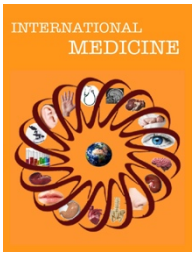
International Medicine 2019; 1(5): 274-279



International Medicine

https://www.theinternationalmedicine.com

Original Article

Comparison of the efficacy of six-week versus twelve-week antibiotic therapy for the treatment of nonsurgical diabetic foot osteomyelitis

Manouchehr Iranparvar, Mohsen Arzanlou, Elnaz Afrouzeh

Faculty of Medicine, Ardabil University of Medical Science, Ardabil, Iran

Received: 25 June 2019 / Accepted: 01 September 2019

Abstract

Background: There is little evidence regarding the optimal duration of antibiotic therapy for diabetic foot osteomyelitis (DFO). So, the optimal duration of antibiotic treatment of osteomyelitis complicating foot wounds in non–surgically treated diabetic patients is currently unknown and needs more studies in the future. This study aimed to compare six-week versus twelve-week antibiotic therapy for the treatment of nonsurgical DFO.

Methods: This was an interventional study that was performed on 30 patients with DFO without surgical indications who were randomly divided into two groups (six-week versus twelve-week antibiotic therapy). Changes of parameters such as C-reactive protein (CRP), albumin, erythrocyte sedimentation rate (ESR), HbA1c, creatinine, fasting blood sugar (FBS) at baseline, FBS after two hours, white blood cell (WBC), absolute count of neutrophil and clinical outcomes (percentage of complete healing and non-healing, the time of complete healing, radiological abnormality and recurrence of the disease after treatment) were measured in the two groups and then analyzed by statistical methods in SPSS version 21.

Results: During the study period, values of CRP (p=0.03), ESR (p=0.03), two-hour glucose (p=0.02), WBC (p=0.04) and absolute neutrophil count (p=0.04) in the six-week treatment group and the values of CRP (p=0.02), ESR (p=0.02), HbA1c (p=0.04), FBS at baseline (p=0.04), FBS after two-hour (p=0.01), WBC (p=0.02) and absolute neutrophil count (p=0.04) in the twelve-week treatment group changed significantly. There was no significant difference concerning the clinical outcomes between the two groups.

Conclusions: The results showed that six and twelve-week antibiotic therapy had the same efficacy in the treatment of non-surgically DFO. Therefore, six-week antibiotic therapy of DFO could be sufficient in these patients.

Keywords: ciprofloxacin, clindamycin, diabetic foot, osteomyelitis

Address for Correspondence: Manouchehr Iranparvar, Faculty of Medicine, Ardabil University of Medical Science, Ardabil, Iran.
E-mail: m.iranparvar@arums.ac.ir

DOI: 10.5455/im.53372

Introduction

Patients with diabetes mellitus are at risk of severe infections due to neuropathy, vascular dysfunction and decreased neutrophil function, that of them, neuropathy is very important [1,2]. Today, the incidence of foot ulcer in diabetic patients ranges from 4% to 10% which is reported to be 1.5% to 3.5% in young people, 5% to 10% in the elderly and of them less than 3.6% belong to patients with type I and II diabetes yearly [1]. Food infection has different clinical manifestations, especially osteomyelitis in diabetic patients can ultimately lead to lower limb amputation. The successful treatment of diabetic foot osteomyelitis (DFO) depends on the proper administration of antibiotics, debridement of the wound and control of blood glucose levels [1,3].

More recent clinical studies have shown that DFO can be prevented in more patients by using antibiotic therapy without bone amputation. So, the optimal duration of antibiotic treatment of osteomyelitis complicating foot wounds in non-surgically treated diabetic patients is currently unknown and needs more studies in the future [4,5].

By considering the various complications of antibiotics, determining the optimal time to antibiotics prescription, its type and amount, method and duration of administration are important. Treatment is usually started empirically and treatment protocols should be selected according to the severity of the infection, previous treatment, previous culture responses, presence and absence of drug sensitivity and liver and kidney function status. Depending on the severity of the infection and response to treatment with the use of various antibiotics as injectable and then orally, treatment may require to be continued for up to twelve weeks [6-10]. However, the optimal duration of antibiotic treatment of osteomyelitis complicating foot wounds in non-surgically treated diabetic patients is currently unknown and needs more studies [11]. Based on recent studies, the six-week antibiotic therapy in patients with non-surgical DFO could be sufficient [12]. Based on available studies, antibiotic therapy has been associated with significant improvement by using compounds such as rifampin and fluoroquinolones on average after 12 months of continuous follow-up. So, in patients with DFO, reducing the duration of treatment may help reduce medical interventions and their consequences [11]. The aim of this study was to compare six-week versus twelve-week antibiotics therapy for the treatment of non-surgically DFO.

Methods

Study design and sample size

This prospective interventional study was conducted on 30 hospitalized patients with DFO without surgical indications or amputation who referred to the diabetes clinic of Ardabil City Hospital. The sample size was calculated based on 80% power analysis, 95% confidence interval by estimated necessary parameters from similar studies and used the necessary formula for sample size in a randomized clinical trial.

Patient's selection criteria

Patients with a diagnosis of DFO without surgical indications were selected based on clinical examination such as bone probe test, radiography, laboratory diagnosis (including leukocytosis, ESR) and divided randomly by random table data generation into two groups of clindamycin and ciprofloxacin which received antibiotic for six and twelve-week, respectively. Two groups were compared in terms of wound healing and response to treatment at the end of the study.

Inclusion and exclusion criteria

DFO patients with no surgical osteomyelitis, no chronic liver, kidney and coronary artery disease, anemia, rheumatism, lack of drug resistance to ciprofloxacin and clindamycin, without history of ciprofloxacin use in recent year and severe obesity (BMI above 30) were included in the study and patients who need for surgical intervention in any time, presence any causes of the disorder during follow-up time and treating patients, presence of the etiologic factors against the used antibiotics, none of anterior and posterior foot pulses (using arterial Doppler test), history of gastrointestinal complications, history of drug side effects such as gastrointestinal side effects of ciprofloxacin and clindamycin during the study, drug resistance to ciprofloxacin and clindamycin and also pregnant women were excluded from the study.

Treatment and criteria for response to treatment

All patients in both groups, in addition to antibiotics, received a similar dose of aspirin, losartan, atorvastatin and insulin. One group received clindamycin for six weeks and another group received ciprofloxacin for twelve weeks by oral administration for the entire duration of treatment. The two groups were followed about three months for relapse based on clinical and laboratory findings. The response criteria to the treatment include absence of scarring, absence of bad scent, decreasing trend of ESR, improvement of systemic symptoms and

fever with osteomyelitis origin and improvements in radiographic criteria. The criteria for recurrence of osteomyelitis include wound secretion, scarlet smell, high ESR and fever with osteomyelitis origin.

Ethical considerations

This research was registered at the Ethics Committee of the Ardabil University of Medical Sciences by code IRI-ARUMS-REC-1395-54 and at the Iranian Clinical Trials System (IRCT) by code IRCT 2016110830793N1. This study was conducted in accordance with the declaration of Helsinki and informed consent was obtained from all participants.

Statistical analysis

Collected data were analyzed by using the ANOVA test to compare the continuous variables between more groups and $\chi 2$ test for comparing the difference between the frequency of recovery or failure rates between two groups in SPSS version 23. The $p<0.05$ was considered as significant.

Results

The two groups were the same in terms of age, gender, height, weight, BMI, depth of wound and location of wound (Table 1).

Table 1. Demographic characteristics of studied patients

Variables		6 weeks	12 weeks	All patients	*p*
Gender (f/m)		4/11	4/11	8/22	1
Age, years, mean±SD		52.8 ± 6.5	53.3 ± 5.8	53.2 ± 6.1	0.77
Height (cm)		173 ± 10	175 ± 11	174 ± 9	0.61
Weight (kg)		82.1 ± 9.5	83 ± 6.3	84 ± 7.4	0.8
BMI (kg/m^2)		27.4 ± 1.5	27.1 ± 2.7	27.7 ± 2.1	0.83
Radiographic criteria need to elaborate		11 (73.3%)	13 (86.6%)	24 (80%)	0.42
Size of ulcer (mm^2)		11.2 ± 3.5	9.1 ± 2.7	10.1 ± 3.1	0.21
Depth of ulcer (mm)		6.4 ± 1.24	6.6 ± 1.34	6.5 ± 1.74	0.71
Positive probe-to-bone test		15 (100%)	15 (100%)	30 (100%)	1
Location of ulcer	Metatarsal head of the first ray	5 (33.3%)	6 (40%)	11 (36.6%)	0.87
	Metatarsal head of the fifth ray	4 (26.6%)	4 (26.6%)	8 (26.6%)	1
	Other metatarsal locations	4 (26.6%)	2 (13.3%)	6 (20%)	0.49
	Hallux	3 (20%)	2 (13.3%)	5 (16.6%)	0.53
Surface of wound, mm^2, mean±SD		9.1 ± 2.7	10.1 ± 3.1	11.2 ± 3.5	0.2
Depth of wound, mm^2, mean±SD		6.6 ± 1.34	6.5 ± 1.74	6.4 ± 1.24	0.7

There were no significant differences between the two groups regarding the administration duration of antibiotics based on laboratory findings (Table 2).

There was no significant difference in the incidence of adverse effects between the two drug groups (Table 3).

After the intervention, the values of CRP (p=0.03), ESR (p=0.03), two-hour glucose (p=0.02), total white blood cell (p=0.04) and absolute neutrophil (p=0.04) had a significant difference between the two groups (Table 4).

There was no significant difference between the two groups in the complete recovery rate and the recovery rate was slightly higher in the twelve-week treatment group than the six-week treatment group and the minimum recovery time was obtained from the fourth week after the start of treatment (Table 5).

Table 2. Biochemical and blood parameters of the patients at baseline

Variables	6 weeks	12 weeks	All patients	*p*
CRP (mg/L)	17.1 ± 4.5	18.9 ± 5.3	17.2 ± 4.1	0.52
Albumin (g/dL)	3.6 ± 0.7	3.5 ± 0.9	3.5 ± 0.4	0.33
ESR (mm/hour)	62.3 ± 20.3	67.2 ± 24.3	64.2 ± 22.4	0.41
HBA1c (%)	8.9 ± 0.6	9.3 ± 0.7	9.21 ± 1.1	0.22
Creatinine (mg/dL)	1.11 ± 0.3	1.36 ± 0.4	1.21 ± 0.41	0.82
FBS (mg/dL)	154.4 ± 17.2	163.1 ± 13.1	158.7 ± 14.2	0.45
Glucose (two-hour late)	286.5 ± 11.4	280.1 ± 19.1	281.7 ± 24.9	0.42
WBC	10.4 ± 1.3	10.61 ± 1.1	10.5 ± 1.4	0.78
Neutrophils	8424 ± 116	8798 ± 118	8610 ± 235	0.34
RBC	5.7 ± 0.6	5.6 ± 0.8	5.6 ± 0.7	0.70
Hb (g/dL)	14.4 ± 1.3	14.6 ± 2.1	14.5 ± 2.4	0.43
HCT (%)	43.4 ± 4	45.2 ± 4.3	45.3 ± 4.4	0.33
MCV	84.4 ± 6.2	90.3 ± 7.1	88.3 ± 5.4	0.37
MCH (pg)	32.4 ± 4.2	33.2 ± 5.2	32.1 ± 3.2	0.47
MCHC (%)	33.1 ± 1.1	33.4 ± 1.2	33.2 ± 1.4	0.78
Platelet (l/10^5)	292.5 ± 45.2	279.1 ± 54.1	286.7 ± 44.9	0.37

Table 3. Outcomes after the intervention

Outcomes	6-week treatment group N (%)	12-week treatment group N (%)	*p*
Nausea	1 (6.6)	3 (20)	0.12
Vomiting	1 (6.6)	2 (13.3)	0.41
Diarrhea	1 (6.6)	2 (13.3)	0.41

Table 4. Blood and biochemical markers of patients after the intervention (6-month antibiotic therapy)

Biochemical and blood markers	Status	0	2	4	6	*p*
CRP (mg/L)	Improved	17.02 ± 3.6	14.2 ± 7.7	9.32 ± 4.1	4.32 ± 2.1	0.03
	Non-Improved	17.11 ± 4.4	16.55 ± 5.31	15.2 ± 3.43	17.73 ± 4.47	0.43
Albumin (g/dL)	Improved	3.6 ± 0.4	3.5 ± 0.4	3.4 ± 0.6	3.5 ± 0.3	0.67
	Non-Improved	3.6 ± 0.8	3.5 ± 0.2	3.3 ± 0.5	3.3 ± 0.9	0.39
ESR (mm/hour)	Improved	64.2 ± 18.4	54.3 ± 17.4	47.3 ± 11.6	37.3 ± 12.4	0.03
	Non-Improved	66.2 ± 21.4	61.3 ± 17.5	57.3 ± 23.4	54.3 ± 17.6	0.4
HBA1c (%)	Improved	8.67 ± 0.6	8.54 ± 0.7	8.57 ± 0.6	8.62 ± 0.8	0.51
	Non-Improved	8.91 ± 0.5	8.78 ± 0.8	8.72 ± 0.8	8.67 ± 0.5	0.53
Creatinine (mg/dL)	Improved	1.11 ± 0.3	1.23 ± 0.5	1.21 ± 0.4	1.18 ± 0.4	0.66
	Non-Improved	1.16 ± 0.7	1.21 ± 0.3	1.19 ± 0.6	1.2 ± 0.2	0.71
FBS (mg/dL)	Improved	154.4 ± 10.2	149.1 ± 16.3	148.1 ± 15.3	147.1 ± 16.2	0.26
	Non-Improved	156.4 ± 17.3	150.4 ± 13.6	153.2 ± 14.4	153.1 ± 11.3	0.73
Glucose (two-hour late)	Improved	282.5 ± 24.5	250.5 ± 11.5	235.5 ± 13.2	201.5 ± 20.1	0.02
	Non-Improved	289.5 ± 26.4	265.5 ± 17.7	274.5 ± 10.5	276.5 ± 17.4	0.77
WBC	Improved	10.6 ± 1.7	8.7 ± 2.6	8.4 ± 2.3	7.4 ± 1.9	0.04
	Non-Improved	10.3 ± 1.1	9.4 ± 2.3	8.7 ± 2.2	8.7 ± 2.8	0.52
Neutrophils	Improved	8624 ± 223	7528 ± 954	7132 ± 435	7096 ± 601	0.04
	Non-Improved	8342 ± 221	7731 ± 789	7535 ± 763	7712 ± 980	0.56

Table 5. Clinical results of the treatment at the end of study (6 and 12 weeks after the intervention)

Results	6-week treatment group N (%)	12-week treatment group N (%)	*p*
Complete improvement	11 (78.6)	11 (84.6)	0.74
Non-improvement	3 (21.4)	2 (15.4)	0.61
Time of complete improvement	14.8 ± 11.6	17.2 ± 15.1	0.23
Severity of radiologic symptoms	2 (14.3)	1 (7.7)	0.34
Relapse after stopping treatment	1 (7.1)	1 (7.7)	0.92

Discussion

The results indicated that six-week treatment of DFO patients without surgical indications had similar results to the twelve-week treatment group. In patients with the diabetic foot without bone infections, the duration of antibiotic treatment was typically twelve-week [12]. So, there was no evidence about the effect of antibiotic therapy for more than six weeks on the rate of disease recovery. According to the American Infectious Disease Association, antibiotic therapy should continue for six to twelve weeks in the course of persistent bone and soft tissue infection. Also, antibiotics should be given for twelve-week or more in patients who have not been treated for necrosis and infection of the bone for any reasons. The results of this study confirmed the possibility of treatment of DFO without surgical indication with six-week antibiotic administration. According to available reports, antibiotic therapy and surgical treatment of patients with neuropathic ulcers with non-ischemic osteomyelitis or soft tissue necrosis had similar results [12-15]. DFO therapy due to side effects of antibiotics, particularly bacterial and diarrheal (caused by *Clostridium Difficile*), as well as its cost-effectiveness is often considered as a side therapeutic approach. In this study, gastrointestinal complications were observed in both groups, but the proportion of these complications was higher in the twelve-week treatment group than the six-week treatment group. Reducing the duration of antibiotic therapy deals to reduce the undesirable and negative effects of drugs on the bacterial intestinal flora and so, the observation of the low ratio of gastrointestinal disorders in the six-week treatment group also confirms this. Tone et al, in their study, showed that rifampin and ciprofloxacin had same effects on DFO which in line with our study results and in 10% of patients in twelve-week treatment group, they observed gastrointestinal complications [12,14-17]. In this study, in both groups, CRP values showed a significant decreasing trend in patients during the treatment period. Regarding that CRP is one of the positive acute-phase proteins, reducing its levels in infectious and inflammatory conditions such as DFO indicates improvement in the condition of the disease and the response to the treatment as well as the reduction of the processes involved in the occurrence of inflammation. This protein increases faster than other acute-phase proteins and returns to the normal level sooner than other markers [16-19]. The findings of this study were in line with other reports about changes in this protein level during study and results of DFO treatment [11,16,18]. Plasma albumin, unlike CRP, did not show a significant change in this study in the two groups. This protein is a negative acute-phase protein which is changed based on infectious and inflammatory processes in the direction of the decreasing trend [3,12]. Considering that this protein has slightly changed over time in both groups, this could be a sign to the positive response to treatment in this study. The ESR like CRP showed a significant decrease in both groups. ESR can be used for follow-up trend of response to treatment of patients with osteomyelitis and its changes in comparison to other proteins had a slower trend [17,19]. ESR has been multiplied in osteomyelitis cases, so, its significant decrease in patients in both studied groups compared to untreated patients could be a reason for the positive response to treatment and recovery in this study. According to the Barati et al study, ESR levels in diabetic patients without bone involvement were significantly lower than patients with DFO (p=0.001) [18]. In a study performed in Boston, ESR and CRP levels in penetrating skin ulcers were higher in diabetic patients than non-diabetic and non-ulcerated diabetic patients [18]. Other studies in this area also suggest an increase in ESR in cases of bone involvement that was in line with the findings of this study. In the present study, the HbA1c levels only showed a significant decreasing trend in patients with the twelve-week treatment group. Given the fact that this scale shows blood glucose changes in the past three months, so observing this change in this group is obvious. If changes in glucose and fasting glucose levels are considered both measurements in both groups have significantly decreased in the patients and this itself indicates the control of blood glucose in these patients. Asten et al and Tone et al have shown similar changes in HbA1c levels and their results were consistent with the results of this study [12,17].

In this study, the total number of WBC, as well as the absolute number of neutrophils, had significant changes and their values decreased in both groups in improved patients. Given that one of the reasons for them is inflammatory and infectious diseases, so, a significant decrease of them showed the positive trend of improvement and repair of DFO in patients in the two groups. The results of this study were in line with other reports on the decreasing trend of the above values in the treatment of DFO [9,17-18].

Conclusion

The results of this study suggest that six-week duration of antibiotic therapy for DFO treated no surgically is associated with a similar outcome to that of twelve-week duration and also the gastrointestinal complications in the six-week treatment group were lower than the other group. Additionally, given the fact that MRI is the golden standard method for the diagnosis of osteomyelitis, it is recommended to be used in the future for all non-surgically DFO patients.

Conflict of interest

All authors declare that they have no conflict of interest.

Funding

There was no funding received for this study.

References

1. Ayatollahi J, Mirshamsi MH, Ardakani MR. Diabetic foot osteomyelitis. Journal of Shahid Sadoughi University of Medical Science 2011;19:123-32.
2. Zahmatkash M, Rashidi M. Treatment of diabetic leg ulcer by local application of honey and olive oil mixture. JMP 2009;4:36-40.
3. Fischbach F. A manual of laboratory and diagnostic tests. 7th ed. USA: Lippincott Williams & Wilkins; 2004.
4. Embil JM, Rose G, Trepman E. Oral antimicrobial therapy for diabetic foot osteomyelitis. Foot Ankle Int 2006;27:771–9.
5. Lazaro-Martinez JL, Aragon-Sanchez J, Garcia-Morales E. Antibiotics versus conservative surgery for treating diabetic foot osteomyelitis: a randomized comparative trial. Diabetes Care 2014;37:789–95.
6. Izadi M, Mosavi SA, Araqizadeh H, Forutran KS, Shirvani S, Joneidi N, et al. Clinical and paraclinical features of chronic osteomyelitis in war handicapped patients in Sasan hospital in 1385-1387. J Mil Med 2008;10:63-8.
7. Bakhtiari MR. A review on the latest criteria for laboratory diagnosis of diabetes mellitus, pre-diabetes and gestational diabetes. Journal of Laboratory & Diagnosis 2014;6:4-8.
8. Azizi F. Prevalence of metabolic syndrome in an urban population: Tehran lipid and glucose study. Diabetes Res Clin Pract 2003;61:29-37.
9. Leese G, Nathwani D, Young M, Seaton A, Kennon B, Hopkinson H, et al. Use of antibiotics in people with diabetic foot disease: A consensus statement. The Diabetic Foot J 2009;12:1-10.
10. Powers AC. Diabetes mellitus: diagnosis, classification, and pathophysiology. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jamesson JL, Loscalzo J, editors. Harrisons principles of internal medicine. 19th ed. New York: Mc Graw Hill Education; 2015:2399–406.
11. Jeffcoate WJ, Lipsky BA. Controversies in diagnosing and managing osteomyelitis of the foot in diabetes. Clin Infect Dis 2004;39(Suppl. 2):S115–S122.
12. Tone A, Nguyen S, Devemy F, Topolinski H, Valette M, Cazaubiel M, et al. Six-week versus twelve-week antibiotic therapy for non-surgically treated diabetes foot osteomyelitis: A multicenter open-labeled controlled randomized study. Diabetes Care 2015;38:302-7.
13. Ristow M. Neurodegenerative disorders associated with diabetes mellitus. J Mol Med 2004;82:510.
14. Lipsky BA. Empirical therapy for diabetic foot infections: are there clinical clues to guide antibiotic selection? Clin Micro & Infec 2007;13:351-3.
15. Baltazar JC, Ancheta CA, Aban IB, Fernando RE, Baquilod MM. Prevalence and correlates of diabetes mellitus and impaired glucose tolerance among adults in Luzon, Philippines. Diabetes Res Clin Pract 2004;64:107-15.
16. Lam TH, Liu LJ, Janus ED, Lam KS, Hedley AJ. Fibrinogen, other cardiovascular risk factors and diabetes mellitus in Hong Kong: a community with high prevalence of type 2 diabetes mellitus and impaired glucose tolerance. Diabet Med 2000;17:798-806.
17. Asten SAV, Jupiter DC, Mithani M, Fontaine JL, Davis KE, Lavery LA. Erythrocyte sedimentation rate and C-reactive protein to monitor treatment outcomes in diabetic foot osteomyelitis. Int Wound J 2017;14:142-8.
18. Barati M, Eshaghi M, Noori N. Evaluation of correlation between ESR and CRP with osteomyelitis in diabetic foot. RJMS 2003;10:9-15.
19. Talebi Taher M, Abasi M, Barati M. The study of diabetic foot infection: bacteriology, antimicrobial resistance pattern, treatment and outcome in inpatient cases in Rasoul-Akram and Firoozgar hospitals, 2005-2006. J Ardabil Univ Med Sci 2010;10:232-40.