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Investigation of Asymmetric and Symmetric Dimethylarginine Levels after Iloprost Treatment in Patients with Buerger's Disease

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WHAT THIS PAPER ADDS

The study results suggest that iloprost treatment decreases ADMA and SDMA levels, which are associated with endothelial dysfunction in patients with Buerger's disease.

Objective: The aim of this study was to compare the levels of acetyl-dimethylarginine (ADMA), symmetric dimethylarginine (SDMA), and the L-arginine/ADMA ratio before and after iloprost treatment in patients with Buerger's disease.

Methods: Between January 2011 and December 2015, data from 44 patients (36 males, 8 females, mean age 48.7 ± 18.1 years) with the diagnosis of Fontaine Stage III–IV Buerger's disease were included. Iloprost infusion was administered intravenously through the forearm veins for 7 days at a dose of 0.5–1.5 ng/kg/min over 16 h. Blood samples were collected before and after treatment for measurement of ADMA, SDMA, and L-arginine. ADMA, SDMA, L-arginine levels were measured using high performance liquid chromatography (HPLC).

Results: After iloprost treatment, ADMA and SDMA levels significantly decreased ($p = .001$). The increase in the L-arginine levels was not significant ($p = .16$). However, the L-arginine/ADMA ratio increased significantly ($p = .001$).

Conclusion: Iloprost treatment decreases ADMA and SDMA, which are associated with endothelial dysfunctions in patients with Buerger's disease. Of note, the still higher than normal range of SDMA levels after iloprost treatment suggests that treatment should continue until SDMA levels are within the normal range in this patient population.

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INTRODUCTION

Buerger's disease (thromboangiitis obliterans) is one of the non-atherosclerotic, segmental, inflammatory, peripheral obstructive vascular diseases involving medium sized and small arteries.[1] Although the disease is directly related to smoking and tobacco use, genetic factors, hypercoagulability, vascular endothelial structure, and immunological mechanisms have also been reported to play a role in the etiology of the disease.[1,2] One of the interesting features of Buerger's disease is its geographical distribution in the world. It is more frequently seen in the Middle and Far East than in the United States. The prevalence of Buerger's disease is less than 1% among other peripheral arterial diseases in the United States. Its prevalence is 0.5–5.6% in Western Europe, and approximately 10% in Turkey; however, it is 50% in the Far East.[1] Prostacyclin analogues and anti-aggregants are the most frequently used agents in the treatment of this frequently seen disease.[1,2] Iloprost, which is a prostaglandin analogue, is widely used in the treatment of other ischaemic conditions, such as peripheral vascular disease, diabetic foot, and pulmonary arterial hypertension.[3] It has a direct effect on dilated arteries and veins, inhibiting platelet aggregation and release of endothelin-1, and inhibiting tumour necrosis factor-α and soluble adhesion molecules, namely intercellular adhesion molecule and vascular cell adhesion molecule-1. E-selectin inhibits production of profibrotic growth factors, namely transforming growth factor and connective tissue growth factor.[3–5] Nitric oxide (NO) is produced from an amino acid, L-arginine, by endothelial nitric oxide synthase (NOS) and it regulates vascular tone and plays an important role in the maintenance of vascular homeostasis.[6] The formation of acetyl-dimethylarginine (ADMA), and symmetric dimethylarginine (SDMA) is carried out by the addition of a class of enzymes and methyl groups to residues of the protein arginine.[7] ADMA is the endogenous inhibitor of endothelial NOS. SDMA does not inactivate the NOS enzyme; however, it has

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an indirect effect on NO production, inhibiting the cellular entry with arginine and ADMA.[8] ADMA is the endogenous competitive inhibitor of endothelial NOS and it decreases production and bioavailability of endothelial NOS.[9] In vascular diseases, ADMA levels increase before the onset of clinical symptoms. The levels are also associated with endothelial dysfunction, and ADMA has been shown to be a better indicator for endothelial injury than cholesterol levels.[10,11] The major pathway for the maintenance of endothelial function is the presence of NO produced by NOS.[11] ADMA was previously considered to be the main molecule in this pathway, being at the junction of the effects of all risk factors.[11,12] Several previous studies have demonstrated that the Arg/ADMA ratio was associated with impaired organ function, cardio- and cerebrovascular diseases, and mortality.[13] Therefore, the Arg/ADMA ratio was examined in the present study. In this study, the aim was to compare the levels of ADMA, SDMA, and the L-arginine/ADMA ratio before and after iloprost treatment in patients with Buerger's disease.

MATERIAL AND METHODS

Between January 2011 and December 2015, data from 44 patients (36 males, 8 females, mean age 48.7 ± 18.1 years) with a diagnosis of Fontaine Stage III–IV Buerger's disease were included in the study. An iloprost (Ilomedin, Bayer Schering Pharma AG, Berlin, Germany) infusion was administered intravenously at a dose of 0.5 ng/kg/min over 16 h through the forearm veins.[14] On the first day of treatment, the dose was titrated up to 1.5 ng/kg/min with 0.5 ng/kg/min increments every 30 min. Probable side effects were closely monitored. The drug was then given for 7 days at a dose of 1.5 ng/kg/min depending on the tolerability profile of the patient. Blood samples were collected on Day 8 following treatment. The diagnosis of Buerger's disease was made on the basis of Shionaya's criteria, which include clinical symptoms and pathognomonic angiographic findings of the collateral vessels. Patients with Buerger's disease who might need a major amputation without any history of vascular reconstruction or lumen opening interventions (angioplasty) or fibrinolytic therapy and had not smoked within the past 2 weeks were included. All people included in this study smoked cigarettes. Those with myocardial infarction within the past month, with acute coronary syndrome, kidney or liver dysfunction, or any known systemic disease, cardiovascular risk factors (hypertension, obesity, hyperlipidemia [> 2.5 g/L], and diabetes mellitus) and those who were unable to tolerate iloprost treatment were excluded. Substance abusers were also excluded. A single study protocol was applied to all patients during treatment. The patients were informed about the study and informed consent was obtained from each patient. The study protocol was approved by the local ethics committee. All patients underwent a detailed physical examination and their demographic characteristics were recorded.

Table 1. Patient demographics.

	n	%
Age, years	48.7 ± 18.1	
Sex		
Male	36	81.8
Female	8	18.1
Clinical stage		
Fontaine stage III	34	77.2
Fontaine stage IV	10	22.7
Ischaemic wounds		
Upper limb	4	9
Lower limb	40	90.9
Level of amputation		
Distal phalanx	2	4.5
Lower extremity (metatarsal)	8	18.1
Smokers	44	100

ADMA, SDMA, and L-arginine

Blood samples collected from the antecubital veins before and after treatment were put into pre-cooled test tubes containing ethylenediaminetetraacetic acid (EDTA), and the tubes were put into ice. The samples were centrifuged at 3,000 *g* for 10 min. Then, serum and plasma were separated and kept at −80 °C until analysis. On the day of analysis, serum and plasma were thawed promptly. The levels of ADMA, SDMA, and L-arginine were measured in thawed plasma samples using high performance liquid chromatography (HPLC) (Shimadzu 10 AVP, Japan) and appropriate commercial kits according to the manufacturers' instructions.[15]

Statistical analysis

Statistical analysis was performed using SPSS (Statistical Packages for the Social Sciences; SPSS Inc., Chicago, IL, USA) v12.0 software. The data were presented as mean ± standard deviation. The paired samples *t* test was used to compare pre- and post-treatment variables. A *p* value < .05 was considered statistically significant.

RESULTS

The demographic and clinical characteristics of the patients are shown in Table 1. Among the patients with Fontaine Stage III–IV Buerger's disease, 77.2% were Fontaine Stage III and 22.7% were Stage IV. All patients had ischaemic trophic changes (the skin is pale and hairless), most of them in the lower extremity (90.9%), and the minority in the upper extremity (9.1%). The findings were limited to the fingers and toes in all patients. Ten (22.7%) patients who had tissue necrosis and Gram negative infection before iloprost administration had amputations after treatment. Necrosis was the main determinant for the decision to do amputation. All 44 patients included in the study completed their therapy at a pre-specified dose and duration. Sixteen patients (36.4%) had adverse effects during treatment. The most frequent adverse effects were headache in eight (18.2%) cases and nausea in four (9.1%). The adverse effects

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