

Efficacy, safety and feasibility of intravenous iloprost in the domiciliary treatment of patients with ischemic disease of the lower limbs

R. POLIGNANO¹, C. BAGGIORE¹, F. FALCIANI², U. RESTELLI³, N. TROISI⁴, S. MICHELAGNOLI⁴, G. PANIGADA⁵, S. TATINI¹, A. FARINA⁶, G. LANDINI¹

¹Medical Department, USL Centro Toscana, Florence, Italy

²Skin Lesions Observatory, USL Centro Toscana, Florence, Italy

³School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; Centre for Research on Health Economics, Social and Health Care Management, Carlo Cattaneo University – LIUC, Castellanza (Varese), Italy

⁴Department of Surgery, Vascular and Endovascular Surgery Unit, San Giovanni di Dio Hospital, Florence, Italy

⁵Internal Medicine Unit, Santi Cosma e Damiano Hospital, Pescia, Italy

⁶Medical Affairs Department, Italfarmaco S.p.A., Cinisello Balsamo, Milan, Italy

Abstract. – OBJECTIVE: Intravenous iloprost is an important option in the treatment of ischemic disease of the lower limbs; however, the administration of therapy is frequently compromised because of the need for long cycles of infusion in a hospital setting. The aim of the study is to evaluate the efficacy, safety, feasibility, and the economic impact of infusion therapy in the outpatient setting.

PATIENTS AND METHODS: Twenty-four consecutive patients were treated with iloprost at their homes where they were administered a slow rate of infusion for 24 hours a day, during 9.9 ± 2.3 days, with a portable syringe pump (Infonde®).

RESULTS: The clinical condition of patients evaluated with the modified SVS/ISCVS scale significantly improved after treatment ($+1.29 \pm 1.04$ points vs. baseline, $p < 0.001$). The drug was well tolerated; neither significant adverse events associated with medication nor problems related to venous access were recorded at home. Ninety-six percent of patients successfully completed the entire treatment cycle, and the evaluation questionnaire showed a high acceptance of the therapy. From the perspective of the hospital authority, lower direct medical costs were estimated for the domiciliary infusion process compared with the inpatient infusion setting.

CONCLUSIONS: Treatment with iloprost in the outpatient setting is effective, safe, feasible, and more acceptable to patients than infusion at the hospital. In addition, it has a favorable economic and organizational impact on the medical ward.

Key Words:

Critical limb ischemia, Iloprost, Home treatment, Quality of life.

Introduction

The term ischemic disease of the lower limbs defines a wide number of pathological conditions of both large and small peripheral arteries and veins, including peripheral artery disease (PAD), diabetic microangiopathy, thromboangiitis obliterans or Buerger's disease, and other inflammatory vasculitis¹. Although these conditions are characterized by different pathogenetic mechanisms, similar clinical manifestations may occur due to the common mismatch between the supply of oxygen and nutrients and the metabolic demand of tissues, with microcirculatory defects including endothelial dysfunction, altered hemorheology, white blood cell activation and inflammation, and maldistribution of the cutaneous microcirculation¹. Symptoms may be more or less severe, depending on the seriousness and location of the disease, and may range from intermittent claudication during exercise to the most serious manifestation of critical limb ischemia (CLI). CLI represents a major healthcare issue, since it is characterized by a poor long-term prognosis, a high occurrence of major cardiovascular events and a high degree of disability because of frequent and severe rest pain, ulcers and amputations of the lower limbs^{1,2}.

The primary goals of the treatment are to improve patient function and quality of life, relieve ischemic pain, heal ischemic ulcers, prevent limb loss, and, possibly, prolong survival². Revascularization could optimally achieve some of these

goals, but the severity of comorbidities, along with the durability of the reconstruction in patients with CLI, demands a risk-benefit analysis to determine the optimal therapy. Some patients who turn to vascular surgeons for surgical or endovascular procedures are poor candidates for such interventions because of medical comorbidities, non-ambulatory status, or poor outflow vessels in the limb³. Thus, medical treatment, including aggressive modification of cardiovascular risk factors, control of pain and infection in the ischemic leg, prevention of progression of systemic atherosclerosis, and restoration of microcirculation, is a crucial option in the management of CLI⁴⁻⁶.

To date, the only pharmacotherapy for CLI recommended by current guidelines in patients unsuitable for revascularization is represented by prostanoids, particularly intravenous iloprost^{1,5,6}. Several randomized studies have shown that iloprost administration has a favorable impact on patient function, pain, ulcer healing, amputation rates, and mortality⁷⁻⁹. Moreover, a pharmacological approach to improve the microcirculation may enhance the results of revascularization^{1,10}.

One of the main issues related to iloprost treatment is the need for prolonged cycles of administration, consisting of many hours per day up to 4 consecutive weeks, in a hospital setting, as indicated by the manufacturer recommendations. This approach is no longer consistent with the current needs of the National Health System (NHS), which increasingly requires the optimization of resources by reducing the number of hospitalizations, health care staff, and budgets. Moreover, many patients show a poor compliance to such treatments, because of the need to stay in the hospital for a long period. Altogether, these factors may limit the access to important treatments for a large number of patients, and, when administered, such treatments are often inadequate from the economic and organizational point of view.

In this paper, we report the clinical and economic results obtained with the home administration of intravenous iloprost in a group of outpatients with peripheral vascular diseases of the lower limbs at the Hospital of Florence, Italy.

Patients and Methods

This was a prospective observational study that included 24 consecutive patients with peripheral vascular diseases (peripheral arterial disease, diabetic microangiopathy, Buerger's disease, and

other vasculitis) for which the treatment with intravenous iloprost was deemed clinically appropriate, at the Hospital of Florence, Italy. The study was conducted in accordance with current ethical standards and with the Declaration of Helsinki. Inclusion criteria involved ability (though reduced) to walk, adequate ability to understand instructions, cooperative family, adequate tolerability to the first infusion of iloprost received in a hospital setting, normal standard blood tests and ECG, informed consent. Patients with severe medical conditions requiring hospitalization were excluded from the study. Patients that matched the inclusion and exclusion criteria were offered the opportunity to continue the treatment at home. Figure 1 describes the complete operative procedure.

Iloprost was administered with a low infusion rate, equal to 0.5 ng/kg/min for 6 hours in a hospital setting on the first day of treatment and at the fixed rate of 2 µg/hour for 24 hours/day the following days, at the patient's home. A low rate of infusion was used to promote the tolerability of the treatment and to administer the whole contents of a vial of medication avoiding any waste of an active ingredient. The length of treatment ranged from 6 to 16 days depending on the clinical conditions of the patients.

Clinical evaluations included the clinical condition of the patient measured by the modified SVS/ISCVS (Society for Vascular Surgery/International Society for Cardiovascular Surgery) scale¹¹, the occurrence of adverse events, the percentage of completion of treatment, and the satisfaction of patients at the end of the treatment period, which lasted 9.9 ± 2.3 days. Patient satisfaction was evaluated by a questionnaire that included three statements to which patients were asked to assign a score ranging from 1 (completely disagree) to 10 (completely agree), and one question. The statements were: "I am in favor of home therapy"; "I consider home therapy safe"; "I can perform my daily tasks easily"; and the question was "If I could choose between treatment at home or in the hospital, which one would I choose?". In case of loss to follow-up (1 patient), the scores were considered as "totally disagree" and "not willing to repeat the treatment at home".

Statistical Analysis

Data were expressed as means \pm standard deviations (SD). The SVS/ISCVS score at follow-up was compared with baseline using a paired samples t-test. Statistical significance was considered at p -values <0.05 .

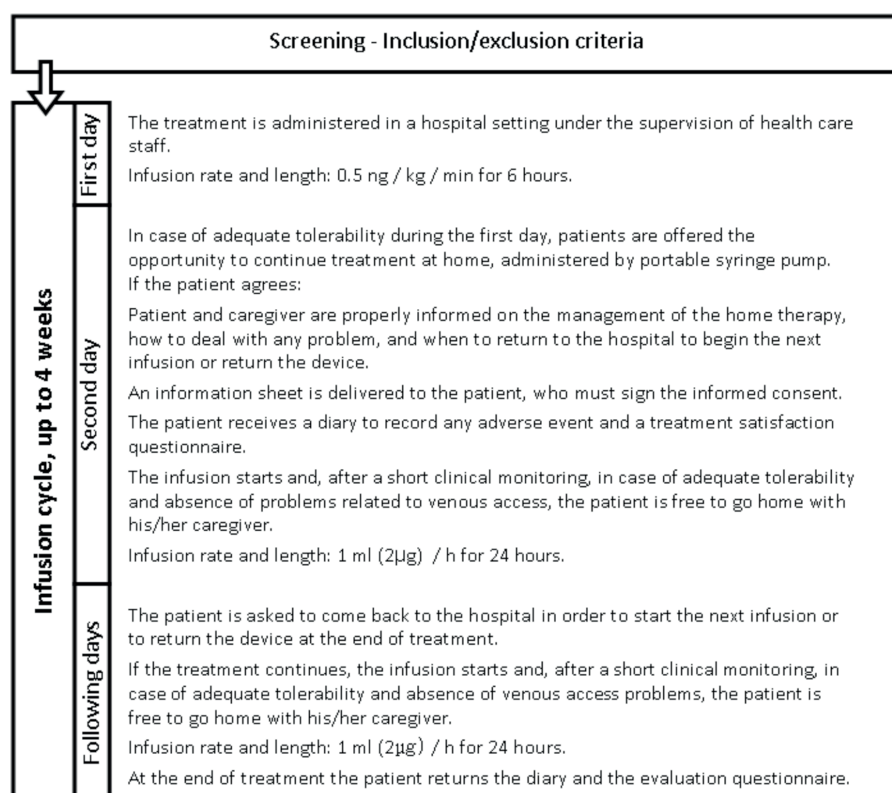


Figure 1. Operative procedure for the domiciliary treatment with intravenous iloprost.

Economic Analysis

To evaluate the economic impact of the management of domiciliary iloprost from the point of view of the hospital authority and the Italian NHS, we investigated the process of infusion in both an outpatient and a domiciliary setting. The process analyses were performed through interviews with 8 key opinion leaders (with a medical background), to assess the phases of the processes and the related consumption of resources of a standard patient without complications.

Portable Syringe Pump Infonde®

Infonde® (Italfarmaco S.p.A., Milan, Italy) is a portable syringe pump with reduced dimensions (84.9 x 49.3 x 32.1 mm) and a weight of 118 g. It is specifically designed for the controlled administration of intravenous iloprost, and uses dedicated syringes 25.5 ml. The pump administers doses of 7.44 µl at intervals that depend on the flow set. The programming software is specifically designed for the administration of iloprost and, for the set up of the infusion, only patient weight and flow velocity need to be entered. The infusion duration may vary from 1 to 24 hours.

Among the devices on the market, Infonde® is the one that best fits the home administration of iloprost thanks to its small size, ease of use and the option for patients to stop infusions in the case of side effects.

Results

The study included 24 patients with ischemic diseases of the lower limbs who had indications for the treatment with intravenous iloprost. The overall characteristics of the population are described in Table I.

As expected, treatment with iloprost was effective in improving the clinical condition of patients: the SVS/ISCVS score at the end of the treatment was significantly improved compared to baseline ($+1.29 \pm 1.04$, $p < 0.001$).

The treatment was generally well tolerated by patients, with a low occurrence of side effects both at the beginning of treatment in the hospital setting and during its continuation at the patient's home (Figure 2). During the home stay, no significant problems related to venous access were registered.

The home therapy proved feasible because 96% of patients (23 of 24) completed the entire treatment cycle which lasted an average of 9.9 ± 2.3 days.

The analysis of the evaluation questionnaire revealed a high acceptance of the therapy (Figure 3).

Economic Analysis

The economic analysis, in terms of direct medical costs, showed that the two processes (inpatient and outpatient) do not differ in terms of drug costs and usage of disposables. A lower use of human resources was observed in the outpatient setting, due to lower nursing time dedicated to patients (estimated by key opinion leaders to be on average 180 minutes per patient, considering a total of 10 infusions). The lower direct medical costs for the hospital authority related to the domiciliary treatment of patients are estimated to account for € 86 per patient's infusion cycle. Therefore, we saved a total of approximately € 2,064 for the 24 patients included in the study.

From the point of view of the Italian NHS, there are no differences between the two different settings in terms of reimbursement of the health service delivered and the impact of the domiciliary treatment is therefore considered nil.

Table I. Characteristics of the study population.

Number of patients	24
Age (mean \pm SD)	62 \pm 14
Sex	100% M
Number of infusions at home	237
Number of infusions per patient \pm SD	9.9 \pm 2.3
Diagnosis	
– PAD	58.3%
– Buerger's disease/vasculitis	33.3%
– Microangiopathy	8.3%
Cardiovascular comorbidity	
– None	29.2%
– Diabetes mellitus	45.8%
– Hypercholesterolemia	20.8%
– Arterial hypertension	12.5%
– Ischemic heart disease	4.2%
– Chronic kidney disease	4.2%
Concomitant medications	
– Antiplatelet	91.7%
– Anticoagulant	4.2%
– Statin	25.0%
– Antihypertensive	12.5%

Discussion

Our results confirm the efficacy and tolerability of slow prolonged infusions and indicate

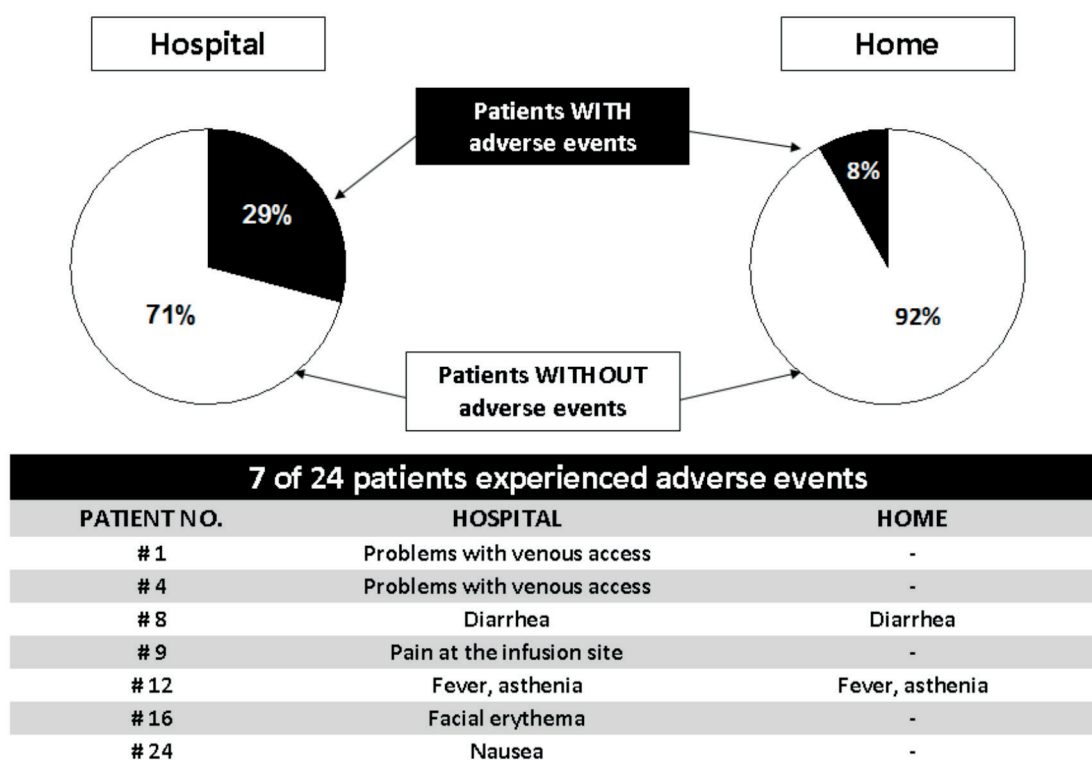


Figure 2. Overall adverse events recorded in the cohort of patients (n=24).

Patient Questionnaire (mean score ± SD)	Completely disagree										Completely agree	
	☹	1	2	3	4	5	6	7	8	9	10	☺
I am in favor of home therapy												8.88 ± 2.09
I consider home therapy safe												9.08 ± 1.86
I can perform my daily tasks easily												8.67 ± 2.20
if I could choose between treatment at home or in the hospital, which one would I choose?												92% Home

Figure 3. Results of the evaluation questionnaires administered to patients (n=24).

the feasibility of treatment with iloprost at the patient’s home. As expected, the home therapy was appreciated by the patients, and it is estimated to be a cost-saving strategy for the hospital authority.

The decision to treat patients with peripheral vascular disease with iloprost at home came from the need to optimize the resources of our department and from the availability of a new portable syringe pump specifically designed for the administration of iloprost, a device which has replaced the old bulky syringe pumps that significantly restricted the mobility of patients. Our results confirm that home therapy is a safe, effective and convenient option, provided that some precautions related to the clinical conditions and the behavior of the patient are followed. In particular, we would like to emphasize that it is important that patients undergo an accurate clinical evaluation in order to rule out serious heart complications and to evaluate the thrombotic/bleeding risk. In fact, patients with peripheral vascular disease are often treated with dual antiplatelet or oral anticoagulant therapy, so physicians should consider the possible withdrawal of at least one of the oral agents during the administration of iloprost, due to a possible enhancement of the antithrombotic effect. This assessment must be carefully made by physicians, on the basis of the clinical profile of each patient. Another important aspect is the willingness of the patient to follow the instructions provided by healthcare professionals, e.g. not perform strenuous movements

during the stay at home and come back regularly to the hospital to start the new infusions or to return the device at the end of therapy. Moreover, patients should be accompanied by caregivers, usually members of the family or friends.

Our results are consistent with those from previous clinical trials in which patients were successfully treated with iloprost at home¹²⁻¹⁶. However, in the present study, a specific portable syringe pump for iloprost infusion was used for the first time, unlike previous studies in which elastomeric pumps, not designed for the administration of iloprost, were used. The use of Infonde[®] provides greater reliability in the controlled administration of iloprost, and users can stop the infusion in case of need. To date, this is the only portable device for iloprost infusion. Previous studies suggest that Infonde[®] is an appropriate device for iloprost administration in a hospital setting, with remarkable satisfaction both from patients and health care personnel^{17,18} and a favorable economic and organizational impact¹⁹. In particular, a recent Health Technology Assessment showed that the use of Infonde[®] allowed nurses to save up to 66% of the time spent monitoring patients when compared with other devices, thus potentially requiring a lower number of nurses (e.g. 1 instead of 3) to perform this activity¹⁹. Our study suggests that Infonde[®] is also suitable for infusion outside hospitals.

Our economic analysis considered direct medical costs, however, indirect costs are likely to be reduced by the use of domiciliary infusions as

well. Patients and caregivers would need to go to the hospital only once a day to have their pumps set by the nursing and medical staff, with a potential reduction of absences from work and with the opportunity for patients to continue the infusion at their workplace. Moreover, from an organizational point of view, the home setting for infusion may lead to an increased number of patients treated within each healthcare center, thanks to the avoided need to use armchairs and beds inside the medical ward and to the fewer activities required by the nursing staff which attend patients receiving iloprost. This might have further positive effects on shortening waiting lists.

This study has some limitations mainly due to the observational and single-center design that may reduce the generalizability of results. The questionnaire – although similar to those administered in previous studies^{17,18} – were not validated for the assessment of patient satisfaction or quality of life. Even if the number of patients included was relatively low, unequivocal results were obtained.

Conclusions

Our results demonstrate the efficacy, safety and feasibility of home iloprost infusion with the portable syringe pump Infonde®. The outpatient setting seems to be an appropriate and convenient therapeutic strategy also from the point of view of health economics and organization. Due to the relatively small number of patients enrolled and single-center design, the results need to be confirmed in larger populations.

Conflicts of interest

Alberto Farina is an employee of Italfarmaco S.p.A., Cinisello Balsamo, Milan, Italy. The other authors report no conflict of interest in the preparation of the present article.

References

- 1) MEINI S, MELILLO E, MIGLIACCI R, NICOLOSI G, PANIGADA G, LANDINI G. Peripheral arterial occlusive disease and ischemic disease of the lower limbs are not the same condition. A proposed unambiguous Italian terminology for defining Peripheral arterial disease of lower limbs and related clinical/therapeutic implications. *It J Med* 2014; 8: 1-5.
- 2) NORNGREN L, HIATT WR, DORMANDY JA, NEHLER MR, HARRIS KA, FOWKES FG, RUTHERFORD RB; Tasc II

Working Group. Inter-society consensus for the management of peripheral arterial disease (Tasc II). *Eur J Vasc Endovasc Surg* 2007; 33: S1-75.

- 3) VARU VN, HOGG ME, KIBBE MR. Critical limb ischemia. *J Vasc Surg* 2010; 51: 230-241.
- 4) HERNANDO FJS, CONEJERO AM. Peripheral artery disease: pathophysiology, diagnosis and treatment. *Rev Esp Cardiol* 2007; 60: 969-982.
- 5) HIRSCH AT, HASKAL ZJ, HERTZER NR, BAKAL CW, CREA-GER MA, HALPERIN JL, HIRATZKA LF, MURPHY WR, OLIN JW, PUSCHETT JB, ROSENFELD KA, SACKS D, STANLEY JC, TAYLOR LM JR, WHITE CJ, WHITE J, WHITE RA, ANTMAN EM, SMITH SC JR, ADAMS CD, ANDERSON JL, FAXON DP, FUSTER V, GIBBONS RJ, HUNT SA, JACOBS AK, NISHIMURA R, ORNATO JP, PAGE RL, RIEGEL B; American Association for Vascular Surgery; Society for Vascular Surgery; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology; Society of Interventional Radiology; ACC/AHA Task Force on Practice Guidelines Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease; American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; Vascular Disease Foundation. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). *Circulation* 2006; 113: e463-e654.
- 6) ALONSO-COELLO P, BELLMUNT S, MCGORRIAN C, ANAND SS, GUZMAN R, CRIQUI MH, AKL EA, OLAV VANDVIK P, LANSBERG MG, GUYATT GH, SPENCER FA; American College of Chest Physicians. Antithrombotic Therapy and Prevention of Thrombosis 9th ed: American College of Chest Physicians. Evidence based clinical practice guidelines. Antithrombotic therapy in peripheral artery disease. *Chest* 2012; 141: e669S-e690S.
- 7) LOOSEMORE TM, CHALMERS TC, DORMANDY JA. A meta-analysis of randomized placebo control trials in Fontaine stages III and IV peripheral occlusive arterial disease. *Int Angiol* 1994; 13: 133-142.
- 8) ALTSTAEDT HO, BERZEWSKI B, BREDDIN HK, BROCKHAUS W, BRUHN HD, CACHOVAN M, DIEHM C, DÖRRER J, FRANKE CS, GRUSS JD. Treatment of patients with peripheral arterial occlusive disease Fontaine stage IV with intravenous iloprost and PGE1: a randomized open controlled study. *Prostaglandins Leukot Essent Fatty Acids* 1993; 49: 573-578.
- 9) RUFFOLO AJ, ROMANO M, CIAPPONI A. Prostanoids for critical limb ischaemia. *Cochrane Database Syst Rev* 2010; CD006544.

- 10) DE DONATO G, GUSSONI G, DE DONATO G, ANDREOZZI GM, BONIZZONI E, MAZZONE A, ODERO A, PARONI G, SETACCI C, SETTEMBRINI P, VEGLIA F, MARTINI R, SETACCI F, PALOMBO D. The ILAILL study: iloprost as adjuvant to surgery for acute ischemia of lower limbs: a randomized, placebo-controlled, double-blind study by the Italian society for vascular and endovascular surgery. *Ann Surg* 2006; 244: 185-193.
- 11) RUTHERFORD RB, BAKER JD, ERNST C, JOHNSTON KW, PORTER JM, AHN S, JONES DN. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997; 26: 517-538.
- 12) SANFILIPPO R, SIONIS C, GIAU MA, MONTISCI R, BROTZU G. Infusione continua di Iloprost mediante pompa elastomerica nelle arteriopatie obliteranti croniche degli arti inferiori stadio IIB e III. *G Ital Chir Vasc* 2003; 10: 121-128.
- 13) PIBIRI L, PETRUZZO P, ANGIUS D, RUIU G, POLO F, RESCIGNO A, BROTZU G. A new infusion method for a prostacyclin analogue. *Minerva Cardioangiol* 1997; 45: 621-625.
- 14) SABADINI L, SACU O, ROSATI F, MARZO E, FUSCONI L, BRISCHETTO R. Nuove esperienze cliniche: trattamento infusivo con iloprost mediante elastomero: esperienza clinica di una nuova modalità infusione nel fenomeno di Raynaud secondario a sclerosi sistemica. *Reumatologia Pratica* 2011; 6: 53-57.
- 15) BANYAI S, JENELTEN R, WAGNER S, ALLMANN J, BANYAI M, KOPPENSTEINER R. Outpatient treatment of severe peripheral ischemia with intravenous intermittent low-dose iloprost. An open pilot study. *Int Angiol* 2002; 21: 36-43.
- 16) VEROUX P, VEROUX M, MACARONE M, BONANNO MG, TUMMINELLI MG. 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. *Curr Ther Res Clin Exp* 2004; 65: 255-265.
- 17) FAGGIOLI P, SCIASCERA A, GIANI L, MAZZONE A. Un nuovo device per la somministrazione di iloprost mediante pompa a siringa portatile: sicurezza, tollerabilità a e gradimento. *It J Med* 2012; 6: 311-314.
- 18) LARIA A, LURATI AM, RE KA, MARRAZZA MG, MAZZOCCHI D, FARINA A, SCARPELLINI M. User preference for a portable syringe pump for iloprost infusion. *Patient Relat Outcome Meas* 2015; 6: 139-144.
- 19) RESTELLI U, FAGGIOLI P, SCOLARI F, GUSSONI G, VALERIO A, SCIASCERA A, CROCE D, MAZZONE A. Organizational impact of the introduction of a new portable syringe pump for iloprost therapy in Italian hospital settings. *Curr Drug Ther* 2015; 10: 105-112.