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Evaluation of the Vascular Effects of Iloprost in Patients with Thromboangiitis Obliterans (Buerger's Disease)

Tromboanjitis Obliterans (Buerger Hastalığı) Olgularında İloprostün Vasküler Etkilerinin Değerlendirilmesi

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ABSTRACT

Objective: Thromboangiitis obliterans (TAO) is a common vascular pathology that occurs as a result of increased cigarette smoking in individuals with a genetic predisposition. Due to the incomplete understanding of its pathogenesis, the condition's diagnosis, treatment, and prevention processes still present challenges.

Methods: In this study, 15 patients (1 female, 14 male), aged between 20 and 55, diagnosed with TAO, were treated with iloprost, a stable PGI2 analogue. Each patient received intravenous iloprost for six hours daily over 28 days. The dose titration was as follows: treatment started with 0.5 ng/kg/min for the first three days. The dose was increased by 0.5 ng/kg/min every 30 minutes until a maximum dose of 2.0 ng/kg/min was reached and maintained for six hours. Before and after treatment, 20 mCi Tc-99m pyrophosphate injections were administered, and lower extremity perfusion rates were assessed through scintigraphy in both resting and exercising positions. A significant increase in perfusion rates was observed after treatment ($p<0.05$).

Results: In this study, iloprost treatment accelerated ischemic ulcer healing, increased walking distance, alleviated pain at rest, and improved the ankle-brachial index in patients with TAO. These positive effects of treatment persisted for up to six months. Changes before and after treatment were statistically significant, as shown both subjectively and scintigraphically ($p<0.05$).

Conclusion: The aim of this study was to evaluate the effect of PGI2 analogues, such as iloprost, on tissue perfusion reserve in patients with TAO at the microvascular level using scintigraphy.

Keywords: Iloprost, thromboangiitis obliterans, scintigraphy, prostacyclin (PGI2)

ÖZ

Amaç: Tromboanjitis obliterans (TAO), sigara içen bireylerde genetik yatkınlık nedeniyle ortaya çıkan yaygın bir vasküler patolojidir. Patogenezinin tam olarak anlaşılamaması nedeniyle tanı, tedavi ve önleme süreçleri hala zorluklar sunmaktadır.

Yöntemler: Bu çalışmada, TAO teşhisi konulan 15 hasta (1 kadın, 14 erkek), 20-55 yaş aralığında, iloprost ile tedavi edildi. İloprost, bir PGI2 analogudur. Her hasta, 28 gün boyunca günde altı saat intravenöz iloprost aldı. Doz titrasyonu, ilk üç gün için 0,5 ng/kg/dak ile başladı ve her 30 dakikada 0,5 ng/kg/dak artırarak maksimum 2,0 ng/kg/ dak dozuna ulaşıldı ve altı saat boyunca sürdürüldü. Tedaviden önce ve sonra, 20 mCi Tc-99m pirofosfat enjeksiyonları uygulandı ve alt ekstremite perfüzyon oranları, hem dinlenme hem de egzersiz pozisyonlarında skintigrafi ile değerlendirildi. Tedaviden sonra önemli bir perfüzyon artışı gözlemlendi ($p<0,05$).

Bulgular: Bu çalışmada, iloprost tedavisi, TAO'lu hastalarda iskemik yara iyileşmesini hızlandırdı, yürüme mesafesini artırdı, dinlenme ağrısını hafifletti ve ayak bileği-kol kan basıncı indeksini iyileştirdi. Tedaviye bağlı olumlu etkiler altı aya kadar sürdü. Tedaviden önce ve sonra yapılan değişiklikler, hem subjektif hem de sintigrafik olarak istatistiksel olarak anlamlıydı ($p<0,05$).

Sonuç: Bu çalışmanın amacı, skintigrafi kullanarak mikrovasküler düzeyde TAO'lu hastalarda PGI2 analogları gibi iloprostun doku perfüzyon rezervi üzerindeki etkisini değerlendirmekti.

Anahtar Sözcükler: İloprost, tromboanjitis obliterans, sintigrafi, prostaglandin (PGI2)

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INTRODUCTION

Buerger's disease or thromboangiitis obliterans (TAO) is one of the peripheral obstructive vascular disorders presenting as a non-atherosclerotic, segmental, inflammatory condition commonly occurring in lower extremities and rarely in upper extremities, affecting small or medium arteries and adjacent veins. Peripheral endothelium-dependent vasorelaxation is impaired in patients with TAO (1). TAO is distinguished from other vasculitides by the predominantly inflammatory thrombus formation leaving relatively intact areas on the vascular walls (2). The treatment of this common disorder generally consists of antiaggregant drugs, vasodilator agents, and, recently, prostacyclin analogues (3,4). Prostacyclin I2 (PGI2) is a prostacyclin analogue exerting its effects by regulating microcirculation, and is disrupted in ischaemia, inflammatory tissue lesions, vasospasm, and cold stress intolerance. The favourable effects of PGI2 provide dilated precapillary vessels, reduced flow resistance, increased digital blood flow, and prevent microthrombus formation by decreasing leukocyte adhesion in small capillary channels. The agent administered to the patients in the present study was iloprost, a stable PGI2 analogue providing the aforementioned effects. The aim of the present study is to evaluate the therapeutic effects of iloprost, a PGI2 analogue, which is one of the medical treatment options for TAO and for which various treatment protocols are used, including surgical reconstruction, sympathectomy, and medical treatment.

MATERIALS and METHODS

Informed consent forms approved by the Ethics Committee, designated by Atatürk University, were obtained from patients and relatives/caregivers prior to the start of the study (decision number: 1, date: 11.02.2004). Patients were informed that they could withdraw from the study at any time without giving any reason, and that they could be withdrawn from the study at the discretion of the study doctor if the treatment was deemed not indicated or potentially harmful for the patient. A total of 15 patients with Buerger's disease and Fontaine stage IV (claudication, rest pain and/or ischaemic ulcerated wound) were included in the study. One male and one female patient withdrew from the study on iloprost treatment by their own will. Two male patients with Buerger's disease replaced these patients. The general characteristics of the patients are summarized in Table 1.

None of the patients had any chronic disease such as coronary or congestive heart failure, diabetes mellitus, malignancy, or chronic obstructive pulmonary disease. Patients diagnosed with Buerger's disease who were potential candidates for major amputation and who had not undergone any vascular reconstruction or any intervention for lumen enlargement (angioplasty) or fibrinolytic therapy were included in this clinical study. Exclusion criteria of the present study included pregnancy, lactation, abnormal platelet count, bleeding-coagulation disorder, and advanced renal or hepatic dysfunction.

To avoid confounding factors, anticoagulants, pentoxifylline, and low or high molecular weight heparin were not used during the study period. Intensive wound management was continued.

Routine systemic examination, non-invasive vascular investigations (Doppler ultrasound, ankle/brachial index measurements), and haematological and biochemical investigations were performed for the 15 patients prior to the start of the study. Furthermore, results of the scintigraphic extremity assessment were recorded on individual patient follow-up forms. A self-monitoring system was implemented by keeping patients in the same room for as long as possible. One ampoule of iloprost was mixed in a 5% dextrose solution and administered to the patients via an intravenous route with an infusion pump every day. The drug solution was prepared daily. The clinical study group consisted of patients receiving intravenous iloprost over 6 hours for 28 days. Following the initial dose of 0.5 ng/kg/min for three days, the individual dose was titrated every thirty minutes, increasing by increments of 0.5 ng/kg/min to achieve the maximum dose of 2.0 ng/kg/min given intravenously over 6 hours from the forearm vein. The individual tolerable dose was determined by the occurrence of side effects, including flushing, headache, abdominal pain, and nausea. The findings are summarized in Table 2.

Treatment efficacy was evaluated according to the following criteria in this clinical study:

1. Decrease and/or relief of rest pain (using visual analogue pain scale)

2. Wound shrinkage and/or healing in patients with wound in extremities

3. Change in claudication distance

4. Changes in Ankle Brachial Index (ABI).

Patients were monitored closely for arterial blood pressure (BP), and study treatment was initiated after normalization of BP in patients with systolic BP over 140 mmHg. Iloprost therapy was planned as four weeks of treatment (28 days), and 6 months of post-treatment follow-up. On day 1-3-7, and 28 after the initiation of treatment, rest pain was assessed with the visual analogue pain scale and ischaemic wound changes were evaluated. The modified grading scale for Buerger's recommended by SVS/ISCVS (Society for Vascular Surgery/International Society for Cardiovascular Surgery) was used at 6 months, and ankle/brachial index and scintigraphic findings were recorded in patient follow-up forms.

Using a scintigraphic method, the present study aims to evaluate whether iloprost affects perfusion reserves and its effects at the microvascular level. Patients received intravenous Tc-99m pyrophosphate at 20 mCi for the scintigraphic assessment. Foot exercise was performed prior to scintigraphic imaging, and after the Tc injection. The first imaging was performed 15 minutes after Tc injection, and the second imaging was performed following a one-hour rest, after the first imaging. The same scintigraphic imaging was repeated on day 28 of treatment and at 6 months, and scintigraphic images were obtained in anterior and posterior positions. Total counts (Cts) were obtained from the regions of interest (ROIs) of the posterior images, and perfusion rates were calculated using a formula. A double-detector gamma camera (Siemens ECAM) and the computer integrated with this system were used in the present study. A low-energy, high-resolution collimator with parallel holes was selected, and the images were obtained at 140 keV photo peak (the energy peak of Tc-99m) with an energy window of 20%. The images were evaluated with the computers integrated into the gamma camera. Total Cts were calculated from ROIs of the scintigraphic images of the extremity at the posterior position before and after

treatment with iloprost, and these total Cts were recorded. The total Cts of the posterior images were used to calculate the perfusion rates according to the following formula:

$$\% \text{ perfusion reserve} = \frac{\text{PreT (PostT) Ct 15 min.-PreT (PostT) Ct 1 hour x 100}}{\text{PreT (PostT) Ct 1 hour}}$$

*PreT: Pre-treatment *PostT: Post-treatment *15 min: exercise *1 hour: Rest

Statistical Analysis

Statistical analysis of the data was performed using Statistical Package for the Social Sciences (SPSS) version 11.0, the Wilcoxon test, and the t-test. P-values less than 0.05 were considered statistically significant (Table 3).

RESULTS

The iloprost tolerance and side effects were monitored during the clinical study by recording physical findings and investigating patients' complaints. These findings are summarized in Table 2. The patients exhibited no severe side effects requiring discontinuation from the study. The symptoms observed in these patients resolved following a dose reduction by 0.5 ng/kg/min every thirty minutes. Blood samples were obtained from the patients included in this study prior to treatment, on day 28 of treatment, and at the end of the follow-up of six months, and no direct effects were detected in the haematological or biochemical (hepatic and renal function tests) tests. The difficulty in evaluating the objective parameters led to the assessment of more subjective parameters such as rest pain,

Table 1. Demographic characteristics of the patients

Demographic characteristics	n (number of patients)	% (percentage of patients)
Age (years)		
20-30	2	13.3
31-40	3	20
41-55	10	66.7
Gender		
Male	14	93.3
Female	1	6.7
Time from diagnosis		
1-5 years	11	73.4
6-10 years	2	13.3
11-20 years	2	13.3
Sympathectomy		
Yes	6	40
No	9	60
Level of sympathectomy		
Lumbar	4	67
Thoracic	1	16.5
Lumbar+thoracic	1	16.5
Claudication distance		
<100 metres	3	20
100-200 metres	4	26.7
201-300 metres	2	13.3
301-500 metres	5	33.3
>500 metres	1	6.7
Mean ankle/brachial index	0.51±0.18	
Smoking	15	100
Ischaemic wound		
Lower extremity	13	86.7
Upper extremity	2	13.3
Amputation level		
Upper extremity (below elbow)	1	25
Lower extremity (below knee)	2	50
Lower and upper extremity (below knee and below)	1	25

history, related parameters, and use of analgesics. The changes in treatment efficacy parameters before and after iloprost treatment are presented in Table 4.

The evaluation at six months showed (i) further reduction in rest pain during the post-treatment period, (ii) no persistent or new wounds (Figure 1 and Figure 2), (iii) further improvement in claudication distance compared to the increase at 28 days, and (iv) no reduction in ABI rates compared to the rates observed 6 months earlier. The statistical comparison between pre- and post-treatment periods regarding ABI on day 28 and at 6 months, change in claudication distance, recovery rate in ischaemic wounds, and change in rest pain showed that the post-treatment findings were significantly different from the pre-treatment findings ($p<0.05$). While the change in rest pain was not very significant on day 1, and 3, the reduction in rest pain was statistically significant on day 7 ($p<0.05$). The rest pain showed a highly significant reduction on day 28 and at 6 months ($p<0.001$). While the change in claudication distance was not very significant on day 1, 3, and 7, the change was statistically significant on day 28 ($p<0.05$). The difference was highly significant at the end of 6 months ($p<0.001$). To minimize the physician bias during the assessments in this clinical study, simultaneous evaluations were carried out by an external, independent observing physician before and after, (on day 28 and at 6 months), the treatment. These simultaneous evaluations revealed consistent findings.

Table 2. The symptom and severity findings of the patients

Symptoms	Severity-no. of patients		
	Mild	Moderate	Severe
Flushing	2	1	0
Nausea	1	1	1
Head ache	1	1	1
Abdominal pain	0	1	0

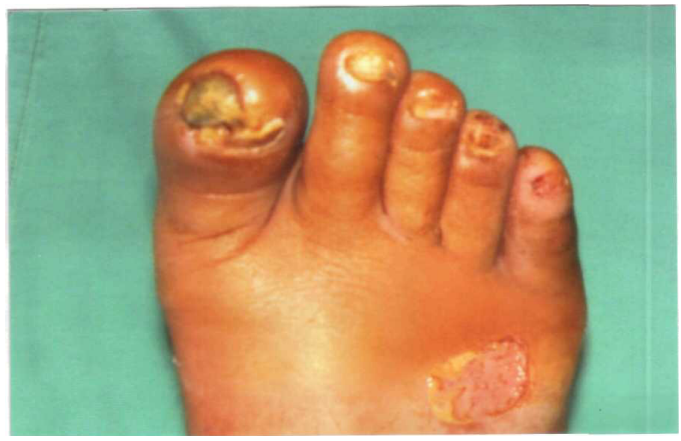

Figure 1. Before treatment with iloprost.

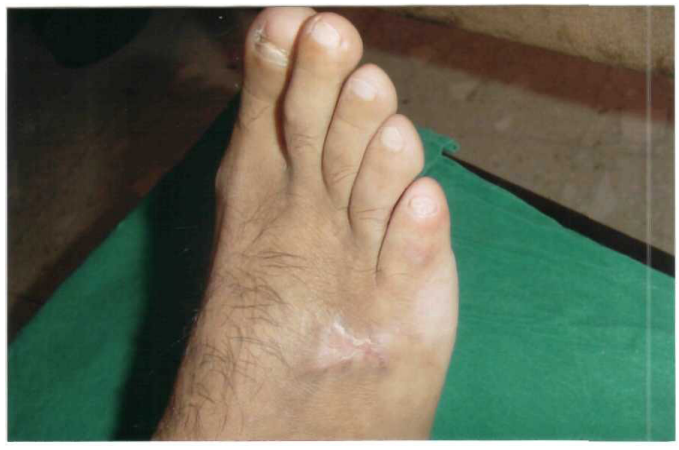

Figure 2. Six months after treatment with iloprost.

Table 3. Comparison of scintigraphic % perfusison outcomes in both extremities before and after treatment with iloprost (t-test)

	Right before treatment	Right after treatment	Left before treatment	Left after treatment	Difference right	Difference left	Right 100	Left 100
Minimum	12.44	17.63	13.16	19.78	-27.07	-37.07	-156.75	-153.5
Maximum	78.84	90.25	75.6	92.68	1.12	6.75	5	5.6
Mean	29.7087	42.454	28.6587	40.287	-12.7453	-11.623	51.8719	48.0114
Standard deviation	16.2323	18.283	14.8494	18.2	8.0862	9.1985	42.0949	43.6744

Table 4. Changes in therapeutic efficacy parameters before and after treatment with iloprost

	Day 1	Day 3	Day 7	Day 28	6 months
Reduction in rest pain	Ø	10-15%	30%	98%	98%
Wound shrinkage	Ø	1-3%	10-15%	75%	100%
Increase in claudication distance	Ø	Ø	3%	80%	95%
Ankle/Brachial Index	Ø	Ø	3%	65%	80%

Ø: No change was observed

DISCUSSION

The disorder commonly associated with smoking or tobacco consumption has also been linked to an aetiology involving genetic factors, hypercoagulability, vascular endothelial structure, and immunological mechanisms (3,4). In 1879, von Winiwarter identified an obstructive arterial disease apart from atherosclerosis and termed the disease "endarteritis obliterans". Pathological investigations revealed intimal proliferation, thrombosis and fibrosis. von Winiwarter was the first to identify that endarteritis and endophlebitis differed from atherosclerosis. In 1908, Leo Buerger termed the disorder "TAO", and provided a detailed description of clinical and pathological characteristics of the disease. Austrian surgeon Alexander von Winiwarter (April 22, 1848-October 31, 1917), born in Vienna, was the first to describe endarteritis and endophlebitis as distinct from atherosclerosis. Leo Buerger, who was born in Vienna and raised in German culture, and was of Jewish descent, described in detail and accurately the clinical and pathological features of the disease he named "TAO" in 1908 (5).

Buerger's definition is based on his observations, which confirmed that the symptoms of the disease are not only in the arteries but in the veins, where the first signs of the disease often appear. Buerger recorded all his experiences and opinions in his book "Über die Kreislaufstörungen der Extremitäten einschliesslich Brand, vasomotorische und trophische Störungen.", published in German. In 1917, F. Parkes Weber of the German Hospital in London reported a series of cases that confirmed Buerger's view. He proposed the name "Nicht syphilitische Arteriitis obliterans der Juden". Although it was generally confirmed that the disease was rare in women, as Buerger had previously stated, it was later decided not to define it as specific to Jews (6).

Following Buerger's description, Allen and Brown reported cases with TAO, the majority of whom were heavy-smoking males of Jewish descent. They reported claudication in the feet, gangrenous ulceration in the toes, or gangrene affecting the toes or the whole foot in these cases. Although Allen and Brown suggested the hypothesis that TAO was an infectious disease, their pathological description was consistent with the original report by Buerger (2). One of the interesting features of Buerger's disease is the geographic distribution. Among peripheral arterial diseases, the incidence of Buerger's disease is less than 1% in the USA. The incidence is 0.5-5.6% in European countries, approximately 10% in our country, and about 50% in the Far East (3). TAO, or Buerger's disease, is an inflammatory vasculitis that causes non-atherosclerotic involvement in small and medium arteries, adjacent veins, and neighbouring nerves of extremities (2-7). Histopathology is generally diagnostic in the acute phase of the disease and is characterized by acute inflammation involving all layers of the vascular wall. In terms of arteriographic and pathological aspects, TAO is a partial, (i.e. characterized by both affected and unaffected regions), vascular entity. It is typically seen in young males (aged 20-50 years) heavy smokers or consume tobacco products. The patients included in the present study exhibited heavy smoking habits.

TAO is a panarteritis with several controversial treatment options. Approximately 76% of patients have ischaemic ulcerations at the time of presentation (8). When revascularization is not possible in patients with critical extremity ischaemia and ischaemic ulcerations, the last option to provide pain relief is often amputation.

Extremity amputations are historically considered one of the oldest surgical interventions. Such procedures are generally evaluated negatively, and indications for amputations performed for reasons other than trauma are delayed and often rejected by the patient and their relatives. This situation, which creates a psychological and emotional void in addition to the physical loss in the individual, can be exemplified in German literature as a traumatic reflection of the internal struggle experienced by a 19-year-old soldier, who became an amputee in Erich Maria Remarque's work "Im Westen nichts Neues" (9).

Major amputation rates as high as 70% have been reported (10,11). This rate was 26.7% in the present study (Table 1). Trophic changes and wounds were present in the lower extremities of 13 patients (86.7%) and the upper extremities of two patients (13.3%). 73% of the patients were diagnosed with Buerger's disease within 5 years.

Because the disorder primarily affects distal small arteries, reconstructive surgery is rarely possible or successful. When vessel reconstruction and sympathectomy is insufficient and/or unsuccessful in patients with TAO, rest pain and trophic lesions occur as notable problems. Currently, there is no medical treatment option generally considered effective in TAO. Drugs with different mechanisms of action have been tried in recent years, and among them, the importance of prostanoids such as PGE1 and PGI2 has been studied and discussed (10-12). Iloprost treatment is reported to provide favourable effects on trophic lesion healing, relief of rest pain, decrease amputation rates, and reduce overall mortality. These favourable effects are associated with the increased microcirculation induced by iloprost. Furthermore, iloprost provides a protective effect on endothelial cells by decreasing the production of adhesion molecules and coagulation end-products. The therapeutic potential of PGI2 has been investigated in several conditions under the scope of peripheral arterial diseases (such as atherosclerotic obliterative disease, diabetic angiopathy, TAO of inflammatory/immunological origin, or Raynaud's phenomenon) starting from the demonstration of its robust effects on platelets and vascular wall. However, the use of PGI2 remains limited due to its chemical instability. The main problem regarding the use of PGI2 is the short half-life of the drug. Clinical trials have focused on a more stable PGI2 analogue. Using, a PGI2 analogue showing the aforementioned properties, is used in treatment protocols for 21 and 28 days. Several centres in Germany and France report favourable effects on lesion occurrence and amputation rates in patients with TAO, diabetes mellitus, and obstructive arterial disease, as well as in patients with disease-related rest pain, ulcerations, and gangrene lesions and in patients at the point of amputation (13,14). The findings of the present study are consistent with the literature.

Despite the ongoing advances in lumen enlargement methods and bypass surgeries, which have been used for decades in peripheral arterial diseases, these interventions are still associated with high rates of failure. The PGI2-like iloprost has been comprehensively studied in patients with critical leg ischaemia, and the results of the studies have shown a possible reduction in amputation rates with this drug (15,16). Although the present study does not reflect a study with grafts, the intra-graft iloprost injections administered at the end of peripheral arterial bypass intervention in patients with peripheral arterial disease have been shown to increase continuous

blood flow in femorodistal vascular grafts. They show favourable effects on bypass outcomes by reducing distal vascular resistance, providing endothelial protection, and regulating microcirculation at the capillary level (14-17). Amputation rates are higher with aspirin therapy, compared to iloprost therapy. Furthermore, intravenous iloprost is significantly more effective in reducing rest pain and promoting trophic lesion healing in patients with TAO compared to low dose oral aspirin (14-18). The present study also demonstrates improved rest pain and wound healing with iloprost treatment. Clinical success rates as high as 96% have been reported following iloprost therapy (19). Higher response to iloprost therapy (improvement in rest pain and ulcerations) has been reported with the treatment duration of 4 weeks (28 days) than with 2 weeks (14 days) or 3 weeks (21 days) (17-22). The treatment duration selected to evaluate the therapeutic efficacy, of iloprost in the present study was 28 days, and the findings are consistent with the literature.

Iloprost has been shown to provide beneficial effects compared to placebo in patients with ulcers or gangrene. The therapeutic effects are maintained up to 6 months following completion of therapy and result in lower amputation rates. In addition to improving clinical symptoms, several controlled studies have shown the favourable effects of iloprost on amputation rates and mortality (20-22). In the present study, patients exhibited significant improvement in terms of clinical presentation, and none of the patients underwent amputation following the treatment. Iloprost treatment was used for 14-21 days in a multi-centre study in patients undergoing below-knee amputation. The wounds healed in 59% of these patients without requiring amputation at upper levels. Furthermore, the probability of recovery has been reported to increase by twofold in patients previously managed with revascularization via surgical or radiological methods (16-23). This outcome is associated with the ability of iloprost to prevent platelet aggregation, induce vasodilation, and fibrinolysis, prevent leukocyte activation through its effects at the microcirculatory level (24). Iloprost also provides a protective effect on endothelial cells by decreasing the production of adhesion molecules and coagulation end-products (25,26) and shows therapeutic effects by regulating microcirculation through normalisation of the disrupted mechanisms without changing the total blood flow in extremities (27).

According to the studies on iloprost, the possible side effects which may occur in the beginning of treatment include headache, flushing, nausea, and vomiting (28). The side effects of iloprost are commonly associated with its vasodilator effect. These side effects can be managed by decreasing infusion rate or discontinuing treatment for short periods in the majority of the cases. The mild side effects do not require dose reduction. None of the patients included in the present study experienced severe side effects requiring discontinuation of treatment. According to the comments of the TASC study group on studies using iloprost therapy in patients with peripheral arterial disease, iloprost is the drug that has been investigated in randomised controlled studies with the largest number of patients in advanced, critical extremity ischaemia. There is no available method to predict which patients would respond to treatment; however, the relative safety of iloprost is considered potentially beneficial in all patients until early amputation is inevitable (29-31).

In the present study, the pre- and post-treatment assessment of the effects of iloprost therapy using Tc-99m pyrophosphate showed a statistically significant difference in post-treatment perfusion rates in 13 (87%) patients ($p<0.05$), and no significant difference in 2 (13%) patients (Table 2 and Table 3). This outcome indicates that iloprost improves perfusion in regions with previously disrupted blood flow at distal parts of the obstruction, and this can be assessed using scintigraphic methods. Currently, intravenous prostaglandins or prostacyclin analogues seem the most widely used medications in patients with Buerger's disease with critical limb ischemia. We believe that it may also be used as an adjunctive follow-up method to evaluate the treatment outcome in similar peripheral arterial disorders. The findings of the present study are consistent with the results of similar studies in the literature (32,33).

Although pre-surgery signs and symptoms of the disease reoccurred in the short or long term in patients undergoing sympathectomy among the patients included in this clinical study, the durable reduction or improvement of symptoms observed during the post-treatment period compared to the pre-treatment period, led to the question whether iloprost therapy may be an alternative treatment option to sympathectomy. Sympathectomy is an invasive intervention, while iloprost therapy is a non-invasive method.

CONCLUSION

Iloprost showed favorable clinical efficacy and safety in the fifteen TAO patients included in the present study. We believe that, to gain general acceptance in relevant indications, it may be used as a beneficial treatment option to gain general acceptance in relevant indications, and may also for the scintigraphic assessment of treatment efficacy. In our opinion, these results require further studies to ethically support using different treatment approaches in larger patient populations.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Atatürk University (approval number: 1, date: 11.02.2004).

Informed Consent: Informed consent were obtained from patients and relatives/caregivers prior to the start of the study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: M.A.K., Concept: M.A.K., Design: M.A.K., Data Collection or Processing: M.A.K., Ş.K., Analysis or Interpretation: M.A.K., Ş.K., Literature Search: M.A.K., Ş.K., Writing: M.A.K., Ş.K.

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REFERENCES

1. Makita S, Nakamura M, Murakami H, Komoda K, Kawazoe K, Hiramori K. Impaired endothelium-dependent vasorelaxation in peripheral vasculature of patients with thromboangiitis obliterans (Buerger's disease). Circulation. 1996; 94: 211-5.
2. Olin JW. Thromboangiitis Obliterans (Buerger's Disease). In: Coffman JD, Eberhardt RT, eds. Peripheral Arterial Disease. Contemporary Cardiology. Totowa, NJ: Humana Press; 2003:303–318. Available from: https://doi.org/10.1007/978-1-59259-331-6_18
3. Siemionow M, Arslan E. Ischemia/reperfusion injury: a review in relation to free tissue transfers. Microsurgery. 2004; 24: 468-75.
4. Eltzschig HK, Collard CD. Vascular ischaemia and reperfusion injury. Br Med Bull. 2005; 70: 71-86.
5. Buerger L. Thoromboangiitis obliterans a study of the vascular lesions leading to presenile spontaneous gangrene. Am J Med Sci. 1908; 136: 567-80.
6. Linder DO. Die Geschichte Buergerschen der Krankheit [dissertation]. Lausanne: Universität Lausanne, Imprimerie C. Risold & Fils; 1938. p. 8. Available from: chrome-Extension://efaidnbmnnnibpcajpcglclefindmkaj/https://ia801203.us.archive.org/11/items/b3063118x/b3063118x.pdf
7. Olin JW. Thoromboangiitis obliterans. Curr Opin Rheumatol. 1994; 6: 44-9.
8. Cacione DG, Macedo CR, do Carmo Novaes F, Baptista-Silva JC. Pharmacological treatment for Buerger's disease. Cochrane Database Syst Rev. 2020; 5: 11033.
9. Remarque, Erich Maria. Im Westen nichts Neues. 1. Auflage. Köln: Kiepenheuer & Witsch Verlag. 2014. https://www.kiwi-verlag.de/buch/e-m-remarque-im-westen-nichts-neues-9783462046335.
10. Spittell JA. Tromboangiitis obliterans: an autoimmune disorder? N Engl Med. 1983; 308: 1157-58.
11. Lie JT. Thromboangiitis obliterans (Buerger's disease) in an elderly man after cessation of cigarette smoking- a case report. Angiology. 1987; 38; 864-7.
12. Carslon LA, Eriksson I. Femoral -artery infusion of prostaglandin E1 in severe peripheral vascular disease. Lancet. 1973; 1: 155-6.
13. Szczeklik A, Gryglewski RJ, Nizankowski R, Szczeklik J, Skawinski S, Gluszko P. Prostacyclin in the therapy of peripheral arterial disease. Adv Prostaglandin Thromboxane Res. 1980; 687-9.
14. Sakaguchi S, Kusaba A, Mishima Y, Kamiya K, Nishimura A, Furukawa K, et al. A multi-clinical double-blind study with PGE1 (cyclodextrin clathrate) in patients with ischemic ulcer of the extremities. Vasa. 1978; 7: 263-6.
15. Bell PR. Are distal vascular procedures worthwhile? Br J Surg. 1985; 72: 335.
16. Collaborative overview of randomised trials of antiplatelet therapy--II: Maintenance of vascular graft or arterial patency by antiplatelet therapy. Antiplatelet Trialists' Collaboration. BMJ. 1994; 308: 159-68.
17. Loosemore TM, Chalmers TC, Dormany JA. A meta- analysis of randomized placebo control trials in Fontaine III and IV peripheral occlusive arterial disease. Int Angiol. 1994; 13: 133-42.
18. Eichhorn J, Sima D, Llndschau C, Turowski A, Schmidt H, Schneider W, et al. Thromboangiitis obliterans: diagnose und therapie im licht neuer immunologischer Befunde. Schweiz Med Woschensohr 1979; 109: 537-43.
19. Fiessinger JN, Schafer M. Trial of iloprost versus aspirin treatment for critical limb ischaemia of thromboangiitis obliterans. The TAO Study. Lancet. 1990; 335: 555-7.
20. Nogren L, Alwark A, Angqvist KA, Hedberg B, Berqvist D, Takolander R, et al. A stable prostacyclin analogue (iloprost) in the treatment of ischaemıc ulcers of the lower limb. A Scandinavian -Polish placebo -controlled, randomised multicentre study. Eur J Vasc Surg. 1990; 4: 463-7.
21. Diehm C, Abri O, Baitsch G, Bechara G, Beck K, Breddin HK, et al. Iloprost, ein stabiles Prostacyclinderivat, bei arterieller Verschlusskrankheit im Stadium IV. Dtsch Med Wochenschr. 1989; 114: 783-8.
22. Treatment of limb threatening ischaemia with intravenous iloprost: a randomised double-blind placebo controlled study. U.K. Severe Limb Ischaemia Study Group. Eur J Vasc Surg. 1991; 5: 511-6.
23. Dormandy JA. Clinical experience with iloprost in the treatment of critical leg ischaemia. In: Rubanyi GM, editor. Cardiovascular significance of endothelium-derived vasoactive factors. New York: Futura Publishing; 1991. p. 335-47. Available from: https://openlibrary.org/works/OL19206850W/Cardiovascular_significance_of_endothelium-derived_vasoactive_factors?edition=cardiovascularsi0000unse
24. Grant SM, Goa KL. Iloprost. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peripheral vasculer disease, myocardial ischemia and extracorporeal circulation procedures. Drugs. 1992; 43: 889-924.
25. Dormandy J, Belcher G, Broos P, Eikelboom B, Laszlo G, Konrad P, et al. Prospective study of 713 below- knee amputations for ischaemia and the effect of a prostacyclin analogue on healing. Br J Surg. 1994; 81: 33-7.
26. Beischer W, Dembski JC, Gruss JD, Hofgartner F, Horsch A, Horsch S, et al. Low - dose iloprost infusions compared to the standard dose in patients with peripheral arterial occlusive disease Fontaine IV. DAWİD Study Group. Vasa. 1998; 27: 15-9.
27. Cronenwett JL, Zelenock GB, Whitehouse WM Jr, Lindenauer SM, Graham LM, Stanley JC. Prostacyclin treatment of ischemic ulcers and rest pain in unreconstructable peripheral arterial occlusive disease. Surgery. 1986; 100: 369-75.
28. Mazzone, Faggioli P, Cusa C, Stefanin C, Rondena M, Morelli B. Effects of iloprost on adhesion molecules and F 1+2 in peripheral ischemia. Eur J Clin Invet. 2002; 32: 882-8.
29. Olasson AG, Thyresson N. Healing of ischaemic ulcers by intravenous prostaglandin E1 in a woman with thromboangiitis obliterans. Acta Derm Venereol. 1978; 58: 467-72.
30. Bliss BP, Wilkins DC, Campbell WB, Charlesworth D, Clarke RJ, Dandona P, et al. Treatment of limb threatening ischaemia with intravenous Iloprost: a randomised double – blind placebo controlled study. Eur J Vasc Surg. 1991; 5: 511-6.
31. Watson HR, Smith FC, Shearman CP, Hildebrand M. Pharmacokinetics and pharmacodynamics of intra-gaft iloprost in femorodistal bypass surgery. Prostaglandins Leukot Essent Fatty Acids. 1997; 56: 389-93.
32. Bozkurt AK, Cengiz K, Arslan C, Mine DY, Oner S, Deniz DB, et al. A stable prostacyclin analogue (iloprost) in the treatment of Buerger's disease: a prospective analysis of 150 patients. Ann Thorac Cardiovasc Surg. 2013; 19: 120-5.
33. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). J Vasc Surg. 2000; 31: S1-S296.