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Alprostadil treatment of critical limb ischemia in hemodialysis patients:

A retrospective single-center analysis

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Summary

Background—Peripheral artery disease and critical limb ischemia are common in patients undergoing chronic hemodialysis treatment and are associated with a high rate of amputation and mortality. The effect of treatment with prostanoids in this specific group of patients is unknown.

Methods—A retrospective single-center analysis of hemodialysis patients with critical limb ischemia was performed who were treated with the prostanoid analogue alprostadil as an infusion during hemodialysis in the period from 2000 to 2013. The primary study outcome was a combined end-point including amputation and death 1 year after start of alprostadil. Kaplan-Meier curves

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were used to describe amputation-free survival and overall survival. A multivariable adjusted Cox proportional hazards model was calculated for the primary outcome.

Results—A total of 86 patients (60 males, 69.7%) were studied. The median alprostadil treatment period was 1.8 months. The 1-year amputation-free survival was 41%. In 36% of patients an amputation was necessary and 35% died. Despite alprostadil treatment, 36% of the study patients additionally underwent an endovascular procedure and 16% had bypass surgery. Men had a significantly higher amputation rate (45%) than women (15%) ($P=0.009$). Male sex and dialysis vintage were significantly associated with an increased risk for primary outcome.

Conclusions—Despite treatment with alprostadil the mortality, amputation rate and the need for revascularization procedures in hemodialysis patients with critical limb ischemia remained high. The outcome, however, was comparable with that of other treatment, such as endovascular procedures and bypass surgery. The effect of any current treatment strategy on amputation rate or mortality in that patient group remains uncertain.

Keywords

Peripheral artery disease; Mortality; Amputation; Arteriosclerosis; Revascularisation; Bypass surgery

Introduction

Peripheral artery disease (PAD) is a widely underestimated and neglected condition with a prevalence of 4% in the general adult population [1]. The frequency of PAD is even higher in individuals suffering from chronic kidney disease, with the prevalence increasing with declining glomerular filtration rate (GFR) [1–3]. The presence of PAD in patients with chronic kidney disease (CKD) stage 3 and higher including dialysis patients reaches 25% [2, 4]. Critical limb ischemia, the most severe stage of PAD, defined by pain at rest or tissue necrosis, is a devastating condition with very high amputation rates and mortality. The prognosis for CKD patients including those on dialysis seems to be particularly poor despite modern endovascular and surgical interventions [5–7]. For those patients in whom revascularization procedures are not possible or have failed, intravenous prostanoids are a therapeutic option approved by regulatory authorities. Prostanoids (the prostaglandin PGE_1 analog alprostadil and the prostacyclin PGI_2 analogue iloprost) have been tested in several small randomized placebo-controlled trials [8–10]; however, they have not been formally studied in the hemodialysis population despite their broad use in these patients, at least in Central Europe. To better define the efficacy of alprostadil in patients with PAD undergoing chronic hemodialysis treatment, a retrospective analysis of amputation rate and mortality in all hemodialysis patients treated at this center with alprostadil was conducted.

Patients and methods

A retrospective analysis was performed of all chronic hemodialysis patients who underwent treatment with alprostadil, a synthetic prostaglandin E_1 analogue (Prostava[®], UCB Pharma, Vienna, Austria), at the Department of Nephrology and Dialysis of Feldkirch Academic Teaching Hospital between 2000 and 2013. Alprostadil was initiated in all

patients who suffered from PAD Fontaine stage 3 or 4 (pain at rest or tissue necrosis) in order to avoid or delay bypass surgery or amputation in this vulnerable population. Data were retrieved from electronic patient charts. Information on patient sex and age, renal disease, dialysis vintage, hemodialysis access, comorbidities (e.g. diabetes, coronary artery disease, cerebrovascular disease and heart failure), laboratory results, i.e. hemoglobin, albumin, calcium, phosphate and parathyroid hormone (PTH) and location of the arterial stenosis were collected at baseline.

The primary end point of the study was the combination of amputation and death within the follow-up period of 1 year after commencement of alprostadil therapy. In addition, data on endovascular procedures and myocardial infarction were collected. Each individual patient was followed for 12 months after initiation of alprostadil.

The study was approved by the Ethics Committee of the State of Vorarlberg (number 2014–9/3).

Statistical analysis

Data are presented as number (%) or mean $\pm$ SD, as appropriate. Kaplan-Meier curves were used to describe amputation-free survival and overall survival over 1 year. Survival differences between men and women were assessed using the log-rank test. A multivariable adjusted Cox proportional hazards model was used to calculate hazard ratios (HR) with 95% confidence intervals (CI) for the primary outcome (1 year amputation or mortality). A two-sided P value <0.05 was deemed to indicate statistical significance. All statistical analyses were performed with SPSS 20 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

During the observation period from 2000 to 2013 a total of 672 patients were on chronic hemodialysis. Of these patients 86 (12.8%) were treated with alprostadil and were available for investigation. The study population included 60 males (69.7%) and the mean age was 70.5 ± 10.9 years (median 72 years). Dialysis vintage ranged from 0.1 to 280.3 months (median 18.5 months).

Causes of end-stage kidney disease were diabetic kidney disease in 54 patients (63%), hypertensive/vascular nephropathy in 19 (22%), glomerulonephritis in 5 (6%), renal cell or urothelial carcinoma in 3, analgesic nephropathy and autosomal dominant polycystic kidney disease (ADPKD) in 1 and unknown in 3 patients.

Table 1 shows the stage and location of PAD, comorbidities and the type of vascular dialysis access. The great majority had stage 4 disease with a distal location. Of the patients 50% ($n = 43$) were current or former smokers.

Laboratory results at initiation of alprostadil treatment are shown in Table 2.

Following a local standardized protocol, alprostadil was administered to all patients at a fixed dose of 40 μ g as a continuous infusion during the last 3h of the hemodialysis session.

The median treatment period lasted 1.8 months (range 0.2–12.2 months). Overall, 51 (59.3%) patients died or underwent amputation within 1 year (1-year amputation-free survival 40.7%), 31 patients had an amputation and 30 died. The 1-year amputation and mortality rates were 36% and 35%, respectively. Of the amputations only 7 were classified as major (above the ankle) and 24 were minor amputations. A summary of primary and secondary end-points is presented in Table 3. Despite alprostadil treatment 31 patients (36.0%) needed an endovascular procedure and 14 (16.3%) underwent bypass surgery. Of the patients 4 (4.7%) suffered from acute myocardial infarction during the observation period.

A gender-specific evaluation showed that 42.3% of women and 31.0% of men died after 1 year ($P = 0.34$). Men, however, had a significantly higher amputation rate than women (45.0% vs. 15.4%; $P = 0.009$). Amputation-free survival was higher for women (53.8%) than for men (35.0%). This difference, however, was not significant ($P = 0.10$).

Fig. 1 shows Kaplan-Meier survival curves for the combined primary end-point (amputation-free survival), and for overall survival and amputation separately for the whole patient group. The same curves separated for male and female patients are shown in Fig. 2. A trend towards better amputation-free survival in women ($P = 0.064$) was observed. This trend was driven by a significantly lower amputation rate in women than in men ($P = 0.009$), whereas mortality did not differ between genders ($P = 0.4$).

The results of a multivariable-adjusted Cox regression analysis determining the risk of the primary outcome are shown in Table 4. Male sex and dialysis vintage were significantly associated with increased risk. The presence of diabetes was of borderline significance.

Discussion

Prostanoids exert a presumed beneficial effect in PAD via multiple mechanisms. These include vasodilation, fibrinolysis, decreased blood viscosity and inhibition of platelet aggregation. They also have inhibitory effects on macrophages and neutrophils, decrease the expression of adhesion molecules and the release of cytokines and modify gene expression [11]. Meta-analyses of available studies suggested that prostanoids relieve resting pain and accelerate ulcer healing. They may also have a positive effect on the amputation rate [12]. The low quality of studies, however, has precluded a clear recommendation for or against their use so far. The occurrence of PAD in CKD and dialysis patients differs from that in patients without kidney disease, especially by the high degree of vessel wall calcification. It can therefore be speculated that the vasodilatory effect of prostanoids is impaired, meaning that prostanoids would be less effective in patients with kidney disease. The only report on prostacyclin use in hemodialysis patients with PAD describes its short-term effect in intermittent claudication in five individuals [13]. No positive effect on foot temperature, walking distance or platelet aggregation was demonstrated. Therefore, the present retrospective analysis is the only available study on alprostadil, a prostaglandin PGE₁ analog in the treatment of PAD in the hemodialysis population. In general, randomized studies of other medicinal and invasive treatment modalities for PAD in this patient population are lacking.

Overall, this study found a 1 year amputation free survival rate of 41%, an amputation rate of 36% and a mortality rate of 35%. How do these results compare with other reports? A large study of nearly 42,000 PAD patients including 1436 CKD stage 5 patients, of whom 65% had a revascularization procedure, reported a 1-year survival of 60% and amputation-free survival of 55% [5]. These numbers are comparable to those in this study for cumulative survival (65%), but higher for amputation-free survival (41% in our cohort). In that study, however, only half of the CKD 5 patients had critical limb ischemia. Several other studies described outcomes after revascularization procedures, either percutaneous endovascular intervention (PCI) or bypass surgery, in hemodialysis patients: three older studies of bypass surgery found an amputation rate after 1 year of 35%, 30% and 37% [14–16]. The 1-year survival rates were 74% and 52% in diabetic patients [14, 16]. Another 2 recent studies reported an amputation-free survival rate of 64%, a limb salvage rate of 89% and 80% and a survival rate of 68% and 60%, respectively [17] and 2 studies described outcomes after endovascular repair or bypass surgery. In 800 patients in the United States Renal Data System the amputation rate was 24%, the 2-year mortality was 57%, 63% after bypass and 43% after angioplasty [18]. Another study of 689 patients found a 1-year survival of 60% and amputation-free survival of 40% [19]. Studies including only patients undergoing percutaneous interventions described an amputation rate of 11% and 14% and a mortality rate of 56% after a mean follow-up of 36 months and 34% after 1 year [6, 20]. Study populations, interventions and definitions for minor and major amputations differed between studies, and therefore comparisons of outcomes were difficult. Table 5 summarizes the outcomes of the abovementioned and additional studies.

Survival of hemodialysis patients with critical limb ischemia remains poor, with about 60% being alive after 1 year. It also appears that rates of major amputation (above the ankle) are around 10% and of all amputations around 30% after 1 year, irrespective of the revascularization technique. Among interventions, angioplasty seems to have become the preferred procedure. Some authors claim that angioplasty may offer some benefit over bypass surgery in terms of vessel patency and limb salvage [18, 19, 21]. In reality, however, the patient's clinical condition and vascular situation and the availability of various techniques will eventually determine whether the patient undergoes bypass surgery or a percutaneous intervention.

Although a direct comparison between different treatment options is not possible due to the retrospective study design, the results of this study suggest that alprostadil treatment does not offer a relevant benefit in terms of mortality or limb salvage as compared to surgical or endovascular repair. On the other hand, outcomes are not worse than for other interventions. In addition, half of the patients required an endovascular procedure or bypass surgery despite alprostadil treatment.

It is clear that not only the type of intervention, but also other factors will determine patient outcome. It was shown that male patients had significantly worse 1-year amputation-free survival. This difference was mainly due to the higher rate of amputation observed in males. The risk for the primary outcome was also significantly associated with an increasing dialysis vintage. In addition, patient age and comorbidities such as diabetes and coronary heart disease have also been shown to affect amputation rates and mortality [18].

The fact that alprostadil, bypass surgery and endovascular interventions seem to have comparable outcomes in hemodialysis patients may give rise to the assumption that neither of these interventions is of any benefit and that high mortality and amputation rates reflect the natural course of PAD in that population. Arteriosclerotic disease and PAD in dialysis patients are not only driven by conventional risk factors, but also by factors specifically found in CKD [22–24]. None of the medicinal interventions, such as statins or antiplatelet therapies, which work in the non-CKD population, have been shown to be vasoprotective in dialysis patients. It is understandable that an intervention in a peripheral artery will not improve cardiovascular mortality. More disappointing is the fact that despite surgical and endovascular interventions many patients still need an amputation in the following year. A reason for this outcome may be the fact that almost all dialysis patients present with ischemic ulceration or gangrene at the time of initial diagnosis [25]. The authors therefore believe that the most promising approach is active surveillance for PAD and early intervention before ischemic ulcerations or necrosis develop.

The authors are aware of only one study that compared the outcome of patients with an intervention (bypass or PCI) and of patients with no intervention or amputation without prior intervention [25]. In that study patients undergoing any intervention had a significantly higher 1-year survival rate than those without intervention or amputation. In addition, the patients with an intervention had a very high 1-year amputation rate. The retrospective design, however, prevents exclusion of bias by indication. It is possible that the healthier patients were offered a revascularization procedure more often than the less healthy ones. The same holds true for another retrospective analysis showing reduced mortality in patients who underwent bypass surgery as compared to those with a primary amputation [26].

The present study is limited by its retrospective design, the small number of patients and the lack of a control group. Also no data were available on the effect exerted by treatment on pain management, walking distance or wound healing, other possible outcomes favorably affected by alprostadil. Likewise, no data on side effects were available. Especially alprostadil's effect on blood pressure is of concern and may preclude its use in hemodynamically unstable hemodialysis patients.

Conclusion

This study showed that despite treatment with alprostadil the amputation rate, need for revascularization procedures and mortality remained high in hemodialysis patients with critical limb ischemia. Outcome remained equally poor after revascularization procedures. Therefore, effective treatment strategies to reduce progressive vascular calcification in hemodialysis patients are urgently needed.

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Fig. 1. Amputation-free survival probability (primary end-point; **a**), overall survival probability (**b**) and amputation-free probability (**c**). The number of patients at risk is given for each 50 days of observation

Fig. 2. Gender-stratified amputation-free survival probability (**a**), overall survival probability (**b**) and amputation-free probability (**c**). The number of patients at risk in both groups is given for each 50 days of observation. Log-rank test for gender difference

Table 1

Baseline clinical characteristics

	Number (%)
<i>PAD stage</i>	
Stage 3	7 (8.1)
Stage 4	79 (91.9)
<i>PAD location</i>	
Iliac	9 (10.5)
Femoral	22 (25.6)
Popliteal	8 (9.3)
Distal	47 (54.7)
<i>Comorbidities</i>	
Diabetes	55 (64.0)
Coronary heart disease	66 (76.7)
Cerebrovascular disease	33 (38.4)
Heart failure	18 (20.9)
<i>Vascular dialysis access</i>	
Arteriovenous fistula	64 (74.4)
Graft	11 (12.8)
Central venous catheter	11 (12.8)

PAD peripheral artery disease

Table 2

Baseline laboratory characteristics

Parameter	Mean± SD
Hemoglobin (g/l)	115± 15
C-reactive protein (mg/dL)	4.2± 5.9
Albumin (g/dL)	3.5± 0.6
Calcium (mmol/L)	2.16± 0.20
Phosphorous (mmol/L)	1.83± 0.54
PTH (pg/mL)	256± 167

PTH parathyroid hormone

Table 3

Frequency of mortality, amputations, location of amputation and revascularisation procedures

End point	Number (%)
<i>Primary outcome (amputation or death within 1 year)</i>	51 (59.3)
<i>Death within 1 year</i>	30 (34.9)
<i>Amputation within 1 year</i>	31 (36.0)
<i>Location of amputation</i>	
Upper leg	3 (3.5)
Lower leg	4 (4.7)
Foot	5 (5.8)
Toe	19 (22.1)
<i>Procedure</i>	
Endovascular procedure	31 (36.0)
Bypass surgery	14 (16.3)

Table 4

Multivariable-adjusted Cox regression analysis for primary end-point (1-year mortality or amputation)

Parameter	HR (95% CI)	P-value
Age (per year)	1.01 (0.98–1.03)	0.703
Male sex	2.07 (1.03–4.15)	0.042
Diabetes mellitus	1.72 (0.84–3.52)	0.137
Smoking	0.88 (0.45–1.52)	0.530
Coronary artery disease	0.61 (0.31–1.21)	0.157
Cerebrovascular disease	0.94 (0.49–1.79)	0.847
Heart failure	0.88 (0.40–1.97)	0.758
Dialysis vintage (per month)	1.01 (1.00–1.01)	0.041
PAD stage	0.99 (0.36–2.79)	0.995

HR hazard ratio, CI confidence interval, PAD peripheral artery disease

Table 5
Outcome of hemodialysis patients undergoing revascularization for critical limb ischemia

Reference	Number of patients	Intervention	Survival (%; year[s])	Amputation-free survival	Definition of amputation	Amputation rate (%; year[s])
Lumsden et al. 1994 [14]	27	Bypass	30; 2	Not given	Unknown	35; 1
Baele et al. 1995 [15]	44	Bypass	74; 1	Not given	Major	30; 1
Hakaim et al. 1998 [16]	23	Bypass	52; 1	Not given	Unknown	37; 1
Ramdev et al. 2002 [27]	146	Bypass	60; 1	Not given	Unknown	20; 1
Jaar et al. 2004 [18]	800	Bypass 63.5%	37; 2	Not given	Unknown	24; 3
		PCI 36.5%	57; 2			6; 3
Logar et al. 2005 [26]	1896	Bypass	50; 1	Not applicable	Not applicable	Not applicable
O'Hare et al. 2006 [25]	371	Bypass or PCI	65; 1	Not given	Major	44; 1
Graziani et al. 2007 [20]	107	PCI	66; 1	Not given	Major	14; 1
Kodama et al. 2014 [17]	89	Bypass	68; 1	64% 1 y	Major	11; 1
Fallon et al. 2015 [19]	689	Bypass 43%	60; 1	17% 2 y	Unknown	28; 1
		PCI 57%				
Parvataneni et al. 2016 [6]	64	PCI	56; 3	41% 3 y	Major	11; 3
					Any	28; 3
Lüders et al. 2016 [5]	1436	Bypass 12%	22; 4	55% 1 y	Unknown	56; 4
		PCI 43%				
This study	86	Alprostadil	65; 1	41% 1 yr	Major	8.2; 1
					Any	34; 1

Major amputation is defined as an amputation above the ankle; *Unknown* denotes that the respective study gives no details *PCI* percutaneous endovascular intervention