(2.86)	3(4.29)	
48 hours after admission	Negative	18(51.43)	16(45.71)	34(48.57)	0.35
	Escherchia coli	3(8.57)	2(5.71)	5(7.14)	
	Klebsiella spp.	5(14.29)	4(11.43)	9(12.86)	
	Pseudomonas spp.	0(0)	4(11.43)	4(5.71)	
	Acinetobacter spp.	9(25.71)	9(25.71)	18(25.71)	

Variables are expressed as frequency (%).

negative urine cultures of control and intervention groups 48 hours later was 51.43% and 45.71%, respectively (P= 0.63). Also, the prevalence of side effects was higher in the intervention group (31.4%) compared with the control group (22.9%) (P=0.42).

Discussion

Nosocomial infections are one of the most challenging issues for healthcare systems. Overusing and improper administration of antibiotics can increase antibiotic resistance and resistant strains. Also, long-term hospitalization is another reason for increasing the prevalence of bacteria with multiple resistance patterns, which leads to several therapeutic challenges and increases mortality[12]. In this study, we compared the effectiveness of colistin alone with colistin and meropenem to treat patients with UTIs. Based on our results, the duration of hospitalization was shorter in patients who received colistin and meropenem than in those who received colistin alone. So, simultaneous use of the two drugs mentioned could reduce the duration of hospitalization, but the issue is open to discussion.

Montero et al. examined the effect of colistin on treating patients with UTIs, which was favorable in 84% of them[13]. Also, in another study in 2017, Karakkattu and coworkers investigated the effects of colistin in 80 patients with UTIs[14]. *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli* were identified as infectious bacteria,

all of which were multidrug-resistant. Besides, the proper response to treatment was reported in 80% of UTI cases. However, in the present study, treatment with colistin was compared with colistin and meropenem, and which was no significant difference between the two groups except for the length of hospital stay.

In 2018, Paul et al. examined the efficacy of colistin alone versus colistin and meropenem in treating patients with infections caused by carbapenem-resistant bacteria[15]. Based on the results of this study, there was no significant difference between colistin treatment and combination therapy, which was in line with our results. A discrepancy in our results was the reduction in the length of hospital stay in patients who received combination therapy, which reduces the cost of treatment and the risk of other nosocomial infections. In another study, Falagas et al. found no significant difference between the response to treatment comparing colistin alone with colistin and meropenem[16], which was inconsistent with our results. This discrepancy can be attributed to the fact that in our study, the effectiveness of the drugs was evaluated only in patients with urinary tract infections. In contrast, in the study by Falagas, patients with all infections caused by gram-negative bacteria were included.

Another study by Falagas et al. reported that there was no difference in the effectiveness of the following groups in treating drug-resistant gram-negative bacterial infections (P=0.32): colistin monotherapy (85.7%) versus combination therapy with colistin and meropenem (68.7%). Besides, there was no significant difference between the two groups regarding nephrotoxicity[17]. The study by Katib et al. aimed to compare the effectiveness and nephrotoxicity of the loading dose of colistin monotherapy and combination therapy with colistin and meropenem for the treatment of carbapenem-resistant *Acinetobacter baumannii*. Based on the results of this study, the clinical outcome, mortality rate, culture clearance rate, and nephrotoxicity were not significantly different between the two groups, which is in line with our findings. Drug side effects such as nephrotoxicity are issues that should always be considered when prescribing antibiotics. Failure to follow the patient's creatinine before and during antibiotic administration could increase mortality and morbidity[18].

In contrast, it should be noted that in the previous in vitro studies, combination therapy of colistin with other antibiotics had a synergistic effect[19]. Despite the evidence of synergism in the laboratory, this effect is not observed in the clinical setting. Discovering the cause of this difference requires further studies[20].

Our study had some limitations. The sample size of our study was small, and it is better to do studies with a larger sample size for more reliable results. Also, no action was taken to control the confounding factors in this study.

Conclusion

The administration of colistin and meropenem to treat UTIs was associated with a shorter length of hospital stay. It can reduce treatment costs and decrease the risk of other nosocomial infections. However, whether they were treated with colistin alone or with combination therapy did not matter regarding response to treatment.

Acknowledgment

None.

References

1. Medina M, Castillo-Pino E. An introduction to the epidemiology and burden of urinary tract infections. Therapeutic advances in urology. 2019;11:1756287219832172.

2. Chu CM, Lowder JL. Diagnosis and treatment of urinary tract infections across age groups. American journal of obstetrics and gynecology. 2018;219(1):40-51.

3. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nature reviews microbiology. 2015;13(5):269-84.

4. Kim JW, Lee YJ, Chung JW, Ha YS, Lee JN, Yoo ES, et al. Clinical characteristics of postoperative febrile urinary tract infections after ureteroscopic lithotripsy. Investigative and clinical urology. 2018;59(5):335-41.

5. Tan CW, Chlebicki MP. Urinary tract infections in adults. Singapore medical journal. 2016;57(9):485.

6. Colgan R, Keating K, Dougouih M. Survey of symptom burden in women with uncomplicated urinary tract infections. Clinical drug investigation. 2004 Jan;24(1):55-60.

7. Gajdács M, Ábrók M, Lázár A, Burián K. Increasing relevance of Gram-positive cocci in urinary tract infections: A 10-year analysis of their prevalence and resistance trends. Scientific Reports. 2020;10(1):1-1.

8. Behzadi P. Classical chaperone-usher (CU) adhesive fimbriome: uropathogenic Escherichia coli (UPEC) and urinary tract infections (UTIs). Folia microbiologica. 2020;65(1):45-65.
9. Yelin I, Snitser O, Novich G, Katz R, Tal O, Parizade M, Chodick G, Koren G, Shalev V, Kishony R. Personal clinical history predicts antibiotic resistance of urinary tract infections. Nature medicine. 2019;25(7):1143-52.
10. Sorlí L, Luque S, Li J, Campillo N, Danés M, Montero M, et al. Colistin for the treatment of urinary tract infections caused by extremely drug-resistant Pseudomonas aeruginosa: Dose is critical. Journal of Infection. 2019;79(3):253-61.
11. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement. Clinical and Laboratory Standards Institute; Wayne, PA, USA: 2015. CLSI document M100-S25.
12. Voicu MN, Ahmet AM, Turcu-Stiolica M, Turcu-Stiolica A, Barbulescu AL, Popescu F. Antibiotic Resistance, Still a Global Challenge. Current Health Sciences Journal. 2021;47(2):284-9.
13. Montero M, Horcajada JP, Sorli L, Alvarez-Lerma F, Grau S, Riu M, et al. Effectiveness and safety of colistin for the treatment of multidrug-resistant Pseudomonas aeruginosa infections. Infection. 2009;37(5):461-5.
14. Karakkattu J, Mohan A, James E, Kumar A. Effectiveness and safety of colistin in multi drug resistant urinary tract infections. J Appl Pharm Sci. 2017;7(9):148-52.
15. Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. The Lancet Infectious Diseases. 2018;18(4):391-400.
16. Falagas ME, Bliziotis IA, Kasiakou SK, Samonis G, Athanassopoulou P, Michalopoulos A. Outcome of infections due to pandrug-resistant (PDR) Gram-negative bacteria. BMC infectious diseases. 2005;5(1):1-7.
17. Falagas ME, Rafailidis PI, Kasiakou SK, Hatzopoulou P, Michalopoulos A. Effectiveness and nephrotoxicity of colistin monotherapy vs. colistin–meropenem combination therapy for multidrug-resistant Gram-negative bacterial infections. Clinical microbiology and infection. 2006;12(12):1227-30.
18. Katip W, Uitrakul S, Oberdorfer P. The effectiveness and nephrotoxicity of loading dose colistin combined with or without meropenem for the treatment of carbapenem-resistant A. baumannii. International Journal of Infectious Diseases. 2020;97:391-5.
19. Abdul-Mutakabbir JC, Yim J, Nguyen L, Maassen PT, Stamper K, Shiekh Z, et al. In vitro synergy of colistin in combination with meropenem or tigecycline against carbapenem-resistant Acinetobacter baumannii. Antibiotics. 2021;10(7):880.
20. Cuba GT, Ramos JF, Kiffer CR. Re:'Colistin plus meropenem for carbapenem-resistant Gram-negative infections: in vitro synergism is not associated with better clinical outcomes' by Nutman et al. Clinical Microbiology and Infection. 2021;27(3):497-8.