Efficacy of a Novel Method of Intravenous Infusion of the Prostaglandin Analogue Iloprost for the Treatment of Lower-Limb Critical Ischemia: An Open-Label, Nonrandomized Study in Two Cohorts

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ABSTRACT

Background: Patients with advanced peripheral atherosclerotic occlusive disease who are no longer candidates for either surgical or intravascular treatment or who have undergone unsuccessful surgical revascularization may be treated with IV prostanoids.

Objective: The aim of this study was to assess the efficacy, tolerability, compliance, and cost of a new system of prostanoid administration that provides a constant plasma concentration of iloprost and maintains the efficacy of the drug while reducing the risk for adverse effects (AEs) and the overall cost of treatment compared with the actually adopted infusion system.

Methods: This open-label, nonrandomized study was conducted at the University Hospital of Catania (Catania, Italy). Patients with chronic critical ischemia who were not candidates for surgical revascularization were observed. The study population was divided into 2 groups: patients in group A were treated with a continuous 6-hour IV infusion of iloprost 0.5 to 2.0 ng/kg-min once daily for at least 14 consecutive days, and patients in group B were treated with a 20-day iloprost continuous IV infusion at a mean dosage of 25 µg/d by means of a portable elastomeric infusion system. Every 5 days the patient was admitted to the day-hospital setting to replenish the drug. Primary end points were rates of major and minor amputations and death; secondary end points were complete relief or a marked reduction of pain at rest, as reflected by discontinuation of analgesic therapy and by a decrease in the patients' complaints of pain, as well as by the satisfactory healing of ulcerations. Tolerability, compliance, and cost also were assessed.

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Results: Fifty-six patients (34 men, 22 women; mean [SD] age, 67 [11] years) entered the study. Group A comprised 25 patients; group B, 31 patients. The rate of major amputation in patients at Fontaine stage IV was higher in group A (33.3%) compared with group B (20.0%). The death rate was higher in group A (4.0%) than in group B (3.2%). Pain at rest completely subsided in 37.5% of patients in group A and 68.8% of patients in group B. Trophic lesions healed in 44.4% and 73.3% of patients in groups A and B, respectively. In group A, 40.0% of patients experienced AEs (ie, hyperemia, headache, flushing) that required a reduction in dose. In group B, 6.5% of patients had hyperemia at the injection site that required a reduction in dose. Total cost was €8745.20 in group A, with a mean hospital stay of 20 days; total cost in group B was €1995.60, with a mean hospital stay of 6 days. Overall, patients' quality of life, assessed as the ability to resume their normal social activities, improved.

Conclusions: In this study of patients with chronic lower-limb critical ischemia, due to the consistent blood level achieved with iloprost, 20-day iloprost continuous IV infusion at a mean dosage of 25 µg/d administered by means of a portable elastomeric infusion system was shown to be similarly or more effective than the methods used by the most important European trials (ie, iloprost 0.5–2.0 ng/kg.min once daily for at least 14 consecutive days). Furthermore, the patients were more compliant and the cost of treatment and the length of hospitalization were reduced compared with iloprost 0.5 to 2.0 ng/kg.min once daily for at least 14 consecutive days. (*Curr Ther Res Clin Exp.* 2004;65:255–265) Copyright © 2004 Excerpta Medica, Inc.

Key words: peripheral atherosclerotic occlusive disease, iloprost, critical ischemia, pain at rest, Fontaine classification, portable elastomeric infusion system.

INTRODUCTION

Peripheral atherosclerotic occlusive disease (PAOD) is associated with macrocirculatory and microcirculatory damage leading to a progressive decrease in tissue perfusion. The resulting ischemia is classified as 2 chronic types—functional (intermittent claudication) and critical (signs and symptoms include pain at rest, detectable in 1.5% and 5.0% of patients aged ≤50 years and >50 years, respectively,¹ and trophic lesions [ie, ulceration and gangrene]).

The classification *critical ischemia of the lower limbs* is based on the Fontaine classification²; however, the TransAtlantic Inter-Society Consensus³ has redefined *critical ischemia* as the presence of recurrent pain at rest of an ischemic nature (Fontaine stage III) or, alternatively, as the presence of an ulcerative or gangrenous lesion (Fontaine stage IV) associated with a systolic blood pressure (SBP) ≤70 mm Hg at the knee and ≤50 mm Hg at the foot.

Treatment of lower-limb critical ischemia (Fontaine stages III and IV) is challenging because the condition relentlessly evolves toward a need for major amputation if left untreated.

Currently, the “gold standard” of treatment for PAOD at Fontaine stages III and IV is a surgical and/or intravascular approach. However, despite treatment, ~45% of patients with severe PAOD undergo a major amputation or die within 1 year of the onset of pain at rest, ulceration, and/or gangrene.⁴ In these patients, although the underlying pathology is occlusion of a major artery, the pain at rest and trophic lesions are the results of a microcirculatory perfusion deficit.

Based on such a pathophysiologic presupposition, patients with advanced PAOD who are no longer candidates for either surgical or intravascular treatment or who have undergone unsuccessful surgical revascularization may be treated with IV prostanoids.^{5,6} Prostanoids have been shown to work by inhibiting platelet adhesion and activation, by dilating arterioles and venules, and by inhibiting leukocyte adhesion and migration after endothelial injury.^{7–9}

The chemical instability of prostaglandin I₂ (PGI₂) severely limited the therapeutic use of this prostanoid. In 1981, the introduction of a PGI₂-stable analogue (iloprost¹⁰) that retains the pharmacologic properties of the active molecule provided a potential new treatment option for lower-limb critical ischemia.

Several prospective, randomized studies^{11–15} in 1990–1991 attempted to verify the effectiveness of IV iloprost. These trials recommend a dose ranging from 0.5 to 2.0 ng/kg·min administered via a 6-hour IV drip daily for 2 to 4 weeks. They showed a higher rate of improvement in ischemic ulcers and lower incidences of major amputations and death,^{11–14} as well as complete relief of pain at rest,^{15–17} not only in patients with lower limb atherosclerotic arteriopathies but also in those with thromboangiitis obliterans, compared with placebo.¹⁸

In subsequent years, however, the route and methods of administration, the need for prolonged hospitalization, and the high cost of IV iloprost limited the study of its efficacy, while further studies of treatments that were simpler to administer were emphasized. In 2000, a review of 2 multicenter trials of oral iloprost given to patients with lower-limb critical ischemia reported contrasting results and lesser overall effectiveness than that seen with IV iloprost.⁶

The Dawid Study Group¹⁹ attempted to identify an optimum dose that would warrant good efficacy and tolerability. Four different dosing schedules, ranging from 25 to 100 µg/d, were investigated. No increase in the efficacy of iloprost was found in conjunction with an increment in dosing; however, a relative dose-dependent increase in adverse effects (AEs; ie, headache, nausea, and flushing) was observed.

We developed a novel system of drug administration by continuous IV drip with the aim of providing a constant therapeutic plasma iloprost concentration and concomitantly retaining the drug's efficacy, as well as reducing the incidence of AEs and the overall cost of treatment.

This article describes a system for the administration of iloprost at a mean dosage of 25 µg/d via continuous IV drip for 20 days by means of a portable elastomeric infusion system. We assessed the reduction in, or the complete relief of, pain at rest, the improvement in trophic lesions, and the rates of major

and minor amputations and death. Finally, we compared our system with a conventional infusion protocol.

PATIENTS AND METHODS

Study Design

The retrospective period for this open-label, nonrandomized study began on January 1, 1996, and ended on May 30, 2000. The ethics committee at the study site (Department of Surgery, Transplantation and Advanced Technologies, University Hospital of Catania, Catania, Italy) approved the study.

Patients

Consecutive patients aged 33 to 81 with chronic lower-limb critical ischemia who were not candidates for surgical revascularization were enrolled. Surgical or intravascular treatment was not an option for these patients, either because the arterial system appeared inadequate or because they were in generally poor health. To be eligible for the study, patients also had to have either trophic skin lesions (ulcerations or gangrene) or pain at rest due to severe occlusive arteriopathy of the lower limbs; the pain at rest had to require the administration of analgesics and had to be present for at least 2 weeks before enrollment. Finally, only patients whose underlying atherosclerotic disease had produced an SBP ≤ 70 mm Hg at the ankle and ≤ 50 mm Hg at the toes as measured using Doppler ultrasonography were included in the study. Pregnant, possibly pregnant, or breastfeeding women were excluded from the study.

Exclusion criteria were acute onset or rapid deterioration of ischemia; surgical revascularization within the previous 2 weeks; extensive cellulitis; ongoing treatment with antiaggregant medications, except acetylsalicylic acid; and the need for a major amputation within the next 2 weeks due to gangrene.⁶ Patients with thromboangiitis obliterans also were excluded from the study.

Written informed consent was obtained from all enrolled patients, and each patient included in the study underwent a complete diagnostic examination (color Doppler ultrasonography and aortography for imaging the lower limbs).

Methods

Treatment

The study population was divided into 2 groups. Patients in group A were treated during the 2-year period of January 1, 1996, to December 31, 1997, with continuous 6-hour IV infusion of iloprost* at a dosage of 0.5 to 2.0 ng/kg-min once daily for at least 14 consecutive days. The dosage was individually adjusted according to each patient's tolerance. Patients in group B were treated

*Trademark: Endoprost® (Italfarmaco S.p.A., Milan, Italy).

during the 2-year period of January 1, 1998, to May 2000 with continuous 20-day IV infusion of iloprost at a mean dosage of 25 µg/d by means of a portable elastomeric infusion system. The investigators administered the study drugs. Every 5 days, patients were admitted to the day-hospital setting to replenish the drug and to monitor its effects. If a patient experienced AEs (eg, flushing, hyperemia at the infusion site, cardiac palpitations, headache), the dosage was reduced. Patients underwent color Doppler ultrasonography at 3, 6, and 9 months after the start of treatment and every 6 months thereafter until treatment discontinuation. Treatment was discontinued when a patient, despite the dosage adjustment, manifested a persistent (≥ 1 week) intolerance to iloprost.

Efficacy and Tolerability Assessments

The investigators established the outcome variables. Primary end points were efficacy and tolerability of the therapy at 24-month follow-up, including rates of major and minor amputations and death. At 24-month follow-up, secondary end points were complete relief or a marked reduction of pain at rest, as reflected by discontinuation of analgesic therapy and by a decrease in the patients' complaints of pain, as well as by the satisfactory healing of trophic lesions. Also, each patient's comfort was assessed.

Compliance Assessment

Compliance was assessed based on patients' quality of life and their capacity to resume their normal social activities (eg, work, sexual activities).

Cost Assessment

The overall cost of each treatment was determined by adding the costs of the study drug, the elastomeric pump, and the total cost of hospitalization.

We assessed direct medical costs, including physicians' office visits, diagnostic tests, medications, and hospitalizations. We did not include lost wages because we assumed that patients would not be employed. The medical costs of the diagnostic tests performed before treatment, including color Doppler ultrasonography and aortography, were assumed to be similar between the 2 groups and were not calculated.

The cost for each treatment was assessed as the total expenses for iloprost during a 20-day treatment period (unit cost of the ampule containing iloprost 0.050 mg/0.5 mL = €159.07 [the retail price provided by the manufacturer]) and for a regular 20-day hospitalization period for patients in group A and for a hospitalization for the first administration of iloprost plus the days of admission to day-hospital for patients in group B. Cost data were calculated on a per-patient basis.

RESULTS

The baseline demographic and clinical characteristics of the 56 patients (34 men, 22 women; mean [SD] age, 67 [11] years) included in the study are

shown in **Table I**. Group A comprised 25 patients; group B, 31 patients. Patient demographic characteristics were generally similar in the 2 groups, although patients in group B had a mean age 5 years higher than patients in group A, and patients in group B had higher rates of smoking, type 1 diabetes mellitus, chronic renal insufficiency, stroke, and coronary artery disease. In group A, 3 patients (12.0%) at Fontaine stage IV had had surgical revascularization for limb salvage followed by bypass occlusion. In group B, 10 patients (32.3%) had undergone an unsuccessful revascularization procedure for limb salvage, with persistence of chronic critical ischemia. One patient (3.2%) had previously undergone amputation of 2 toes, which was incompletely healed at the time of the study. In the remaining 21 patients (67.7%), an indication for surgical or intravascular treatment was not expressed, either because the arterial system appeared inadequate or because the general condition of the patient was poor.

Efficacy and Tolerability

Table II shows the results of treatment at 24-month follow-up. The effectiveness of IV iloprost drip was evidenced by the rates of major amputation, death,

Table I. Baseline demographic and clinical characteristics of the study patients.*

Characteristic	Group A (n = 25) [†]	Group B (n = 31) [‡]	All Patients (N = 56)
Age, y			
Mean (SD)	65	70	67 (11)
Range	57–79	33–81	33–81
Sex, no. (%)			
Men	15 (60.0)	19 (61.3)	34 (60.7)
Women	10 (40.0)	12 (38.7)	22 (39.3)
Clinical stage of chronic lower-limb critical ischemia, no. (%) [§]			
III	16 (64.0)	16 (51.6)	32 (57.1)
IV	9 (36.0)	15 (48.4)	24 (42.9)
Risk factors, no. (%)			
Arterial hypertension	10 (40.0)	10 (32.3)	20 (35.7)
Smoking (>15 cigarettes/d for >15 y)	9 (36.0)	15 (48.4)	24 (42.9)
Type 1 diabetes mellitus	8 (32.0)	17 (54.8)	25 (44.6)
Chronic renal insufficiency	1 (4.0)	7 (22.6)	8 (14.3)
History of stroke	0 (0.0)	4 (12.9)	4 (7.1)
Coronary artery disease	0 (0.0)	3 (9.7)	3 (5.4)

*No significant between-group differences were found.

[†]Group A received continuous 6-hour IV infusion of iloprost at a dosage of 0.5 to 2.0 ng/kg·min once daily for at least 14 consecutive days. (The dosage was individually adjusted according to each patient's tolerance.)

[‡]Group B received continuous 20-day IV infusion of iloprost at a mean dosage of 25 µg daily by means of a portable elastomeric infusion system.

[§]Fontaine classification.²

Table II. Outcomes and costs of treatment at 24-month follow up (N = 56).

Parameter	Group A (n = 25)*	Group B (n = 31) [†]
Outcome, no. (%) of patients		
Major amputations		
Patients with stage III disease [‡]	0/16 (0.0)	0/25 (0.0)
Patients with stage IV disease [‡]	3/9 (33.3)	3/15 (20.0)
Death		
Patients with stage III disease [‡]	0/25 (0.0)	0/31 (0.0)
Patients with stage IV disease [‡]	1/25 (4.0)	1/31 (3.2)
Complete pain relief [§]	6/16 (37.5)	11/16 (68.8)
Complete ulcer healing	4/9 (44.4)	11/15 (73.3)
Hospitalization, d		
Mean	20	6
Range	18–25	4–10
Cost of treatment (20 days), €		
Drug	6362.80	1272.60
Hospitalization	2382.40	723.00
Total	8745.20	1995.60

*Group A received continuous 6-hour IV infusion of iloprost at a dosage of 0.5 to 2.0 ng/kg·min once daily for at least 14 consecutive days. (The dosage was individually adjusted according to each patient's tolerance.)

[†]Group B received continuous 20-day IV infusion of iloprost at a mean dosage of 25 µg daily by means of a portable elastomeric infusion system.

[‡]Fontaine classification.²

[§]No. of patients pain free at rest, receiving no continuous analgesic therapy, living, and without major amputation.

resolution of pain at rest, and healing of trophic lesions observed in the patients in group B compared with those in group A. The rate of major amputation in patients at Fontaine stage IV was higher in group A (33.3%) than in group B (20.0%). A similar therapeutic advantage was observed in the decrease in death rate, which was higher in group A (4.0%) compared with group B (3.2%). Pain at rest completely subsided in 37.5% of patients in group A compared with 68.8% in group B.

At 4 months after the completion of treatment, 4 patients in group B had a recurrence of pain at rest. These patients received a repeat cycle of treatment and the pain again subsided. Trophic lesions healed in 44.4% and 73.3% of patients with PAOD at Fontaine stage IV in group A and group B, respectively. Two patients with large leg ulcerations unsuitable for surgical or intravascular treatment did not respond to the therapy. The disease evolved relentlessly toward the need for a major amputation in both patients.

Analysis of blood chemistry findings did not show significant variations from baseline in any patient.

In group A, 10 patients (40.0%) experienced treatment-related AEs (ie, hyperemia, headache, flushing) that required a reduction in dose. In group B, 2 of 31 patients (6.5%) had hyperemia at the injection site, associated with headache, that required a reduction in dose (**Table III**).

Compliance and Cost of Treatment

Total cost was €8745.20 in group A, with a mean hospital stay of 20 days; total cost in group B was €1995.60, with a mean hospital stay of 6 days (Table II). Overall, patients' quality of life (assessed as the ability to resume their normal social activities if general health conditions permitted) improved.

DISCUSSION

For patients who were unsuitable for surgical revascularization procedures or for whom surgical or intravascular treatment had been unsuccessful, a number of trials^{11–15} have demonstrated the effectiveness of treating PAOD at Fontaine stages III and IV by administering iloprost, a stable prostacyclin analogue.

Patients with PAOD and those with thromboangiitis obliterans experienced both relief of pain at rest and improvement in ulcerative lesions.^{11–15} A review by Loosemore et al²⁰ showed that treatment with iloprost resulted in relief of pain at rest, healing of ischemic ulcerations, and a statistically significant reduction in the likelihood of either a major amputation or death during the treatment period and in the subsequent 3 to 6 months.

The stability shown by iloprost in the elastomeric pump²¹ allowed us to develop our system of continuous IV infusion. In all likelihood, the efficacy of

Table III. No. (%) of patients experiencing ≥ 1 treatment-related adverse effect and/or dose change (N = 56).*

Parameter	Group A (n = 25) [†]	Group B (n = 31) [‡]
Adverse Effect		
Headache	8 (32.0)	2 (6.5)
Flushing	6 (24.0)	0 (0.0)
Hyperemia at the injection site	5 (20.0)	2 (6.5) [§]
Dose change	10 (40.0)	2 (6.5)

*No deaths related to treatment occurred.

[†]Group A received continuous 6-hour IV infusion of iloprost at a dosage of 0.5 to 2.0 ng/kg·min once daily for at least 14 consecutive days. (The dosage was individually adjusted according to each patient's tolerance.)

[‡]Group B received continuous 20-day IV infusion of iloprost at a mean dosage of 25 µg daily by means of a portable elastomeric infusion system.

[§]Dose change required for these patients.

the system is linked to the constant blood levels achieved by administering the drug via IV drip. Because the platelet receptors with high affinity for PGI₂ do not become saturated,²¹ the drug has consistent and prolonged action throughout the entire 24-hour period.

The results obtained may be considered as positive. All of the patients treated by the novel infusion system experienced mitigation or a prompt relief of pain at rest, and in 69.0% of patients in group B, the analgesic medications were discontinued, compared with 37.5% in group A. Patient compliance was high, allowing the administration of a repeated cycle of treatment.

In our study, the rate of major amputations (20.0%) in patients in group B was lower than the major amputation rate (25%–55%) reported in most important European trials, which used 0.5 to 2.0 ng/kg·min once daily for at least 14 consecutive days.²⁰ Because our data are limited by the small number of patients, we cannot make definitive statements about the effectiveness of the therapy we were using. However, the administration of iloprost by continuous IV infusion could aid in reducing the major amputation rate in patients with PAOD at Fontaine stages III and IV, as confirmed by other authors.²¹

The fact that only 1 patient in group B died might confirm the observation that IV iloprost may prolong the survival of patients with PAOD at Fontaine stages III and IV,²⁰ with 91.0% of the patients retaining their limbs 1 year after the treatment.²⁰

The patients in group B had a higher mean age and greater incidences of risk factors than the patients in group A; nonetheless, the treatment was well tolerated by all patients. All patients were able to resume their regular social activities, if general health conditions permitted. Only 2 patients complained of a hyperemic reaction at the site of drug injection associated with headache and required a reduction in drug dose.

Our method of administration may be applied on a large scale because of the following characteristics: (1) it can be easily managed by the medical and paramedical staff; (2) patient compliance was greater than that manifested toward traditional treatment methods; and (3) the cost of treatment and the duration of hospitalization decreased.

Additional trials enrolling larger study populations are necessary to verify the long-term effectiveness of this method of continuous IV infusion.

CONCLUSIONS

In this study of patients with chronic lower-limb critical ischemia, due to the consistent plasma drug concentration achieved with iloprost, 20-day iloprost continuous IV infusion at a mean dosage of 25 µg/d administered by means of a portable elastomeric infusion system was shown to be similarly or more effective than the methods used by European trials (ie, iloprost 0.5 to 2.0 ng/kg·min once daily for at least 14 consecutive days). Furthermore, the patients were more compliant and the cost of treatment and the length of hospi-

talization were reduced compared with the method of infusion used in the European trials.

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