**Essay 5**

**A shocking new treatment for intermittent claudication: medium-term follow-up of a double-blind randomised controlled trial for extracorporeal shockwave therapy in intermittent claudication.**

**Background**

Peripheral arterial disease (PAD) is an age-related atherosclerotic condition with increasing prevalence, estimated to affect 3-10% of the population worldwide1. PAD most commonly presents as intermittent claudication (IC). The physical, psychological and social limitations associated with IC are debilitating and often impair quality of life dramatically2.

The initial management of IC includes risk factor modification, such as smoking cessation3. Individuals with PAD are advised to continue walking, and given best medical therapy including anti-platelet agents and statins4. NICE guidelines recommend supervised exercise programmes (SEP) as the first-line intervention for the management of IC5, due to the compelling evidence of the clinical and symptomatic benefits6,7. Despite this, patient uptake and adherence is poor, and the provision of SEP is far from universal8,9. This suggests that alternative treatment options for IC are required.

Extracorporeal shockwave therapy (ESWT) is an established therapy that has been used in urological and musculoskeletal medicine since the early 1980s, in particular for the treatment of urolithiasis and delayed fracture healing10–13. Early studies using ESWT in IC suggest positive effects but lack scientific rigour14. It has recently been demonstrated that ESWT is safe, tolerable and clinically efficacious at 4, 8 and 12 weeks post-treatment in a randomised double blind placebo-controlled trial for IC15. This study followed this cohort of participants at 12 months post-treatment to determine the medium term efficacy of ESWT.

**Study Design & Methods**

Local Research Ethics Committee approval for this trial was granted and written informed consent provided by all participants before enrolment in line with the declaration of Helsinki.

Participants were recruited over a 6 month period from a single, tertiary, vascular surgical unit following a defined trial protocol16. Patients with unilateral IC were randomised in a 1:1 fashion to receive ESWT or a sham treatment (SG) for three sessions per week over three weeks. Primary outcomes were maximum walking distance (MWD) and intermittent claudication distance (ICD) using a fixed-load treadmill test. Secondary outcomes included pre- and post-exertional ankle-brachial pressure indices (ABPIs), safety, and quality of life (QoL) assessed using generic (SF36, EQ-5D-3L) and disease-specific (VascuQol) measures. All outcome measures were assessed at 12-months post-treatment and analysed on an intention-to-treat basis.

**Key Findings**

81 patients were screened for eligibility; of the 81 screened, 30 were eligible and consented to participate. Patients were excluded either because they chose not to participate (n=31), or because they did not meet the inclusion criteria (n=20). Fifteen participants were randomised to AG and fifteen to SG, with no significant differences in demographics between groups. Four participants were lost to follow-up during the initial study phase, leaving a total of n=26 participants (n=13 per group) that were analysed at 12-months post-treatment. A total of 8 participants (n=4 per group) required re-vascularisation before the 12-month follow-up.

At 12 months there was a significant improvement in the AG MWD (191.9m ± SD 156.7) from baseline (94.8m ± SD 45.7) (p=0.005) that was not observed in the SG. Similarly, there was a significant improvement in the AG ICD at 12 months (151m ± SD 155.6) from baseline (58.1 ± SD 32.6) (p=0.008). There were no significant differences between groups at 12 months (p>0.05), however a distinct trend for improvement was seen in the AG walking distances that was not present in the SG.

There were no significant improvements in pre-exertional ABPIs in both groups at 12 months compared to baseline (p>0.05); however post-exertional ABPIs in the AG were significantly improved over the 12-month period (p=0.036) improving from 0.37 (± SD 0.23) at baseline to 0.53 (± SD 0.34).

Significant improvements in generic QoL in the AG, but not in the SG, from baseline to 12 months were observed in the SF36 role-physical (p=0.049) and SF36 vitality (p=0.004) domains, but not in any of other SF36 or EQ-5D-3L domains. The VascuQol pain domain was significantly improved in the AG from baseline to 12 months (p=0.045), suggesting less pain and better QoL; no other improvements were seen in the other VascuQol domains. There were no significant differences between groups at 12 months for all QoL measures, except the VascuQol activities domain (p=0.033) where the AG was superior to the SG.

**Discussion**

This research was the first study known to investigate ESWT in the management of intermittent claudication for a follow-up period of 12 months.

At 12 months in the AG there was a statistically significant improvement in both MWD and ICD, both of which more than doubled. This suggests that an intensive three week course of EWST is effective in producing durable, medium-term beneficial effects on walking. Comparing these improvements to those reported in a number of reviews, ESWT appears to be comparable to SEP and percutaneous angioplasty (PTA) for improving walking distances17–19.

No changes in pre-exertional ABPIs were observed at 12 months, however a statistically significant overall improvement in post-exertional ABPIs was demonstrated. Improvements in vascular supply to the legs, measured using the ABPI, is an important diagnostic tool in PAD, yet is limited as a prognostic marker20. Similarly, although SEP is clinically efficacious for the treatment of IC, studies have shown that it does not result in an improvement in ABPI21. The value of ABPI to assess intervention effectiveness is thus probably limited to those involving direct revascularisation (e.g. angioplasty or bypass).

Whilst this research demonstrates that ESWT is effective in improving walking distances, there are little in the findings that support a positive impact on QoL. When comparing domains at all time-points in this trial, there are a variety of significant domains that are inconsistent across the follow-up points15; this lack of consistency suggests a possible Type 2 statistical error. Data in this RCT has failed to show that ESWT provides a measurable improvement in quality of life as previously reported for trials in SEP or PTA7,22,23.

With no complications or safety concerns reported, shockwave therapy can be viewed as a non-invasive, safe alternative to the current treatment options and would appear to be as safe as SEP24, and potentially safer than PTA25.

The underlying mechanism of action of shockwave therapy in claudication is not well understood, but has been hypothesised to involve angiogenesis and vasculogenesis26, with studies suggesting a complex interplay between vascular endothelial growth factor (VEGF), placental growth factor (PlGF), hypoxia-inducible factor 1 (HIF-1) and stromal cell-derived factor 1 (SDF-1)27–30. Human endothelial progenitor cells (EPCs) are also believed to play a role in vasculogenesis through VEGF and SDF-1 receptors that enable them to target sites of ischaemia31. Research into mechanism of action is primarily focussed on animal studies, therefore future trials should conduct muscle biopsies and measure inflammatory markers to establish the local and systemic effects.

There are a few limitations of the present study. One possible explanation for the lack of intergroup significance in walking distances is the ceiling effect, a consequence of capping the treadmill test at 10 minutes (500m), resulting in skewed mean walking distances that may not be truly representative. Furthermore, excluding thigh IC and bilateral calf IC has resulted in only a small proportion (approximately 15-20%) of the disease population being eligible for inclusion in this trial32. Exclusion of these patients reduced the effect of confounding factors; however, future research should investigate whether ESWT is effective in patients with more proximal arterial disease.

SEP is the first line recommendation for the management of IC, however the prolonged duration of SEPs has been cited as a common reason for patients with IC declining participation8. The relatively short 3-week duration of ESWT may appeal to patients, perhaps making it a more acceptable option than SEP; this is supported by 31 out of 60 declining to participate (48% uptake rate) compared to the 33% uptake rate reported in SEP8. This may be because ESWT is seen as a ‘quick fix’ by patients, but unlike SEP it does not encourage patients to make healthy lifestyle changes33. Perhaps ESWT followed by SEP may be more suitable to combine the durability and longevity of this treatment with the management of overall cardiovascular fitness. It is therefore possible that, with further evidence to support this hypothesis, future practice may include ESWT followed by SEP as the first line management for IC.

**Conclusions**

The management of intermittent claudication is difficult; SEP has been shown to have clear benefits, but is not attractive to patients. PTA is effective in directly improving blood flow to the limb, but is costly and associated with surgical risk. There is a clear indication for a safe, durable and attractive treatment option for IC; this pilot RCT has demonstrated that ESWT may offer a promising, non-invasive alternative for patients. Further work investigating the mechanism of action of shockwave therapy, as well as evaluation of the economic aspect of this treatment, is crucial to understanding how this novel treatment can fit into everyday clinical practice.

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