Eur J Vasc Endovasc Surg **34**, 194–198 (2007)
doi:10.1016/j.ejvs.2007.02.002, available online at http://www.sciencedirect.com on ScienceDirect

Acute Limb Ischemia in Elderly Patients: Can Iloprost be Useful as an Adjuvant to Surgery? Results from the ILAILL Study

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Objectives. *To evaluate the effects of iloprost, in addition to surgery, on the outcome of acute lower limb ischemia (ALLI).*
Design. *Post-hoc analysis of a randomized, double-blind, placebo-controlled study.*
Methods. *In the context of the ILAILL (ILoprost in Acute Ischemia of Lower Limbs) study, 192 elderly patients (>70 years old) undergoing surgery for ALLI were assigned to receive perioperative iloprost (intra-arterial, intra-operative bolus of 3000 ng, plus intravenous infusion of 0.5–2.0 ng/kg/min for six hours/day for 4–7 days following surgery), or placebo (iloprost:* $n = 100$*; placebo:* $n = 92$*). Patients were followed-up for three-months following surgical revascularization.*
Results. *The combined incidence of death and amputation (primary study end-point) was significantly reduced in patients treated with iloprost (16.0% vs 27.2% in the placebo group; hazard ratio 1.99, 95% confidence interval 1.05–3.75,* $p = 0.03$*). A statistically significant lower mortality (6.0%) was reported in patients receiving iloprost, compared to controls (15.2%) (hazard ratio 2.93, 1.11–7.71,* $p = 0.03$*). The overall incidence of death and major cardiovascular events was lower in patients receiving iloprost compared to those assigned placebo (24.0% and 35.9%, respectively), at the limits of statistical significance (relative risk 1.64, 0.97–2.79,* $p = 0.06$*).*
Conclusions. *These results confirm the poor outcome in elderly patients with ALLI. Based on a subgroup analysis iloprost, as an adjuvant to surgery, appears to reduce the combined end-point of death and amputation.*

Keywords: Acute limb ischemia; Elderly patients; Iloprost; Surgical revascularization; Reperfusion.

Introduction

Acute lower limb ischemia (ALLI) continues to be associated with a high morbidity and mortality despite improvements in perioperative care.[1] Elderly patients are at particular high risk of severe local and systemic complications.[2] Co-morbidity, the metabolic derangement associated with acute ischaemia and reperfusion injury have all been implicated in the poor prognosis.[3] Due to its pharmacological profile, iloprost, a synthetic prostacyclin analogue, is a candidate as adjuvant treatment in patients with ALLI.[4] Under the endorsement of Italian Society for Vascular and Endovascular Surgery (S.I.C.V.E.), we performed a randomized, placebo-controlled, phase III study (ILAILL), to assess the effects of perioperative treatment with iloprost in 300 patients with ALLI undergoing surgical revascularization (thromboembolectomy or by-pass, in native vessel or graft). In this study a significant reduction of mortality and incidence of total major cardiovascular events was shown in patients treated with iloprost.[5] The incidence of combined death and amputation in the ILAILL study was significantly related to age

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1078–5884/000194 + 05 $32.00/0

(21.3% in patients > 70 years, *vs* 9.3% in patients less than 70 years, $p < 0.01$). As a post-hoc analysis we therefore focused our attention on the effects of iloprost as adjuvant to surgery in this group of elderly patients with a high rate of complications.

Materials and Methods

One-hundred and ninety-two patients (92 in the placebo and 100 in the iloprost group) over 70 years old were enrolled in ILAILL. Patients were considered for inclusion if they presented with acute onset (less than 14 days) of symptoms suggestive of ischemia of lower limbs (native vessels and/or graft occlusions) and were to be treated with surgical revascularization. Patients with lower limb ischemia due to trauma were excluded. Other exclusion criteria included: acute myocardial infarction or stroke within the last 6 months prior to enrolment; cardiac failure (NYHA Class > I); unstable angina; *angina pectoris* (Canadian classification > II); hyperkinetic ventricular arrhythmias; severe hypertension (sitting systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg) or hypotension (systolic blood pressure <90 mmHg); haemorrhagic diathesis; concomitant clinical conditions in which iloprost might increase the risk of bleeding (i.e. active peptic ulcer, trauma, cerebral haemorrhage); thrombocytopenia (<80.000/mm^3) or thrombocytosis (>500.000/mm^3); severe hepatic failure (cirrhosis); renal failure requiring dialysis treatment.

Iloprost (*Endoprost*®, Italfarmaco S.p.A., Milan, Italy, under licence of Schering AG, Berlin, Germany) or placebo were administered as an intra-arterial bolus of 3000 ng over 1−3 minutes immediately after revascularization and in the same affected artery. Starting from the first day after surgery, a daily 6-hour intravenous infusion of iloprost (or placebo) at doses of 0.5−2.0 ng/kg/min was performed for 4−7 days (7 days recommended), depending on the length of hospital stay. Patients were followed-up for 90 ± 5 days after surgery, for occurrence of major clinical events. The primary efficacy end-point of ILAILL was the combined incidence of death and amputation during a three-month follow-up period. Secondary efficacy end-points were the incidence of each single major clinical event (acute myocardial infarction, stroke, peripheral embolism, pulmonary embolism, other major cardiovascular events, amputation and death) during the study, and the total event rate (death plus major cardiovascular events).

Baseline continuous variables were compared between the two treatment groups by unpaired t-test, categorical variables were compared by Chi-square test or Fisher exact test, as appropriate. Multivariable analyses, adjusting for potential confounders, were performed using the Cox proportional hazard regression model, to compare the outcomes (combined death + amputation, death, total event rate) in the two treatment groups. Apart from experimental treatment (placebo *vs* iloprost), the following variables were selected for the multivariable analyses, on the basis of their clinical importance: duration of ischemia (>24 hours *vs* ≤ 24 hours); class of ischemia according to SVS−ISCVS−TASC criteria[1,6] (IIb-III *vs* IIa-I); previous cardiovascular event(s) (acute myocardial ischemia, stroke, peripheral revascularization, yes *vs* no); type of surgery (thromboembolectomy *vs* other modalities). Proportional hazard assumption were tested for all the covariates included and no relevant violations were found. All statistical tests were two-sided and p-values below 0.05 were considered as significant. Statistical analyses were performed by using SAS software (version 8.2, SAS Institute, Cary, NC, USA), on the basis of the intention-to-treat.

The study was conducted according to the ethical principles stated in the Declaration of Helsinki and local regulations. The protocol was approved by the Ethics Committee of each participating center, and written informed consent was obtained by all patients before randomization.

Further details on study design, and overall results of the trial, have been described elsewhere.[5]

Results

Baseline characteristics of the two groups of patients were similar (Table 1). The duration of treatment did not differ between the experimental and control group (Table 2). Concomitant therapies during follow-up were very similar for the two groups (heparin 83.7% and 85.0%, oral anticoagulants 27.2% and 29.0%, antiplatelet therapies 27.2% and 24.0%, anti-hypertensive 52.2% and 56.0% in placebo and iloprost groups, respectively). Withdrawal from study without completion of follow-up and without occurrence of major clinical events requiring study discontinuation occurred in 13.0% and 12.0% of patients in the placebo and iloprost group, respectively, due to Investigator's judgement of lack of effect (6.5% for placebo and 3.0% for iloprost), non-compliance or patient lost to follow-up.

The incidences of outcomes and the relevant results of the multivariable analyses (Cox regression model) are reported in Fig. 1. The combined incidence of death and amputation (primary study end-point) was significantly reduced in patients treated with

Table 1. Baseline characteristics of patients. All comparison between study groups were statistically non-significant*. PAD = peripheral arterial disease

Characteristic	Placebo ($N = 92$)	Iloprost ($N = 100$)
Age − yr	81.0 ± 6.5	80.3 ± 6.1
Sex − M/F	47/45	50/50
Medical history/Concomitant conditions (%)		
Ischemic cardiopathy	22.8	24.0
Cerebrovascular disease	27.2	23.0
Atrial fibrillation/arrhythmias	59.8	57.0
Chronic PAD	12.0	18.0
Prev. revascularization lower limb(s)	22.8	28.0
Hypertension	69.6	64.0
Diabetes	17.4	15.0
Tumor	16.3	22.0
Duration of symptoms (%)		
0−6 hrs	15.3	19.2
6−24 hrs	37.4	38.4
>24 hrs	47.3	42.4
Clinical category of acute ischemia (%)		
Class I−IIa	33.7	36.5
Class IIb−III	66.3	63.5
Type of intervention (%)		
Thromboembolectomy	78.3	77.8
By-pass	15.2	16.2
Combined	6.5	6.0

*comparison between treatment groups, t-test or Chi square test, as appropriate.

iloprost (16.0% *vs* 27.2% in the placebo group; hazard ratio 1.99, 95% confidence interval 1.05−3.75, $p = 0.03$). A statistically significant lower mortality (6.0%) was reported in patients receiving iloprost, compared to controls (15.2%) (hazard ratio 2.93, 1.11−7.71, $p = 0.03$). The Kaplan-Meier curve for survival is shown in Fig. 2. The overall incidence of fatal plus major cardiovascular events was lower in iloprost patients *vs* placebo group (24.0% and 35.9%, respectively), at the limits of statistical significance (relative risk 1.64, 0.97−2.79, $p = 0.06$). In Table 3 more specific information on the major complications are shown.

On multivariable analysis, occurrence of death or amputation appeared significantly related to class of ischemia (≥IIb), and less frequent for patients undergoing thromboembolectomy (*vs* other surgical procedures) (Table 4). No serious adverse reactions occurred after iloprost administration, nor significant

Table 2. Duration of experimental treatment for the two study groups

Duration of treatment	Placebo (% of patients)	Iloprost (% of patients)	p value
Bolus → 3 days	15.2	12.0	ns
4 days	35.9	40.0	ns
5−6 days	5.4	6.0	ns
7 days	43.5	42.0	ns

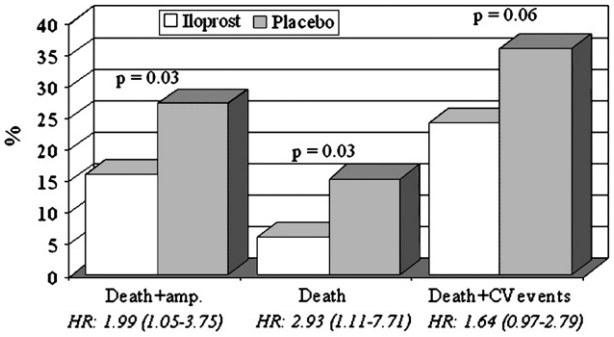

Fig. 1. Incidence (%) and Hazard Ratios (HR) of major events in the two treatment groups.

differences in the incidence of bleeding (2.2% placebo *vs* 3.0% iloprost) or hypotension (8.7% placebo *vs* 9.0% iloprost) between treatment groups.

Discussion

The results of ILAILL study confirm the poor clinical outcome in elderly patients with ALLI. The combined incidence of death and amputation in patients older than 70 years was 27.2% in the control group. Iloprost, as an adjuvant to surgery, significantly reduced the combined incidence of death and amputation (primary study end-point) and mortality in this group of high risk patients. The beneficial effect of iloprost on the systemic component of the reperfusion syndrome is supported by a high relative risk reduction in mortality (65.9%) in treated patients. Iloprost is known to interfere with many of the mechanisms involved in the inflammatory response and systemic damage following ischemia and reperfusion (i.e. through its effects on platelet activation and blood clotting, the reduction of free radicals and cytokines production,

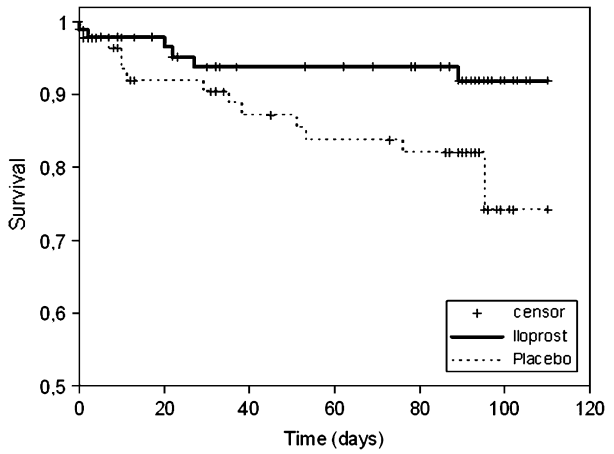

Fig. 2. Kaplan-Meier estimates of the probability of survival in the two study groups.

Table 3. Details of major clinical events in patients treated with placebo or iloprost

Characteristic	Placebo ($N = 92$) N.of cases (%)	Iloprost ($N = 100$) N.of cases (%)	p value
Death	14 (15.2%)	6 (6%)	0.03
Reported causes			
Stroke	2	2	
Acute myocardial infarction	1		
Cardiac failure	2	3	
Arrhytmia	1		
Other thrombotic events	2		
Acute renal failure	1		
Bleeding	1		
Pneumonia	1		
Tumoral progression		1	
Unknown (death at home)	3		
Amputation	11 (11.9%)	10 (10%)	ns
Other major cardiovascular events	8 (8.7%)	8 (8.0%)	ns
Stroke		2	
Acute myocardial infarction		1	
Cardiac failure	1		
Arrhytmia	1		
Additional revascularization	3	4	
Recurrent ALLI	3	1	

and lower expression of intercellular adhesion molecules[4,7–9]). An early modulation of inflammatory self-perpetuating response following ischemia and reperfusion by perioperative iloprost may therefore produce prompt and later benefit in patients' outcome, as assessed by the 3-month follow-up of ILAILL study. Amputation incidence and the occurrence of overall major local complications (amputation + additional revascularization + recurrent acute limb ischemia) were quite similar in the two treatment groups (amputation 11.9% vs 10.0%, overall complications 18.4% vs 15.0% for control and treatment, respectively). These findings are surprising given the hypothesis that iloprost would reduce peripheral complications by improving microcirculation. However, the timing of amputations, quite early after revascularization (median, 8 and 13 days after placebo and iloprost respectively) seems to suggest a critical role for surgery in determining patient outcome. Moreover, the high rate of patients presenting in grade IIb-III acute limb ischemia (around two thirds in the two treatment groups), has probably reduced the potential to detect an effect of the drug. Iloprost was well tolerated in this elderly sick population. This appears to us of relevance, since in our study iloprost was used in emergency conditions, and not in patients with chronic diseases, or as adjuvant to elective surgery, as previously reported.[10]

Table 4. Cox regression model analysis for the primary study endpoint (combined death and amputation). HR = Hazard Ratio; CV = cardiovascular; TE = thromboembolectomy

Variable	Effect	HR	95% CI	p value
Treatment	Placebo *vs* Iloprost	1.99	1.05–3.75	0.03
Previous CV event	Yes *vs* No	0.55	0.29–1.02	0.06
Duration of ischemia	$>$ 24 *vs* $\leq$ 24 hours	1.60	0.82–3.15	0.17
Class of ischemia	$\geq$ IIb *vs* $<$ IIb	3.15	1.44–6.89	$<$0.01
Type of surgery	TE *vs* Other	0.42	0.21–0.87	0.02

Major complications in this study were related to the severity of limb ischemia but not influenced by duration of ALLI. Our study was not powered to address these issues therefore these results have to be considered with caution. However, the absence of a clear relationship between duration of ischemia and major events, together with the evidence of a high amputation-free survival in patients with ischemia classified as ''irreversible'' (60.5%) seems to support a more aggressive treatment strategy in patients with late presentation and severe peripheral ischaemia, particularly if referred to specialized care units (the setting of centres participating in the ILAILL study). A minor occurrence of complications in patients experiencing previous cardiovascular events seems to support the hypothesis of a less intense inflammatory response to ischemia in atherosclerotic ''stabilized'' patients,[11] and a possible influence of a more frequent use of concomitant therapies active at cardiovascular and metabolic levels. Furthermore, a role for the protective effects of ischemic preconditioning in humans was recently claimed in the setting of cerebrovascular disease.[12]

In conclusion, our results confirm the poor clinical outcome of ALLI, particularly in elderly patients. In this high-risk group, iloprost as an adjuvant to surgery significantly reduced the combined incidence of death and amputation. Further data and efforts are needed to support this finding.

Acknowledgments

We are indebted to the Italian Society for Vascular and Endovascular Surgery (S.I.C.V.E.) for the endorsement to ILAILL; to Carlo Bianchini for his scientific advice; to Patrizia Ronchetti and Luisa Siori for secretarial assistance; to Evelina Curatolo, Laura Filiberti, Agostino Lazzaro, Milena Meo, Marzia Martusciello, Matteo Mondellini, Laura Omoboni, Giuseppe Portera, Rossella Rivolta, Elisa Robberto, Antonella Stroppolo, actually or formerly at MDS Pharma Services, Milan, Italy, for monitoring of the study and data management; to Georg Groetzbach (Schering AG, Berlin, Germany) and Laura Ottolenghi (Schering Italy, Milan) for kindly providing study drug; to the Physicians and Nurses of Centres of Vascular Surgery (see list below) participating to the ILAILL study; and to the patients, for whom this study has been planned, for their trust and support.

Sources of financial and material support: The ILAILL project was supported by a grant from Italfarmaco S.p.A., Milan Italy. Experimental treatments were kindly provided by Schering AG, Berlin, Germany.

Possible conflicts of interest: G. Gussoni was formerly an employee of Italfarmaco S.p.A., Milan.

Appendix

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Accepted 8 February 2007
Available online 11 April 2007