Treatment of severe intermittent claudication with PGE1. A short-term vs a long-term infusion plan: a 20-week, European randomized trial - analysis of efficacy and costs


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
A long-term treatment protocol (LTP) for prostaglandin E1 (PGE1) was compared with a short-term treatment protocol (STP) for PGE1 for the treatment of severe intermittent claudication.

Type of intervention
Treatment.

Economic study type
This study reported a cost-effectiveness analysis. The perspective of the study was not reported.

Study population
The study population included patients with severe intermittent claudication. The study sample comprised people with the condition and a total walking distance (TWD) of 50 to 200 metres. Other inclusion criteria were: intermittent claudication lasting more than 4 months; resting Doppler ankle/brachial pressure (ABI) less than 0.8; decrease in ankle pressure of more than 15mmHg after standard exercise test on treadmill; age between 45 and 75; documentation of arterial stenoses, plaques, and arteriosclerosis by colour-duplex imaging. Patients were excluded if angina or exercise-related ischaemia were present and if their maximum walking distance changed more than 25% during the 2-week run-in period. Other exclusion criteria were: previous coronary or vascular surgery or angioplasty; aneurysms; congestive heart failure; renal failure; diabetes requiring insulin treatment; arthritis, pulmonary, cardiac, neoplastic, inflammatory, or immunologic diseases.

Setting
The setting was secondary care in the UK, Greece, USA, Italy, France and Denmark.

Dates to which data relate
The dates relating to the effectiveness evidence and resources used were not reported. The price year was not reported.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
Prospective costing was carried out on the same sample of patients as that used to collect the effectiveness evidence.

Study sample
Power calculations were based on the absolute change in total (or maximum) walking distance (TWD) from a baseline treadmill test. The sample size was based on the assumption of a reasonable effect size index of 0.4 for the logarithm of the difference between the 2 groups in the change in TWD from baseline to end of follow-up. At least 45 patients per group were required to detect a difference of this magnitude with a power of 80% in a two-tailed t-test (alpha = 5%).

The patients entered into the trial were given a preliminary evaluation and exercise cardiac test. The authors did not report how potentially eligible patients were identified for these preliminary evaluations. The number of patients given the preliminary evaluations, the number of patients excluded and the number who refused to participate were not reported. A total of 109 patients were recruited into the study and there were 55 in the LTP group and 54 in the STP group. The authors did not report the rationale for the inclusion and exclusion criteria used or the method of patient selection.

**Study design**

This was a multi-centre, randomised, controlled trial. No details about the number of centres included in the study were reported. Patients were randomised to each group but no details about the method of randomisation were reported. The length of follow-up was 20 weeks. Thirteen patients were lost to follow-up: 7 in the LTP group and 6 in the STP group. There was no method of masking participants or assessors to treatment allocation for the assessment of outcomes.

**Analysis of effectiveness**

The analysis of the clinical study was based on treatment completers (no protocol violations) only. The primary health outcome used in the analysis was the effects of treatment on TWD. ANOVA was performed on TWD using the logarithm of change in baseline TWD as the dependent variable. The secondary health outcome included in the analysis was pain free walking distance. The groups were comparable in terms of walking distance at inclusion, age, gender, and clinical characteristics.

**Effectiveness results**

There was an increase in TWD at 4 weeks in both groups (78.3% in the LTP group and 101.5% in the STP group).

At the end of 8-weeks the increase in TWD was 107.3% in the LTP group and 260.9% in the STP group.

At 20-weeks the increase in TWD was 242% in the LTP group and 351% in the STP group.

The higher change in TWD for the STP group compared to the LTP was statistically significantly (p<0.05) at 4, 8 and 20 weeks.

There was a statistically significant increase in pain free walking distance in both groups.

No serious side effects were reported. Local effects such as reddening, pain at infusion site, dizziness and nausea were observed in 7% of the LTP group and 5% of the STP group.

**Clinical conclusions**

The authors concluded that an increase in walking distance was achieved with the STP and LTP. The STP associated with the exercise plan was more effective than the LTP.

**Measure of benefits used in the economic analysis**

The change in total walking distance was the measure of benefit used in the economic analysis.

**Direct costs**

Quantities and costs were not analysed separately. The costs measured were: infusion costs and hospital costs including transportation to and from the hospital, briefing and lectures. Average costs were reported.
The time horizon for the study was not reported. The method of estimation of the quantities and costs was not reported. The source of quantity and cost data was not reported. The date when the quantity of resources was measured was not reported. The price year was not reported. Discounting was not carried out due to the short time frame (less than one year) of the study.

**Statistical analysis of costs**
No statistical analysis of costs was reported.

**Indirect Costs**
The study included a valuation of 'lost working hours or days' but these were not defined as indirect costs. Quantities and costs were not analysed separately. Average costs were reported.

The authors did not report the time horizon for the study, the method of estimation of the quantities and costs, the source of quantity and cost data was not reported, the date when the quantity of resources was measured was not reported, or the price year. Discounting was not carried out due to the short time frame of the study (less than one year).

**Currency**
European currency units (ECU). No conversion rate was reported.

**Sensitivity analysis**
The authors did not refer to a sensitivity analysis. However, the study did explore the impact on the cost of treatment of changing the 2 infusion days in the STP group from Monday and Tuesday to Saturday and Sunday. Changing the infusion days excluded the cost associated with lost working hours or days.

**Estimated benefits used in the economic analysis**
The reader is referred to the effectiveness results reported earlier.

**Cost results**
The total average cost of the LTP was ECU 6,588, which included ECU 1,647 for lost working days.

The total average cost of the STP was ECU 1,881, which included ECU 470 for lost working days.

If the STP infusion days were changed to a Saturday and Sunday the total average cost was ECU 1,481.

**Synthesis of costs and benefits**
The cost to achieve an improvement in walking distance of 1 metre was ECU 35.6 for the LTP group and ECU 9.45 for the STP group. The authors reported that this was statistically different, (p<0.02).

**Authors’ conclusions**
The authors concluded that, for the management of intermittent claudication with PGE1, the short-term protocol was more effective and lower in cost than the long-term protocol.

**CRD COMMENTARY - Selection of comparators**
The selection of comparators was supported by published evidence from the authors. It was not clear to which country or clinical practice setting the choice of comparators was relevant. You, as a user of this database, should consider whether STP or LTP of PGE1, reflect treatment options for the management of patients with severe intermittent
claudication in your own setting.

Validity of estimate of measure of effectiveness
The study was based on a randomised controlled trial design. The patients and investigators were not masked to treatment allocation. This may bias the results, particularly as the outcome measure was a subjective assessment of total walking distance. The sample size gave only 80% power to detect a statistically significant difference. The study reported several inclusion and exclusion criteria, which may restrict the application of the findings to the study population. The intervention and control groups were comparable at baseline. The analysis used ANOVA to compare differences between groups. Logarithms of change from baseline were used as the dependent variable and the authors noted that this reduces the influence of extreme values in the primary outcome measure. However, the authors did not report why it is important to control for extreme values or other reasons to justify this statistical approach.

Validity of estimate of measure of benefit
This study used the primary measure of effectiveness as the measure of health benefit. The authors did not report how distance walked was related to overall health benefit to the patient.

Validity of estimate of costs
This study reported cost data but did not report details regarding the source of the resources used or unit cost data. The perspective of the study was not made clear so it is not possible to assess whether an appropriate range of costs was included. The study did not report any details about the time horizon or methods of collecting the cost data.

The study included an assessment of the cost associated with not attending work due to the need to receive treatment, but it was not clear how these costs were identified or valued.

It was not clear if the costs were associated with one country or a number of countries. The unit cost data are likely to differ between countries. Similarly the resource use and costs of the treatment process are likely to differ between countries. However, no attempt was made to determine the impact of this.

Other issues
The study did not report a detailed sensitivity analysis. This omission hinders the assessment of the robustness of the results and the generalisability of the study to other clinical settings.

The study reported average cost-effectiveness ratios and compared their magnitude with a statistical test (t test). It is more appropriate to calculate the incremental cost-effectiveness ratio of STP compared to LTP. However, in this study, STP was reported to be more effective and less costly and therefore it dominated the LTP group. It was not appropriate to report any form of cost-effectiveness ratio. Furthermore, it was not valid to compare two ratios of cost per unit of walking distance with a statistical test.

Implications of the study
The authors suggested that the improved effectiveness and lower costs for the short term protocol rather than the longer term protocol was probably due to the need for longer immobilisation times in the LTP group. The STP group required very little time for the infusion of PGE1 and may, therefore, spend more time in the exercise programme. The authors suggested that this might produce the improved outcome.

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