Ann Thorac Cardiovasc Surg 2013; 19: 120–125
Online August 31, 2012
doi: 10.5761/atcs.oa.11.01868

Original Article

A Stable Prostacyclin Analogue (Iloprost) in the Treatment of Buerger's Disease: A Prospective Analysis of 150 Patients

Ahmet Kursat Bozkurt, MD,[1] Koksal Cengiz, MD,[2] Caner Arslan, MD,[1] Demirbas Yilmaz Mine, MD,[3] Suzer Oner, MD,[4] Dedeoglu Burcak Deniz, MD,[4] and Demirkilic Ufuk, MD[5]

Purpose: To assess the efficacy and of iloprost in the treatment of Buerger's disease.
Methods: In this prospective study, 158 patients with rest pain and/or ischemic ulcers from 17 clinics were administered 1 ng/kg/min intravenous iloprost for 28-days. The primary endpoint was complete healing without pain or major amputation at 24 weeks. The secondary endpoints were pain assessment, reduction in ulcer area, 50% reduction of the ulcer size, shift in the modified SVS/ISCVS clinical status grading scale, global assessment by the investigator and an independent observer at 4 and 24 weeks. The comparisons were carried out with the initial values. The final evaluation was carried out in 150 patients.
Results: Complete healing rate was significantly better with iloprost treatment in comparison to the initial values at 24 weeks (<0.001). The secondary endpoints; complete healing rate, pain, the size of the ulcer, 50% reduction of the ulcer size, SVS/ISCVS grading scale, assessment by investigator, assessment by observer parameters were significantly better at 4 and 24 weeks (<0.001). The reduction of the ulcer size was significantly better when comparing 4th and 24th week values (<0.05).
Conclusion: The results of this independent study indicate that intravenous iloprost relieves ischemic symptoms efficiently in the acute phase Buerger's disease patients. Considering unsatisfactory results following surgical revascularisation and sympathectomy in Buerger's disease, prostacyclin analogues might be the first line treatment as long as complete abstinence from smoking is achieved.

Keywords: Buerger's disease, iloprost

Introduction

Buerger's disease is a peripheral arterial occlusive disease, which mainly affects the upper and lower limbs in young smokers and only rarely affects cerebral, coronary and visceral arteries.[1,2] The etiology remains unknown, but there is a close relationship between tobacco use and Buerger's disease.[1,2] The incidence of Buerger's disease

[1]*Department of Cardiovascular Surgery, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey*
[2]*Department of Cardiovascular Surgery, Kosuyolu Cardiovascular Disease Research Hospital, Istanbul, Turkey*
[3]*Department of Cardiovascular Surgery, Ahi Evren Cardiovascular Disease Research Hospital, Trabzon, Turkey*
[4]*Department of Pharmacology, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey*
[5]*Department of Cardiovascular Surgery, Gulhane Military Medical Academy, Ankara, Turkey*

Received: December 12, 2011; Accepted: February 22, 2012
Corresponding author: Caner Arslan, MD. I.U. Cerrahpaşa Tıp Fakultesi, Kalp ve Damar Cerrahisi Anabilim Dalı, 34250, Fatih-Istanbul, Turkey
Email: canerkvc@yahoo.com
©2012 The Editorial Committee of *Annals of Thoracic and Cardiovascular Surgery.* All rights reserved.

seems to decrease over the years.[1,3] As Buerger's disease is considered as an immune-mediated vasculitis, the influence of exogenous factors such as a reduction in smoke consumption among the Western and Japanese population may explain this reduction. However, this disease is still encountered in Middle Asia, Mediterranean countries, and India.[1,2,4]

The cornerstone of therapy is the complete discontinuation of cigarette smoking and all other forms of therapy are palliative. Since the number of patients encountered in any given center is small and the criteria for diagnosis are controversial, it is difficult to perform trials to determine if a given therapy is effective. In 1990 Fiessinger and Schafer conducted a prospective randomized double blind trial comparing a 6 h daily infusion of iloprost, a stable prostaglandin analog, with aspirin.[5] Iloprost was found to be superior to aspirin at 28 days in respect to total relief of rest pain and complete healing of trophic lesions. Furthermore, at 6 months, 88% of the patients treated with iloprost responded favorably to therapy as compared with 21% of the aspirin group. However, oral iloprost was not found as effective as intravenous treatment in Buerger's disease. The results of a European study did not show a significant difference between groups for the primary end point, which was total healing of lesions, at any of the time points evaluated.[6]

Recently our group completed and published a prospective randomized trial comparing surgical lumbar sympathectomy (LS) and intravenous iloprost treatment in Buerger's disease.[7] The final comparison was carried out in 162 patients (iloprost: n = 84; LS: n = 78) and the results of this study indicate that using iloprost relieves ischemic symptoms better than LS. Because of the encouraging results of this study, we decided to continue the patient recruitment in the iloprost arm to clarify the current role of iloprost in the treatment of acute phase Buerger's disease in a large patient population. Hereby, we report the follow-up results of 150 patients; this is the largest reported study on patients with Buerger's disease who were treated and followed up prospectively in a standard fashion.

Materials and Methods

Patient selection: The diagnosis of Buerger's disease is based on Shionoya's clinical criteria, with all five elements required: (1) smoking history, (2) onset of the symptoms before the age of 50 years, (3) infrapopliteal arterial occlusive lesions, (4) either upper limb involvement or phlebitis migrans, and (5) absence of atherosclerotic risk factors other than smoking.[8] Definite Buerger's disease is considered when all five criteria are met. However, Buerger's disease is also considered in patients meeting all requirements except the fourth one, but supplemented with typical angiographic findings (segmental occlusive lesions of the small- and medium-sized arteries with formation corkscrew collaterals, and abrupt occlusion of an otherwise normal artery).

The local ethics committees approved the protocol and all procedures were carried out with the adequate understanding and written informed consent of each subjects. This study was conducted in accordance with the Declaration of Helsinki.

Study design: In this prospective study 158 patients with acute phase of disease associated with rest pain and/or ischemic ulcers were administered 1 ng/kg/min intravenous iloprost for 28-days (Ilomedin, Bayer-Schering AG, Germany). The study was carried out in 17 major vascular surgery centers in Turkey. The treatment started at 0.5 ng/kg/min and, if the patient tolerated the initial dose, the normal dose was administered for 28 days. Epidural blockage was not allowed during the study period of 6 months. Aspirin was given at the usual dosage; however, any other drug with a known vasodilating or hemorheologic effect was precluded. All patients had routine ulcer care. Individualized topical treatment and dressings were used depending on the site and character of the ischemic ulcer. Amputation was carried out when deemed necessary.

Assessments: The primary endpoint of the study was complete healing without pain or major amputation at 24 weeks. Syme's amputation and below-knee and above-knee amputations were included under major amputations. Minor amputation is defined as retention of a functional foot remnant that allows standing and walking without a prosthesis. The secondary endpoints were pain assessment (Visual analogue scale: 0-10), reduction in the size of the ulcer (mm^2), 50% reduction in the ulcer, and shift in the modified Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery (SVS/ISCVS) clinical status grading scale,[9] global assessment by the investigator and by the independent observer at 4 and 24 weeks (0-4). The ulcer area was determined in millimeters by multiplying the largest width (A-B) and length (C-D) of the ulcer (A-B x C-D). The largest ulcer was considered to be the study ulcer when more than one ulcer was present. This simple method was shown to be a good indicator in terms of

Table 1 Recommended scale for gauging changes in clinical status

+3 Markedly improved: No ischemic symptoms, and any foot lesions completely healed;
+2 Moderately improved: No open foot lesions; still symptomatic but only with exercise and improved by at least one category
+1 Minimally improved:
0 No change:
–1 Mildly worse:
–2 Moderately worse: One category worse or unexpected minor amputation
–3 Markedly worse: More than one category worse or unexpected major amputations

Our preliminary study revealed that ankle-brachial index (ABI) could not be accurately measured in Buerger's disease because of the distal occlusion.

† Modified from: Rutherford RB, et al. Recommended standards for reports dealing with lower extremity ischemia: Revised version. J Vasc Surg (1997)26(3): 517-538.

Table 2 Baseline characteristics of the patient population (n = 158)

Age	43.43 ± 9.27
Smoking at admission	96.67%
Female/male ratio	6.04% vs 93.96%
Family history	2.67%
Previous sympathectomy	35.3%
Previous revascularisation	10.67%
Previous amputation	27.33%
Upper extremity involvement	6.04%
Thrombophlebitis migrans	20.81%
Rest pain	92.67%
Ischemic ulcer	60.67%
Initial ulcer size	506.87 ± 529.20

Data were given by the patients, routine cotinine measurement was not carried out.

ulcer healing.[10] The SVS/ISCVS clinical status grading scale was modified slightly for this study (**Table 1**). Our pilot study demonstrated that ankle/brachial pressure index (ABI) measurement is not a good indicator in Buerger's disease and this parameter was excluded from the grading scale.

Statistical analysis: Data were expressed as mean ± SD. Differences within time period were analyzed by repeated measures ANOVA post hoc Tukey for parametric, or Friedman nonparametric repeated measures test post hoc Dunn for nonparametric data values. Contingency tables were analyzed by Chi-square test. p values <0.05 were considered to be statistically significant. All statistical calculations were performed with SPSS 12.0 [SPSS Inc, Chicago, IL, USA].

Results

The comparison was carried out in 150 patients because of insufficient data for the remaining 8 patients. The demographics of the study population were shown in **Table 2**. There was no mortality or major morbidity. Although minor side effects were often, only in 4 patients they were severe enough to stop treatment. The reported side effects were headache (39.01%), flushing (31.62%), nausea (23.91%), and abdominal discomfort (8.53%).

The rate of smoking was 96.67%, 6.12%, 20.87% at 0, 4 and 24 weeks and abstinence from smoking was significant in comparison to the initial values (<0.001). The complete healing rate without pain or major amputation was % 60.23 at 24 weeks (<0.001). Pain assessed by VAS was 7.07 ± 2.12, 2.10 ± 2.18 and 1.72 ± 2.33 at 0, 4 and 24 weeks and the difference was significant both in 4 and 24 weeks (p <0.001). However, the difference was nonsignificant between 4 and 24 weeks. The size of the ischemic ulcers diminished significantly at 4 and 24 weeks. The size of the ulcer as calculated mm^2 between 4 and 24 weeks also reached statistical significance (<0.05). The SVS/ISCVS grading scale demonstrated a greater clinical benefit (p <0.001 at 4th week, and p <0.001 and at 24th week). Global assessments by the investigator and observer had shown significant well-being with iloprost treatment at 4 and 24 weeks (**Table 3**).

Table 3 Initial values and results of the treatment with iloprost at 4 and 24 weeks

	0 day	4 weeks	24 weeks	p value (overall)	p value (0 versus 4)	p value (0 versus 24)	p value (4 versus 24)
Smoking (%) *	96.67	6.12	20.87	<0.001	<0.001	<0.001	<0.001
Complete healing rate (%)	0.00		60.23	<0.001		<0.001	
Pain (Visual analogue scale)	7.07 ± 2.12	2.10 ± 2.18	1.72 ± 2.33	<0.001	<0.001	<0.001	NS
The size of the ulcer (mm^2)	506.87 ± 529.20	272.19 ± 492.08	179.09 ± 502.93	<0.001	<0.001	<0.001	<0.05
50% reduction of the ulcer size (%)	0.00	64.94	77.01	<0.001	<0.001	<0.001	NS
SVS/ISCVS grading scale†	0.00 ± 0.00	1.96 ± 1.03	2.21 ± 1.13	<0.001	<0.001	<0.001	NS
Global assessment by investigator	0.00 ± 0.00	2.86 ± 1.07	3.09 ± 1.16	<0.001	<0.001	<0.001	NS
Global assessment by observer	0.00 ± 0.00	2.93 ± 1.02	3.26 ± 0.99	<0.001	<0.001	<0.001	NS

* Data were given by the patients, routine cotinine measurement was not carried out; †Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery

Discussion

In Buerger's disease the cornerstone of therapy is the complete discontinuation of cigarette smoking or the use of tobacco in any form. Other than discontinuation of cigarette smoking, all other forms of therapy are palliative.[1,2] If patients stop smoking, the natural history of the disease is relatively tolerable without the need for a major amputation. The disease is confined most often to the distal circulation and is almost always infrapopliteal in the lower extremities and distal to the brachial artery in the upper extremities. There is always small and medium-sized vessel involvement, such as the digital arteries in the fingers and toes, as well as the tibial, peroneal, radial and ulnar arteries. Proximal arteries are usually normal demonstrating no evidence of atherosclerosis or aneurysm formation. Thus, direct arterial revascularisation is rarely feasible in Buerger's patients. In a series of 216 patients receiving surgical therapy for Buerger's disease, we were able to perform direct revascularisation in only 21 patients.[11] Although the patency rates do not seem promising, the limb salvage rate was quite satisfactory in this and in other series.[4,11,12] The role of sympathectomy in preventing amputations or in treating pain is unclear. There have been several recent reports demonstrating that sympathectomy can be safely and effectively carried out laparoscopically in the lower,[4,13] and upper extremities.[14]

The difficulty in studying rare diseases such as Buerger's disease is that there are no significant research grants available. Therefore, there has been little progress in the treatment of the disease for decades. There are two therapies that are intriguing and may justify further study: Therapeutic angiogenesis,[15,16] and stimulating angiogenesis using a Kirschner wire placed in the medullary canal of the tibia.[17]A recent phase 1 clinical trial tested intramuscular gene transfer by using naked plasmid DNA encoding the gene for VEGF given by intramuscular injections in seven patients with Buerger's disease.[15] Ischemic pain of the affected limb was relieved or improved markedly in six of seven patients and ulcers healed or improved in four of six patients. Kirschner wire was used in six patients with Buerger's disease.[17] In a mean follow-up of 19 months, significant improvement was observed, including reduced rest pain and increased claudication distance. Ischemic ulcers completely healed after Kirschner wire intervention. However, both of the treatment modalities are still experimental and necessitate further studies with larger study population.

Prostacyclin derivatives have been evaluated in several studies and have been shown to be more effective than placebo in Buerger's disease.[5,18] In a small study with 15 patients Epoprostenol, a prostaglandin I_2 analogue, was administered continuously for 72 hours and showed an improvement in pain and trophic lesions that continued for 6 weeks.[18] In another randomized study, 152 patients with Buerger's disease presenting pain at rest, with or without trophic problems, received intravenous iloprost or placebo.[5] After 21–28 days of perfusion, the trophic lesions had healed, or the pain had disappeared in 85% of the patients on iloprost and 17% of the patients on aspirin. At 6 months, amputation was required in 18% of the patients in the aspirin group and only 6% of the patients in

the iloprost group. On the other hand, the results of two randomized trials comparing oral prostacyclin derivatives with placebo in peripheral arterial disease were less impressive.[6,19] The first one was The European Thromboangiitis obliterans (Buerger's disease) study.[6] In this double blind, randomized, placebo-controlled trial, no significant difference was found between groups for the total healing of lesions. Mohler et al reported another double-blinded, randomized, controlled trial using beraprost sodium, an orally active prostaglandin I_2 analogue for the treatment of intermittent claudication.[19] Beraprost did not improve symptoms of intermittent claudication in patients with peripheral arterial disease.

Currently intravenous prostaglandin's or prostacyclin analogues seem the most widely used medications on Buerger's patients with critical limb ischemia. As a surgical alternative, sympathectomy has been widely used but the results obtained are difficult to evaluate and not very convincing. We and some others were considering that sympathectomy may be helpful in cases of distal trophic lesions, as a last resort before amputation.[4,8,11] Thus, in a previous study we aimed to compare the effects of iloprost and lumbar sympathectomy in the treatment of Buerger's disease.[7] Complete healing rate was 61.9% in the iloprost group and 41% in the LS group at the 4th week ($p = 0.012$). Respective values for the 24th week were 85.3%, 52.3% ($p < 0.001$) and we concluded "in the era of stable prostacyclin analogues, there is no reliable evidence to support the use of LS in Buerger's disease". This was a very strong recommendation, and in order to strengthen our hypothesis, we decided to continue patient recruitment in the iloprost arm and increase the number of patients. Certainly, based on our previous data, to perform another prospective randomized study comparing the efficacy of the iloprost with placebo would have been unethical. We are also aware that smoking cessation rate is quite high in this hospitalized patient population, and only this fact may improve the ischemic lesions in Buerger's disease. Nonetheless, results of treatment with iloprost were impressive and cannot be explained only with abstinence from smoking. The primary endpoint of this study, complete healing rate without pain or major amputation, was % 60.23 at 24 weeks. All secondary endpoints; pain assessment, ulcer size reduction, 50% reduction in the ulcer, shift in the SVS/ISCVS clinical status grading scale, global assessment by the investigator and by the independent observer were in favor of iloprost treatment. Following termination of intravenous iloprost treatment all of the secondary study parameters continue to improve, although only ulcer size reduction did reach statistical significance (<0.05).

It is clearly evident that iloprost, when used intravenously, alleviates rest pain, improves ulcer healing and decreases the rate of amputation of in Buerger's disease.[5–7] It is known that prostaglandin analogues facilitate relaxation of vascular smooth cells, inhibit platelet aggregation, and inhibit chemotaxis and cell proliferation.[19] Nicotine consumption damages vascular endothelium, which is the source of nitric oxide production.[20] Brodman et al showed that iloprost achieves a significant reduction in peripheral vascular resistance and that the vasodilatative effect is independent of nitric oxide.[21]

Conclusion

The mechanism behind the beneficial effect of iloprost on critical limb ischemia has not been completely elucidated. Intravenous iloprost is an ideal vasodilatative drug for treating Buerger's patients with severely impaired endothelial function because of heavy smoking.

References

1) Olin JW, Shih A. Thromboangiitis obliterans (Buerger's disease). Curr Opin Rheumatol 2006; **18**: 18-24.
2) Olin JW. Thromboangiitis obliterans (Buerger's disease). In: Rutherford RB ed.; Rutherford Vascular Surgery. Philadelphia: Elsevier Saunders Press, 2005; pp 404-19.
3) Sasaki S, Sakuma M, Yasuda K. Current status of thromboangiitis obliterans (Buerger's disease) in Japan. Int J Cardiol 2000; **75**: S175-81.
4) Bozkurt AK, Besirli K, Koksal C, et al. Surgical treatment of Buerger's disease. Vascular 2004; **12**: 192-7.
5) Fiessinger JN, Schäfer M. Trial of iloprost versus aspirin treatment for critical limb ischaemia of thromboangiitis obliterans. The TAO Study. Lancet 1990; **335**: 555-7.
6) Oral iloprost in the treatment of thromboangiitis obliterans (Buerger's disease): a double-blind, randomised, placebo-controlled trial. The European TAO Study Group. Eur J Vasc Endovasc Surg 1998; **15**: 300-7.
7) Bozkurt AK, Köksal C, Demirbas MY, et al. A randomized trial of intravenous iloprost (a stable prostacyclin analogue) versus lumbar sympathectomy in the management of Buerger's disease. Int Angiol 2006; **25**: 162-8.
8) Shionoya S. Buerger's disease (thromboangiitis obliterans). In: Rutherford RB ed.; Rutherford Vascular Surgery. Philadelphia: Elsevier Saunders Press, 1989; pp 207-17.
9) Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower ex-

tremity ischemia: revised version. J Vasc Surg 1997; **26**: 517-38.
10) Kalani M, Apelqvist J, Blomback M, et al. Effect of dalteparin on healing of chronic foot ulcers in diabetic patients with peripheral arterial occlusive disease: a prospective, randomized, double-blind, placebo-controlled study. Diabetes Care 2003; **26**: 2575-80.
11) Sayin A, Bozkurt AK, Tüzün H, et al. Surgical treatment of Buerger's disease: experience with 216 patients. Cardiovasc Surg 1993; **1**: 377-80.
12) Nishikimi N. Fate of limbs with failed vascular reconstruction in Buerger's disease patients. Int J Cardiol 2000; **75**: S183-5.
13) Chander J, Singh L, Lal P, et al. Retroperitoneoscopic lumbar sympathectomy for buerger's disease: a novel technique. JSLS 2004; **8**: 291-6.
14) De Giacomo T, Rendina EA, Venuta F, et al. Thoracoscopic sympathectomy for symptomatic arterial obstruction of the upper extremities. Ann Thorac Surg 2002; **74**: 885-8.
15) Isner JM, Baumgartner I, Rauh G, et al. Treatment of thromboangiitis obliterans (Buerger's disease) by intramuscular gene transfer of vascular endothelial growth factor: preliminary clinical results. J Vasc Surg 1998; **28**: 964-73; discussion 73-5.
16) Durdu S, Akar AR, Arat M, et al. Autologous bone-marrow mononuclear cell implantation for patients with Rutherford grade II-III thromboangiitis obliterans. J Vasc Surg 2006; **44**: 732-9.
17) Inan M, Alat I, Kutlu R, et al. Successful treatment of Buerger's Disease with intramedullary K-wire: the results of the first 11 extremities. Eur J Vasc Endovasc Surg 2005; **29**: 277-80.
18) Nizankowski R, Królikowski W, Bielatowicz J, et al. Prostacyclin for ischemic ulcers in peripheral arterial disease. A random assignment, placebo controlled study. Thromb Res 1985; **37**: 21-8.
19) Mohler ER, Hiatt WR, Olin JW, et al. Treatment of intermittent claudication with beraprost sodium, an orally active prostaglandin I2 analogue: a double-blinded, randomized, controlled trial. J Am Coll Cardiol 2003; **41**: 1679-86.
20) Higman DJ, Strachan AM, Buttery L, et al. Smoking impairs the activity of endothelial nitric oxide synthase in saphenous vein. Arterioscler Thromb Vasc Biol 1996; **16**: 546-52.
21) Brodmann M, Lischnig U, Lang B, et al. The evaluation of the no-independent vasodilatative effect of iloprost in isolated perfused Guinea pig hind limbs. Int Angiol 2004; **23**: 72-5.