Intravenous Pentoxifylline for the Treatment of Chronic Critical Limb Ischaemia

The European Study Group

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Objectives: To investigate the safety and efficacy of intravenous pentoxifylline infusion therapy, 600 mg twice daily for up to 21 days, for the management of patients with chronic critical limb ischaemia (CLI).

Design: A prospective, randomised, double-blind, placebo-controlled, parallel-group, multicentre trial.

Setting: County and university hospitals in six European countries.

Materials: A total of 314 patients suffering from CLI were enrolled: 157 patients were allocated to each treatment.

Outcome measures: Patients were reviewed after 7 days of treatment and continued in the study for up to a further 14 days if their condition had not deteriorated. Rest pain (assessed by pain score and visual analogue scale), sleep disturbances and analgesic consumption were measured.

Results: Both intention-to-treat and per protocol analyses showed significantly positive results in favour of pentoxifylline over placebo. Severity of rest pain was consistently and significantly lower as shown by the results of the pre-infusion pain scores (p = 0.007), pain visual analogue scales (p < 0.001) and scores describing rest pain-related sleep disturbances (p = 0.003). Treatment response was not influenced by the presence of diabetes mellitus or by eligibility for surgery.

Conclusion: These results justify the use of intravenous pentoxifylline infusion therapy for the management of rest pain in patients with CLI.

Key Words: Critical limb ischaemia; Rest pain: Visual analogue scale; Pentoxifylline; Randomised controlled trial.

Introduction

Chronic critical limb ischaemia (CLI) is an advanced stage of severe peripheral vascular disease (PVD), with a significant morbidity and mortality. The condition is characterised by persistent rest pain, requiring regular analgesia, and/or ulceration or gangrene of the foot or toes. It may represent the end-stage of progressive deterioration of intermittent claudication. However a considerable number of patients develop critical ischaemia without previous claudication. The prevalence of CLI is not known exactly, but from the numbers of amputations it can be concluded that it constitutes a significant clinical problem. Figures given in the literature for the deterioration rate from intermittent claudication to severe ischaemia vary widely depending on the anatomical distribution of atherosclerotic lesions, the pattern of risk factors, the severity of claudication and other prognostic factors. An estimate of 10–20% may be a conservative but acceptable proportion of patients who progress from intermittent claudication to CLI. Diabetics have a particularly poor prognosis, with an estimated five-fold increase in risk of deterioration.

Current treatment options are generally surgical apart from approaches such as epidural spinal cord electrical stimulation, lumbar chemical sympathectomy and percutaneous transluminal angioplasty.
investigate the efficacy of intravenous pentoxifylline. The aim of this randomised, double-blind, placebo-controlled, parallel-group multicentre study was to evaluate the efficacy of pentoxifylline in the treatment of patients with chronic CLI. Treatment effects on the relief of ischaemic rest pain and acute management of ischaemia were also investigated. These preliminary findings, this multicentre, randomised, double-blind, placebo-controlled study was undertaken to evaluate the efficacy of pentoxifylline in the relief of ischaemic rest pain and acute management of patients with chronic CLI. Treatment effects on walking capacity were also assessed.

A total of 18 hospital centres in Belgium, Denmark, Great Britain, Ireland, The Netherlands and Sweden participated. The study was approved by the relevant hospital ethics committees and conducted in accordance with the Declaration of Helsinki, Venice Revision, 1983. All patients gave their informed consent before entering the trial.

Patients

Patients who were older than 50 years and hospitalized with persistent, severe rest pain due to CLI, and with clinical evidence of severe PVD, were provisionally enrolled in the study. The definition of CLI was based on the proposal of the Working Party of the International Vascular Symposium (1982), which was the most recent proposal for a standardised definition of CLI when the study was started: i.e. persistent and severe rest pain, sleep disturbances and the need for repeated analgesia for pain relief, present for at least 3 weeks. The presence of PVD was confirmed by vascular examination, haemodynamic assessment and angiography. All patients suffered from PVD Fontaine stages III/IV and hence had a limited walking capacity (pain-free claudication distance less than 50 m). Previous treatment with antiplatelet and/or vasoactive drugs was discontinued, and cardiovascular drug therapy was stabilised on study entry. During the trial, analgesic therapy was limited to paracetamol, paracetamol/dextropropoxyphene, morphine sulphate or pethidine on demand.

Patients with evidence of any of the following conditions were excluded: Buerger’s disease, immunological arteritis, renal or hepatic failure, uncompensated heart failure, severe circulatory or metabolic diseases, major infection, acute embolism or thrombosis, active neoplastic disease or malignant disease treated with immunosuppressive or cytotoxic drugs in the last 12 months, myocardial infarction or unstable angina pectoris within the last 3 months, major surgery within the last 4 weeks, xanthine hypersensitivity, abnormal clotting screen, alcoholism or drug addiction. Patients who had received a therapeutic agent with a well-defined potential for major organ toxicity within the last 3 months, or who required intravenous infusion of more than 1000 ml per 24 h, in addition to the study drug vehicle, were also excluded.

Patients and Methods

The aim of this randomised, double-blind, placebo-controlled, parallel-group multicentre study was to investigate the efficacy of intravenous pentoxifylline (Trental®, Hoechst AG, Germany) infusion therapy, 600 mg twice-daily, for the treatment of rest pain due to CLI in patients with severe PVD. Treatment effects on walking capacity were also assessed.

(PTA). Approximately 60% of patients undergo vascular reconstruction, often as surgical emergencies; 20% undergo primary amputation and 20% some other form of temporary treatment. Given the high prevalence of concurrent diseases and other manifestations of atherosclerosis, particularly coronary heart disease and extracranial cerebral vascular disease in this patient group, the above-mentioned procedures are associated with a significant perioperative morbidity and mortality and a poor long-term prognosis. As many patients are not eligible for surgery, pharmacotherapy remains one of the alternative methods of treatment.

An internationally accepted gold standard for the conservative management of CLI has not yet been established. Since CLI patients suffer from abnormalities in the macro- and microcirculation, elevated fibrinogen levels and impaired leucocyte function, the use of vasoactive agents has been a rational approach to conservative management. Numerous studies have investigated the efficacy of vasoactive agents in the treatment of CLI. However, a lack of standardisation in the definition of CLI, varying patient populations, lack of a suitable standard for comparison and the use of different efficacy outcome measures have prevented extrapolation of any positive findings to the general clinical situation. Clinical trial methodology has recently been discussed in the European Consensus Document on Critical Leg Ischaemia. As persistently recurring rest pain is the main symptom, the primary outcome of any trial should be pain reduction that is independent of any analgesic effect of the test medication itself. This reduction in rest pain is important regardless of whether an invasive treatment program follows.

Pentoxifylline, a vasoactive substance with haemorheological properties, is effective in the treatment of PVD. Several open studies have suggested that intravenously administered pentoxifylline may also be effective in the acute management of more severe stages of PVD, including CLI. On the basis of these preliminary findings, this multicentre, randomised, double-blind, placebo-controlled study was undertaken to evaluate the efficacy of pentoxifylline in the relief of ischaemic rest pain and acute management of patients with chronic CLI. Treatment effects on walking capacity were also investigated.
Study Design

Patients were treated for up to 21 days. At baseline, all patients underwent a comprehensive screening procedure, including angiography, determination of peripheral haemodynamics, general physical and vascular examinations, pain and walking assessments, chest X-ray, 12-lead ECG, and routine safety laboratory investigations. During the first 7 days of the study, treatment effects and the patient’s suitability for surgery were evaluated. Patients whose condition had stabilised at the end of 7 days (improvement or no change in pain intensity and/or sleep disturbance questionnaire scores) continued in the study for a further 14 days. Pain assessments and analgesic consumption were recorded daily. Walking capacity assessments and general physical and vascular examinations were conducted at the end of each week of treatment.

Adverse events were obtained by spontaneous reporting. Wherever possible, information on the onset, duration, severity and possible causality (in relation to the study drug) of the event was provided. Details of all withdrawals and of surgery performed within 21 days of commencing the study were also noted. Routine laboratory safety investigations, chest X-ray and ECG were repeated at the final visit.

Treatment

Patients were randomised consecutively to receive either twice-daily intravenous infusions of 600 mg of pentoxifylline or placebo in a carrier of 500 ml normal saline (total daily dose of pentoxifylline 1200 mg) given over 4–6 h. Infusions were administered in a peripheral arm vein; infusion rates were controlled by a pump system or drip counter. The infusion rate was reduced if the patient experienced side effects such as nausea or vomiting. If fluid overload occurred, the volume of vehicle could be reduced (to 250 ml). As an alternative to normal saline another vehicle (5% dextrose or dextrose/saline) was accepted. Patients weighing less than 50 kg received only 300 mg of pentoxifylline or placebo per infusion. Treatment was continued for a maximum of 21 days.

Treatment was discontinued if the patient required emergency surgery, failed to show a benefit in the relief of rest pain after 7 days or developed a serious adverse reaction.

Endpoints

The results of pain assessment (pre-infusion pain, pain relief, sleep disturbances) were used as primary endpoints. Secondary endpoints were the walking capacity and an assessment of global clinical impression by the physician and the patient at the final visit.

Methodology

Angiography

Angiograms were reviewed by an independent radiologist and scored using the method of Bollinger et al. An independent surgical consultant reviewed the angiograms and assessed the patient’s suitability for surgery.

Haemodynamic measurements

Distal perfusion pressures were measured as either toe pressure, using strain gauge plethysmography (for diabetic patients), or as ankle pressures (posterior tibial and dorsalis pedis artery) assessed by Doppler sonography (for non-diabetic patients). Brachial systolic pressures were also recorded, and ankle/arm pressure ratios calculated using the higher pressure value of the two ankle arteries.

Pain assessments and analgesic consumption

Pain was assessed before the morning infusion (with the patient in a supine position, legs not hanging over the side of the bed), 3 h after the start of the morning infusion and at the end of the infusion. No analgesics were given within 4 h prior to the start of the morning infusion unless the patient demanded pain relief.

Three different types of pain indicators were studied: pain intensity, sleep disturbance due to pain and pain relief during the infusion. Pain intensity was assessed using a 4-point score varying from no pain (1) to severe pain (4), and a self-report 100 mm visual analogue (VA) scale varying from no pain (0 mm) to maximum pain (100 mm). Both measures of pain were used in an attempt to objectively assess pain intensity and to avoid investigator bias. The extent of sleep disturbance due to pain was assessed using a 5-point questionnaire varying from excellent, i.e. asleep all night (1), to poor, i.e. awake most of the night with pain (5). Infusion-related pain relief was assessed using a 5-point questionnaire varying from no pain relief (1) to complete pain relief (5), and a comparison of the pain intensity scores before and immediately after the end of infusion. In addition, the Burford Pain Thermometer, a device for simultaneous measurement of pain intensity and analgesic consumption, was used to assess the relationship between pain and analgesic
consumption. The pain assessment of each patient was performed by the same observer each day.

**Walking capacity**

The walking capacity was regarded as a qualitative (not quantitative) secondary endpoint. It was of interest to see whether short-term infusion treatment with pentoxifylline influenced the patients' general mobility. Under these conditions it was considered appropriate to use three methods to assess the walking capacity. Patients completed either a formal treadmill test, performed at 3.2 km/h on a 0% gradient, or a metronome-controlled walking test, performed at 60 steps/min. Both the pain-free and absolute (maximum) claudication distances were recorded where possible. Anecdotal assessments of walking ability were made for the remaining patients.

**Global clinical impression**

Both patients and physicians gave their subjective assessment of the condition at the end of the study relative to baseline (improved/unchanged/impaired).

**Sample size and statistical analysis**

The planned sample size was 120 evaluable patients per treatment group based on an expected response rate of 50% on pentoxifylline compared with 30% on placebo (alpha = 0.05, beta = 0.20). With the exception of centre 22, randomisation was stratified by centre with a block size of 10. A variable block size was used for centre 22.

All statistical analyses were performed using SAS PC (version 6.04). Chi-squared tests, with 95% confidence intervals, were used for comparing treatment effects on the change in preinfusion pain between baseline and the final visit. Within each treatment group, differences between the VA scale at baseline and final visit were compared using Wilcoxon’s matched-pairs signed rank test. Treatment differences in the change in VA scale were compared using Wilcoxon’s rank sum test. Laboratory data were analysed descriptively. For all efficacy analyses, the level of significance was 0.05.

**Results**

A total of 314 patients were enrolled in the study: 157 patients were randomised to each treatment. Demographic and background characteristics are summarised in Table 1; 149 patients on pentoxifylline and 139 patients on placebo presented with a history of intermittent claudication. A history of hypertension was more common in the pentoxifylline group (p = 0.03). However, the blood pressure values at baseline were similar. Otherwise there were no differences between the two groups. The majority of patients had 2- or 3-segmental disease involving the femoro-popliteal segment, with most of the significant disease being occlusive in nature. Approximately one-third of the patients had previously undergone vascular surgery, with amputation in about 10% of patients. Overall, both groups were comparable as regards demographic data, prevalence of risk factors and anatomical distribution of stenoses and occlusions within the lower extremity vascular tree, and representative of a general population suffering from CLI.

Most patients in each group reported rest pain and pain-related sleep disturbance at baseline. A few patients reported no pain at the time when baseline
rest pain was assessed (pentoxifylline \( n = 13 \), placebo \( n = 18 \)); this finding was not unexpected because ischaemic rest pain varies in intensity and patients were receiving analgesia in hospital. Overall, the distribution of pain intensity was similar in each group (Table 2). The walking capacity of the two groups at baseline was also similar, as shown by the absolute claudication distance of patients who underwent treadmill testing [pentoxifylline: 77m [interquartile range (IQR 39–135)], placebo: 58m (IQR 31–100)]. Approximately two-thirds of patients were receiving analgesia in both treatment groups (Table 3).

A total of 74 patients on pentoxifylline and 76 patients on placebo completed the 21-day study; 18 patients on pentoxifylline and 19 patients on placebo were withdrawn before the end of the first week of treatment (day 7). A further 50 (15) pentoxifylline patients and 48 (14) placebo patients discontinued the treatment prematurely before study day 14 (21). The reasons for withdrawal are summarized in Table 4. The median duration of treatment was similar for both groups: 18 days for pentoxifylline and 19 days for placebo.

### Table 2. Baseline pain assessments

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pentoxifylline (( n = 157 ))</th>
<th>Placebo (( n = 157 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain intensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>13 (8)</td>
<td>18 (12)</td>
</tr>
<tr>
<td>Slight</td>
<td>58 (37)</td>
<td>52 (33)</td>
</tr>
<tr>
<td>Moderate</td>
<td>65 (42)</td>
<td>66 (42)</td>
</tr>
<tr>
<td>Severe</td>
<td>20 (13)</td>
<td>20 (13)</td>
</tr>
<tr>
<td>VA score (mm)</td>
<td>Median (IQC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40 (25–60)</td>
<td>40 (25–60)</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asleep all night</td>
<td>17 (11)</td>
<td>18 (12)</td>
</tr>
<tr>
<td>Undisturbed (no pain)</td>
<td>18 (12)</td>
<td>22 (14)</td>
</tr>
<tr>
<td>Good (awake once)</td>
<td>41 (26)</td>
<td>24 (15)</td>
</tr>
<tr>
<td>Fair (awake 2–3 times)</td>
<td>56 (36)</td>
<td>61 (39)</td>
</tr>
<tr>
<td>Poor (awake most of night)</td>
<td>24 (15)</td>
<td>31 (20)</td>
</tr>
</tbody>
</table>

* Data missing for one patient in each group
* Data missing for two patients in the pentoxifylline group and one patient in the placebo group
* IQR, Interquartile range

Efficacy

#### Pain assessment (intention-to-treat population)

Both the pain scores and VA scales showed a statistically significant reduction in the intensity of preinfusion pain in favour of pentoxifylline at the final visit (Table 5). Using the pain score system, pain relief was reported by 90 patients in the pentoxifylline group (58%; 95% C.I. 50–66%). In the placebo group the corresponding number was 66 patients (42%; 95% C.I. 34–49%). The difference in proportion of pain relieved was statistically significant in favour of pentoxifylline (\( p = 0.007 \)). These results were confirmed by a strict “per protocol” analysis (\( p = 0.05 \)). Patients on pentoxifylline and placebo showed a median decrease of 22 and 6 mm respectively on the VA scale (\( p < 0.001 \)). The results of both pain assessment systems correlated (\( r = 0.88 \)).

No difference was found between the two treatment groups in terms of pain relief during the course of the infusion, indicating the lack of an acute analgesic effect of pentoxifylline. Sixty-six patients (43%) in the pentoxifylline group reported an increase in pain relief during infusion at the end of study compared to 58 patients (37%) in the placebo group (\( p = 0.33 \); Table 5). This result was supported by a comparison of the pain intensity scores assessed before, and directly after, the end of the morning infusion on study days 1, 7, 14 and 21. No statistically significant difference between the treatment groups was found on each of these days. The significant reduction in preinfusion pain intensity with pentoxifylline was also associated with a significant reduction in pain-related sleep disturbances; 101 (65%) patients on pentoxifylline and 75 (48%) patients on placebo showed a reduction in pain-related sleep disturbance at the final visit (\( p = 0.003 \); Table 5).

Pain assessment in patients with peripheral pressures \( \leq 60 \text{ mm Hg} \)

In this study severe ischaemia was defined according to the criteria described by Bell et al.\(^{29}\) The European Consensus Document on Critical Limb Ischaemia was published more recently and included haemodynamic parameters to define CLI.\(^{6}\) A total of 201 (out of 314) patients complied with the European Consensus definition and showed peripheral pressures \( \leq 60 \text{ mm Hg} \) (higher value of dors. ped. and post. tib. artery pressure).

As shown in Table 6, 28% (pentoxifylline) vs. 15% (placebo) of these patients showed an improvement of \( \geq 2 \) points in the pain-intensity score system (\( p = 0.026 \)). Using the VA scale pentoxifylline-treated patients showed a median improvement of 20 mm as compared to 5 mm under placebo (\( p = 0.007 \)). Both results are comparable to those for the overall intention-to-treat population. The analgesic consumption was reduced in responders of both groups; however, a
higher number of pentoxifylline than placebo patients discontinued analgesics or switched to a milder analgesia regimen (Table 3). Additionally, Burford pain scores were similar within each treatment, indicating that the intensity of pain requiring analgesia experienced by patients in each group was similar (Table 5).

Retrospective, exploratory subgroup analyses were performed to investigate the effect of prognostic factors on treatment response, particularly for diabetes and/or the patient's eligibility for surgery. In the intention-to-treat population, diabetes was present in 52 patients on pentoxifylline and 39 on placebo. At the end of the study, there was no apparent difference in the reduction of preinfusion pain scores with pentoxifylline between diabetic and non-diabetic patients. For diabetic patients, pain scores were reduced in 58% of patients on pentoxifylline compared with 33% on placebo. For non-diabetics, 58% of patients on pentoxifylline compared with 45% on placebo showed lower pain scores. These results were in agreement with the overall response rates in the intention-to-treat population.

The pain response in patients who were eligible for vascular reconstruction (pentoxifylline: \( n = 100 \); placebo: \( n = 99 \) ) was tested after 1 week of treatment. Reduction of preinfusion pain scores was observed in 66% of patients on pentoxifylline and 47% on placebo at the end of the study. Although response rates were slightly lower in patients ineligible for surgery (reduction in pain scores in 43% of patients on pentoxifylline and 33% on placebo), the trend for each cohort was in the same direction and suggested that there were no major differences in treatment outcome between the groups.

Both patients' and physicians' subjective global assessments of clinical outcome reflected differences in response rates observed between the two groups, and favoured pentoxifylline. Ninety-three (61%) patients on pentoxifylline compared with 67 (44%) patients on placebo considered that their condition had improved at their final assessment\( (p = 0.012) \). On the basis of the physicians' assessments, 86 (56%) patients on pentoxifylline and 53 (34%) on placebo were considered to have improved at their final assessment\( (p < 0.0001) \). The correlation between the two assessments was good\( (r = 0.84) \). Furthermore, a positive outcome in rest pain was associated with a positive outcome in the patients' global assessment.

Walking capacity

The walking ability of patients at final visit compared to baseline showed some qualitative improvement, with a trend in favour of pentoxifylline\( (p = 0.09) \). In the treadmill-tested subgroup there were no statistically significant differences between the pentoxifylline and placebo groups, in either the pain-free or absolute claudication distances, at the final visit.

Safety and tolerability

Adverse events were reported by 92\( (59\%) \) patients treated with pentoxifylline and 74\( (47\%) \) treated with placebo. The higher incidence of adverse events with
Table 5. Change in pain assessments between final visit and baseline (intention-to-treat analysis)

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Treatment comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentoxifylline</td>
<td>Placebo</td>
</tr>
<tr>
<td>Pre-infusion pain intensity score</td>
<td>p-value</td>
</tr>
<tr>
<td>Decrease by ≥ 1 point</td>
<td>90 (58%)</td>
</tr>
<tr>
<td>No change/increase</td>
<td>66</td>
</tr>
<tr>
<td>Decrease by ≥ 2 points</td>
<td>40 (26%)</td>
</tr>
<tr>
<td>Decrease &lt; 2 points/increase</td>
<td>116</td>
</tr>
<tr>
<td>Visual analogue scale</td>
<td>Median (IQR(^c))</td>
</tr>
<tr>
<td>Decrease</td>
<td>-22 (-42–0)</td>
</tr>
<tr>
<td>No change/increase</td>
<td>-6 (-30–5)</td>
</tr>
<tr>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>Median (IQR(^c))</td>
</tr>
<tr>
<td>Decrease</td>
<td>101 (65%)</td>
</tr>
<tr>
<td>No change/increase</td>
<td>55</td>
</tr>
<tr>
<td>- 75 (48%)</td>
<td>81</td>
</tr>
<tr>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Pain relief during infusion</td>
<td>Median (IQR(^c))</td>
</tr>
<tr>
<td>Decrease</td>
<td>66 (43%)</td>
</tr>
<tr>
<td>No change/increase</td>
<td>89</td>
</tr>
<tr>
<td>- 58 (37%)</td>
<td>98</td>
</tr>
<tr>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Burford pain score</td>
<td>Median (IQR(^c))</td>
</tr>
<tr>
<td>Decrease</td>
<td>5 (3.5–6)</td>
</tr>
<tr>
<td>No change/increase</td>
<td>5 (3.5–6.5)</td>
</tr>
</tbody>
</table>

\(^a\) Results are given in millimetres

\(^b\) Results are note readings on the Burford scale

\(^c\) IQR, Interquartile range

Data not recorded for one patient in each group for pain score and sleep disturbance scores, and for two patients on pentoxifylline and one patient on placebo for visual analogue and pain relief scores.

Table 6. Change in pain assessment at final visit in patients with peripheral pressures at baseline ≤ 60 mmHg

<table>
<thead>
<tr>
<th>Pain score (no. of patients)</th>
<th>Number (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentoxifylline (n = 100)</td>
<td>Placebo (n = 101)</td>
</tr>
<tr>
<td>Decrease by 3 points</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Decrease by ≥ 2 points</td>
<td>28 (28%)</td>
</tr>
<tr>
<td>Increase by ≥ 2 points</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Increase by ≥ 3 points</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Visual analogue scale (mm)</td>
<td>Baseline, median (IQR(^c))</td>
</tr>
<tr>
<td>Pentoxifylline (n = 100)</td>
<td>40 (26–60)</td>
</tr>
<tr>
<td>Placebo (n = 101)</td>
<td>40 (21–60)</td>
</tr>
<tr>
<td>Final visit, median (IQR(^c))</td>
<td>11 (0–33)</td>
</tr>
<tr>
<td>Difference (IQR(^c))</td>
<td>-20 (-43–0)</td>
</tr>
</tbody>
</table>

\(^c\) IQR, Interquartile range

Pentoxifylline was largely accounted for by gastrointestinal symptoms (pentoxifylline: 59 cases, placebo: 18 cases; p < 0.0001). There was no evidence of local irritation: only one patient on pentoxifylline and two patients on placebo had evidence of inflammation at the injection site.

Serious events were experienced by 29 patients on pentoxifylline and 38 on placebo. Vascular events were the main cause of morbidity and mortality. There were four cerebrovascular events with pentoxifylline, one of the patients having discontinued treatment 2 weeks prior to the event; there were no reports with placebo. Cardiovascular events were seen in four cases on pentoxifylline and 13 on placebo. Worsening of the underlying peripheral vascular disease necessitated invasive intervention in 36 patients, 17 on pentoxifylline and 19 on placebo. The overall mortality rate was 2.6% (eight patients, four patients in each treatment group).

There were no clinically significant changes in laboratory safety variables, chest X-ray, ECG or physical examination findings with either treatment.

Discussion

There is a clear need for effective conservative management of CLI, both for patients ineligible for vascular reconstruction, in whom amputation is the only alternative, and for patients eligible for reconstruction while being prepared for intervention.

Results of this study have confirmed earlier findings\(^{22–28}\) and justify the use of intravenous pentoxifylline therapy for the acute management of CLI. Both intention-to-treat and protocol analyses have shown that treatment with pentoxifylline significantly alleviated the main symptoms of CLI, namely rest pain and pain-related sleep disturbances. The possibility that these effects were due to an analgesic effect of pentoxifylline, or to an increase in analgesic consumption, was excluded. Results relating to rest pain and sleep disturbances were supported by the outcomes of global assessments made by the patient and the
physician. As rest pain and sleep-related disturbances are the dominant symptoms in CLI patients these global assessments might be used as crude means of evaluating treatment effects on quality of life.

The assessment of pain intensity is a subjective judgement made by the patient and is therefore intrinsically variable; the patient's judgement may also be influenced by the trial staff and other factors. In order to minimize bias, the study included a dual pain assessment system employing a score system and a visual analogue (VA) scale. Furthermore, both tests were performed by the same staff member at the same time of the day (0800h). The pain intensity score shows an unexpectedly high placebo effect of about 40% even under these conditions. The reason for this may be that the patients were asked a biased question which caused them to underestimate their pain by at least 1 scorepoint. A further possible explanation lies in the interpretation of the data, and the definition of the degree of pain alleviation which is regarded as being clinically relevant. It is almost impossible to give a general definition of this for all CLI patients, but it is generally agreed that minimal changes in pain cannot be regarded as being clinically relevant.

There is no scientific justification to view a pain reduction of 1 scorepoint as being minimal and irrelevant. If, however, this is assumed and only improvements of $\geq 2$ points are considered, the response rates for pentoxifylline and placebo treatment are 26% and 17% respectively. The placebo effect thus lies in the expected range and corresponds to results of prostaglandin E$_1$ (PGE$_1$) studies. Prostaglandin E$_1$ is licensed in several European countries for the treatment of CLI). From this discussion it may be concluded that the results of the assessment of pain intensity with the VA scale can be regarded as being more valid than the results of the pain score system. Hence VA scales should be used rather than score systems in future trials on CLI patients.

The definition of CLI has been the subject of considerable discussion. Whereas in this study the Bell criteria were applied the European Working Group on Critical Limb Ischaemia has proposed a definition employing both clinical and haemodynamic parameters. If a pressure cutoff point of 60 mmHg is chosen 201 patients, out of the intention-to-treat population of 314, comply with both the Bell and the European Working Group criteria. As shown in Table 6, the results from this subpopulation are similar to those from the intention-to-treat population. Using the score system, 28% of the pentoxifylline and 15% of the placebo patients described a pain decrease of $\geq 2$ points ($p = 0.026$). In the VA scale the absolute decreases reached with pentoxifylline and placebo amounted to 20 mm and 5 mm respectively ($p = 0.007$). Again, the results from both assessment systems showed an acceptable correlation ($r = 0.90$). It can thus be concluded that the pentoxifylline data remain valid regardless of whether the Bell or the European Consensus criteria are used for the definition of CLI.

Demographic and background characteristics (Table 1) were comparable in all groups described above (intention-to-treat population, subpopulation) and were representative for a general elderly population suffering from severe peripheral vascular disease. Hence results shown in this trial can be extrapolated to a general CLI population at large.

The alleviation of rest pain seen in the pentoxifylline group was independent of an analgesic effect of the drug itself. The most likely explanation for this would be an improvement in microcirculatory perfusion of the end organ, i.e. the skeletal muscle. There is sufficient evidence from the literature that pentoxifylline does improve the intramuscular pO$_2$ in PVD patients. However, in a large scale multicentre clinical trial this is difficult to prove because reliable intramuscular pO$_2$ measurements not only require the instalment of the apparatus in all centres, but also demand adequate skill and experience to use it appropriately. For several reasons, the assessment of cutaneous perfusion parameters (tcpO$_2$, Laser-Doppler, capillary microscopy) is not a true alternative. Firstly, sufficient correlation between muscular perfusion and the perfusion of skin capillaries may only be expected if the cutaneous shunt perfusion remains constant. Secondly, Laser-Doppler sonography and capillary microscopy are characterised by a high inter- and intraindividual variability of the results, which qualifies these techniques for the assessment of dynamic perfusion changes with acceptable accuracy. In the long-term follow-up of a large patient sample, however, their use is rather laborious. Finally, an important determinant for the methodology to be applied in a clinical trial is the number of centres involved. With 18 centres scattered throughout Europe sophisticated techniques, which are extremely helpful in single centre trials, need to be avoided, and if meaningful results are to be obtained, endpoints must aim at clinical variables.

The overall incidence of adverse events was similar for pentoxifylline and placebo and was also similar to side effect rates reported in other studies. However, there were more gastrointestinal symptoms with pentoxifylline, as this is well known from its side effect profile. Taking into account that CLI patients are at risk and severely ill, the risk/benefit ratio for intravenous pentoxifylline appears to be positive; thus the use of this drug for the acute
management of CLI seems to be justified, as has been confirmed in other studies. 40-42

The basis for any therapeutic approach to CLI, whether conservative therapy, thrombolysis, surgery or dilatation, is a risk/benefit assessment for each patient. Published literature on the 30-day mortality, 30-day morbidity and early and late failures in reconstructive surgery or PTA 53-55 ethically justifies these two procedures. PTA- and surgery-related mortality have been estimated to be 0.2-1.4% and 1-9% respectively; estimates for PTA- and surgery-related morbidity are 3-15% and 10-20% respectively. Long-term (2 to 4 years) reocclusion rates are similar for both procedures and estimates range between 20 and 40% for the iliac and between 30 and 60% for the femoropopliteal segment. 43,45,51-53,55 However, it has to be taken into consideration that the above figures represent longitudinal results for a general PVD population consisting of intermittent claudicants and CLI patients who require PTA or bypass surgery. CLI patients often present with an involvement of all three lower extremity vascular segments, an impaired inflow and outflow tract and hence a limited probability of successful surgical reconstruction. Also 50-80% and 30-60% of these patients suffer from symptomatic coronary heart disease and extracranial carotid artery disease respectively, 4,6,10-12,15,57 chronic obstructive pulmonary disorders and cardiac failure are also common in this multi-risk elderly population. Consequently, the true figures for the 30-day morbidity and mortality and data on long-term outcome are considerably higher than those cited above. If a major amputation is required, hospital mortality may be as high as 30% and the percentage of non-lethal complications even higher. These figures are reported by Harris and Moody, 56 and are based on the official British amputation statistics; they have also been confirmed by other authors. 59-62 Furthermore, the chances for rehabilitation and social reintegration after above-knee or below-knee amputation are as low as ≤ 25% and ≤ 40%60 and the mean survival time ranges between 3 and 6 years. 61-65 In diabetics the situation is worse. They do not only carry a five-fold increased risk of PVD progression from intermittent claudication to CLI, 6 but also show a 10-fold increased risk of amputation if CLI occurs. 6

Although long-term outcome was not assessed in this study, there is evidence that pentoxifylline infusion therapy followed by oral treatment may show a long-term benefit. McCollum and Galvin both showed that, in responders, the need for invasive treatment could be reduced in the 6-12 months following acute pentoxifylline infusion. 25, 26 Trübestein et al. 27 compared pentoxifylline to PGE1 treatment and showed that pentoxifylline was efficacious, even though only half of the recommended dose was used for the acute treatment phase, and patients were not switched to oral treatment during the one year follow-up. Taking all available pentoxifylline data together (this study, 23-25) and comparing them with published results on PGE1, PGI2 and prostacyclin analogues, 27,32,64-71 it can be shown that the magnitude of response in terms of acute relief of rest pain, healing rates of ischaemic lesions and results from long-term follow-up is similar.

In conclusion, the infusion of 600 mg pentoxifylline twice daily for a period of up to 21 days gave pain relief in the acute management of CLI. Treatment outcome was not influenced by the presence of diabetes, the eligibility for surgery or by extremely impaired peripheral haemodynamics.

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