INTERNATIONAL JOURNAL OF BIOASSAYS
ISSN: 2278-778X
CODEN: IJBNHY
ORIGINAL RESEARCH ARTICLE
OPEN ACCESS

RANDOMIZED DOUBLE BLIND PLACEBO-CONTROLLED TRIAL OF DOXIUM IN DIABETIC FOOT INFECTION

Fatemeh Ahmadi[1], Reza Shahrami[2] and Shokrollah Salmanzadeh[3*]
Department of Infectious Diseases, Ahvaz Jundishapur University of Medical Sciences, Khuzestan, Ahvaz, Golestan Hwy, Iran.

Received for publication: May 24, 2015; **Revised**: June 15, 2015; **Accepted**: June 22, 2015

Abstract: Foot infection is the most common cause of extremity loss in diabetic patients. Doxium (calcium dobesilate) has antioxidant and anti-endothelin effects and improve blood supply. We assessed doxium as adjunctive drug for treatment of foot infection in diabetic patients. 64 diabetic patients with foot infection in grade 3 of Wagner classification were enrolled in a double blind placebo-controlled study. Patients were randomly assigned doxium therapy (trial n=32) or placebo (control n=32) for 30 days. Both groups received similar antibiotic and insulin treatment. Resolution time of infection, need to surgery, ankle/brachial index (ABI) and transcutaneous oxygen (TCO) were measured in two groups. Doxium therapy was associated with quicker resolution of infection and shorter time of antibiotic therapy (trial= 20.7 days vs. control= 25.4 days, P<0.01). On day 15th of treatment, 9.38% (3 patients) of trail and 34% (11 patients) of control (p < 0.02), needed surgical debridement, but there were no significant differences between two group at the end of study (day 30). Also we did not find, decreasing ABI over time is significant (0.10, P<0.001) but were similar among trail (from day 1 ABI= 0.96±0.04) and control groups (from day 1 ABI= 0.92± 0.04). Also study found TCO rose significantly in trail (from 73.8±11.3 to 79.50 mmHg) and control (from 66.60 to 70.40 mmHg) groups. Doxium can accelerate healing of diabetic foot infection in combination with antibiotic therapy. The mean time of infection resolution and antibiotic therapy decreased 4.7 days in doxium group compared with placebo group. Intervention could not raise the TCO pressure and also change in ABI in this study.

Key words: Doxium; Diabetes Mellitus; Foot infection

INTRODUCTION

Foot ulcer and infections are a major source of morbidity in individuals with diabetes mellitus[1]. Approximately 15% of diabetic patients develop a foot ulcer during their life time and 6% require hospitalization for foot ulcer[2]. Vascular insufficiency, neuropathy (motor, sensory and autonomic), disabilities (reduced vision, limited mobility and previous amputation), and maladaptive patient behaviors are main causes of developing foot ulcer in a diabetic patient. Sometimes diabetic foot ulcers are complicated by infection. This superimposed infection is often multi-bacterial [3]. Diagnosis of diabetic foot infection is based on clinical finding of 2≤ of following condition: swelling, pain, redness, tenderness, warmness and visible wound discharge. Because of poor blood supply and vascular insufficiency, treatment of this infection is difficult [4].

Current treatments for diabetic foot infection include antibiotic and wound care. Treatment failure and uncontrolled sepsis may result in amputation. Except the aforementioned therapies, effectiveness of some drugs such as granulocyte colony stimulating factor (G-CSF) and hyperbaric oxygen has been used in this situation[5-7]. Doxium (calcium dobesilate) is an anti-oxidant, anti-endothelin, anti-platelet aggregation, anti-viscosity and anti-neovascularization agent which is used in diabetic retinopathy prevention and treatment and also in treatment of chronic venous disease[8-13]. Therefore we decided to evaluate the effectiveness of doxium as an adjunctive treatment with antibiotic therapy in accelerating diabetic foot infection improvement. According to our knowledge we didn't find similar agent.

MATERIALS AND METHODS

Subjects and study design

Diabetes patients with foot infection (grade 3 of Wagner classification [14]) referred to RAZI Hospital in Ahvaz, southwest of Iran, were recruited between March 2009 and May 2010. Patients suffering from hypercalcemia, agranulocytosis, multiorgan failure due to sepsis, being pregnant, using other antioxidant and immunosuppressant agents were excluded (n=64 included).

A Randomized, double–blind, placebo–Controlled Trails (RCT) conducted using remote randomization system for continue allocation concealment study was. The study was approved by Ahvaz Jundishapur University of Medical Sciences ethics commity and all patients gave a written informed consent. Patients were randomized through a computerized randomization schedule into two groups A and B.

***Corresponding Author:**
Dr. Shokrollah Salmanzadeh,
Infectious Diseases specialist,
Assistant Professor,
Ahvaz Jundishapur University Of Medical Sciences,
Ahvaz, Golestan Hwy, Iran.

In this study remote randomization system was used to continue allocation concealment and it was conducted through Intention-to-treat method.

In this study all achieved information was confidential and informed written consent was obtained from each participant. 59 patients admitted in infectious disease ward and 5 patients with ability for home nursing were managed outpatient, but under regular supervision. All patients were treated with appropriate antibiotic therapy. The case group also received oral Doxium 500 mg three times daily, control group received placebo capsules containing calcium carbonate three times daily for 30 days.

A combination of antibiotic therapy either ciprofloxacin plus Clindamycin or Ceftazidime plus Clindamycin were given by intravenous rout until cellulitis and ulcer discharge has markedly diminished and then changed to oral therapy[15]. If an infecting pathogen was identified, the appropriate antibiotic was used according to antimicrobial susceptibility testing. Glycemic control was done by multiple dose regimen insulin in all patients.

Study Objectives

Primary study objectives were time to resolution of infection and need to surgery, secondary objectives were wagner grade, ankle/brachial index (ABI) and transcutaneous oxygen measurement (TCO). The ankle/brachial index reflects the severity of peripheral vascular insufficiency and were measured by appropriate sphygmomanometers[16].

The TCO measurement which also shows tissue perfusion and the degree of vasculopathy needs a relatively expensive device which was not available for us, so we calculate TCO indirectly by o_2 saturation measurement of limb via pulse oximeter device and convert the values to TCO by the following formula (21, 22):

$$SO2 = [23{,}400 \times (PO_2^3 + 150 \times PO_2)^{-1} + 1\ ]^{-1}$$

The TCO and ankle/brachial index were measured before the initiation of treatment and at the end of doxium therapy (day 30).

Hospitalized patients were evaluated daily and the outpatients were visited every other day by inspection of ulcer (diameter, depth, discharge) and clinical improvement. Standard hematologic, routine biochemical tests and calcium were made weekly. Smear and culture of deep tissue swab were collected for microbiologic studies. All patients were controlled for adverse effects of drug like anorexia, nausea, constipation, agranulocytosis and hypercalcemia. Patient's clinical and paraclinical assessments, ABI and the TCO measurement were done by researchers.

Statistical analysis

Sample size were estimated based on our pilot study before initiation of clinical trial and based on evidence of a mean time difference of 3.5 days antibiotic time consumption between doxium and placebo groups.

The power of study was 0.80 and significance level was $p<0.05$. Categorical data (relative frequencies) were compared by means of the squared chi (χ^2). For comparing the averages before and after the treatment, we used the paired T test and the differences in averages in two groups were compared by means of independent T test. (Table 1)

Table 1: Differences in averages of two groups

	Doxium group	Placebo group	P. value
Mean age (year)	55.4 +/_ 9.4	58 +/_ 10.5	0.28
Sex	M: 21 (65.6%) F: 11 (34.4%)	M: 19 (59.4%) F: 13 (40.6%)	0.6

RESULTS

64 patients during 13 months, were enrolled in this study. 32 patients were assigned in each group. At the beginning of study the mean of ABI in doxium and placebo groups were 0.96 +/_ 0.04 and 0.92 + /_ 0.04 respectively ($p < 0.001$). The mean of TCO in doxium and placebo groups were 73.8 +/_ 11.3 mmHg and 66.6 + /_ 11.7 mmHg respectively ($p < 0.002$). At the end of study (day 30) ABI decreased about 0.1 ($p < 0.001$) in both groups and TCO raised to 79.5 mmHg in doxium ($p < 0.001$) and to 70.4mmHg in placebo ($p < 0.004$) group.

Based on Wagner classification, on day 15th of treatment, 18 patients (56.25%) from doxium group and 5 patients (15.63%) from placebo group improved to grade 2 ($p <0.001$); 5 patients from placebo group and none of doxium group progressed to grade 4. On day 30, two patients (6.25%) from doxium group and 3 patients (9.38%) from placebo group were situated in grade 4 of Wagner despite of appropriate antibiotic treatment and wound care ($p = 0.07$).

At the beginning of this study, the need for surgical debridement in patients of doxium and placebo group were 19 (59%) and 24 (75%) patients respectively ($p = 0.18$). On day 15th of treatment, 3 patients (9.38%) in doxium and 11patients (34%) in placebo group ($p < 0.02$), and at the end of study 1 and 3 patients in two groups ($p = 0.15$) needed surgical debridement. 2 patients of doxium group and 6 patients of placebo group ultimately needed amputation ($p = 0.257$). The mean time of antibiotic

therapy in doxium group was 20.7 days versus 25.4 days in placebo group ($p < 0.001$).

There was no group deviation. No patient was withdrawn from this study. All patients tolerated the medications and nobody refused them. Anorexia was not seen in doxium group versus 7 cases in placebo group ($p<0.005$). Other GI side effect, hypercalcemia and agranulocytosis were not detected in study.

The mean of arterial oxygen pressure in case group, before starting the treatment with doxium was 73.8 mmHg with 2 standard error. At the end of treatment this amount increased to 79.5 mmHg with 1.8 standard error. ($p<0.001$) (Pierson correlation coefficient = 0.70). The mean of arterial oxygen pressure in control group before treatment was 66.6 mmHg with 2 standard error. At the end of study this amount got to 70.4mmHg with 2.1 standard error. ($p<0.004$) (Pierson correlation coefficient =0.83) (Table 2).

Table 2: Mean of arterial oxygen pressure

Wagner/day		1	2	3	4	total
15	D	0	18 (56.25)	14 (43.75)	0	27
15	P	0	5 (15.63)	22 (68.75)	5	32
	P value		<0.001	<0.001	<0.001	
30	D	2	28	0	2	32
30	P	0	27	2	3	32
	P value		<0.07	<0.07	<0.07	

DISCUSSION

Diabetic foot infection is the most common cause of extremity loss in diabetic patients. Current treatments for diabetic foot infection include antibiotic and wound care and sometimes surgical therapies. New adjunctive therapies are under investigation. This study showed that on the first 15 days of treatment, doxium significantly accelerated resolution of cellulitis, shortened antibiotic therapy time and decreased the need of surgical debridement.

To the best of our knowledge, this study is the first clinical study that suggest, the potential use of doxium as an adjunctive treatment is diabetic foot infection, and therefore it is not possible to draw any comparisons with other trials. According to (low grading) decrease of grading of wagner classification and acceleration of healing, among patients in doxium group clinical improvement was higher on the first 15 days of treatment. The time needed for antibiotic therapy in doxium group was 4.7 days lower than control group that seems it is because of the effect of adjunctive therapy in addition to antibiotic therapy.

The mean of ABI and TCO had some differences from the first of the therapy and had a significant increasing in both group at the end of therapy but it seems that different effects of doxium made no changing on these two criteria.

The improvement acceleration of diabetic foot infection in the group that had the doxium therapy at the 15th first day was very high. In the way that the number of the patients who got to the lower grade of wenger in this group were more than the control group. But at the end of 30th day of therapy there was not any significant increasing. Some other adjunctive therapies has been used to treat diabetic foot infection, such as G-CSF and hyperbaric oxygen [5-7], but in total the results weren't successful enough to be recommended in all patients.

However in one study, the doxium therapy was able to decrease the complication of chronic venus failure [9], It didn't have any clear effect on increasing the TCO and ABI in our study. (More research had been suggested by investigators). In our research the time of using antibiotic in the group who received doxium, decreased 4.7 days less than control group. It was maybe because of anti-endothelin effect of the doxium, increasing of nitric oxide and decreasing of blood viscosity by the doxium.

Using the doxium didn't decrease need to the surgical intervention and although the improvement accelerated on the first two weeks, at the end of 30 days of therapy, we didn't see any sufficient difference in two groups.

Doxium was well tolerated and use of it on this time was safe. Management of the infected diabetic foot requires multidisciplinary approach. Doxium may represent an adjunctive therapy for these patients.

ACKNOWLEDGEMENTS

This study is a part of thesis submitted for MD degree with grant registered number U-88111 in research affairs, Ahvaz Jundishapur University of Medical Sciences (AJUMS), Ahvaz, Iran. We would like to thanks the personnel and the physicians of infectious diseases ward in Ahvaz Razi hospital and also the Research center of infectious and tropical diseases in AJUMS for their help and supports.

REFERENCES

1. Powers AC: Diabetes Mellitus. In Harrison's Principles of Internal Medicine. New York: McGraw-Hill Medical; 2008: 2292.[edition t (Series Editor)

2. Berbari F, Steckelberg JM, Osmon DR: Osteomyelitis in in Mandell's principles and practice of infectious disease. Philadelphia: Churchill Living Stone; 2010: 1461

3. Dezfulian A, Salehian MT, Amini V, Dabiri H, Azimi Rad M, Aslani MM, Alebouyeh M, Fazel I, Zali MR: Bacteriological study of diabetic foot infections in an Iranian hospital. Iranian Red Crescent medical journal 2011, 13:590-591.

4. Powers AC: Diabetes mellitus. In Harrison's Principles of Internal Medicine. New York: McGraw-Hill Medical; 2008: 2153-2169

5. Wunderlich RP, Peters EJ, Lavery LA: Systemic hyperbaric oxygen therapy: lower-extremity wound healing and the diabetic foot. Diabetes care 2000, 23:1551-1555.

6. Grolman RE, Wilkerson DK, Taylor J, Allinson P, Zatina MA: Transcutaneous oxygen measurements predict a beneficial response to hyperbaric oxygen therapy in patients with nonhealing wounds and critical limb ischemia. The American surgeon 2001, 67:1072-1079; discussion 1080.

7. Cruciani M, Lipsky BA, Mengoli C, de Lalla F: Granulocyte-colony stimulating factors as adjunctive therapy for diabetic foot infections. Cochrane database of systematic reviews (Online) 2009:CD006810.

8. Tejerina T, Ruiz E: Calcium dobesilate: pharmacology and future approaches. General pharmacology 1998, 31:357-360.

9. Martinez-Zapata MJ, Moreno RM, Gich I, Urrutia G, Bonfill X: A randomized, double-blind multicenter clinical trial comparing the efficacy of calcium dobesilate with placebo in the treatment of chronic venous disease. European journal of vascular and endovascular surgery: the official journal of the European Society for Vascular Surgery 2008, 35:358-365.

10. Carneiro A, Golay A, Cozma G, Caillon P, Castro-Correia J: Efficacy of Doxium (R) on the Blood-Retinal Barrier Permeability in Early Diabetic Retinopathy Independently of Diabetic Control. Investigative Ophthalmology and Visual Science 2004, 45:4109.

11. Leite E, Mota M, Abreu JF, Cunha-Vaz J: Effect of calcium dobesilate on the blood-retinal barrier in early diabetic retinopathy. International ophthalmology 1990, 14:81-88.

12. Junwu D, Xiaochen L, Shenwei L, Mingbo L, Yanmei X, Bing C: Effects of calcium dobesilate on glomerulus TIMP1 and collagen IV of diabetic rats. Journal of Huazhong University of Science and Technology--Medical Sciences-- 2005, 25:416-418.

13. Cortelekoglu T, Bozkurt A, Ustundag N, Koksal C, Sayin A: The effects of clopidogrel and calcium dobesilate on intimal hyperplasia following vascular injury. Acta chirurgica Belgica 2006, 106:206.

14. Ishikawa SN: Diabetic foot. In Campbell's operative orthopaedics. Volume 11: Mosby Elsevir 2008: 4700

15. Pasternack MS, Swartz MN: Cellulitis, Necrotizing Fasciitis, and Subcutaneous Tissue Infections. In Mandell's principles and practice of infectious disease. Volume 7. Philadelphia: Churchill Living Stone; 2010: 1302

16. Peripheral IO: Peripheral arterial disease in people with diabetes. Diabetes care 2003, 26:3333.

CITE THIS ARTICLE AS:
Fatemeh Ahmadi, Reza Shahrami and Shokrollah Salmanzadeh, Randomized Double Blind Placebo-Controlled Trial of Doxium In Diabetic Foot Infection, International Journal of Bioassays, 2015, 4 (08), 4199-4202.

Source of support: Ahvaz Jundishapur University of Medical Sciences (AJUMS), Ahvaz, Iran
Conflict of interest: None Declared