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Clinical outcomes in intermittent claudication – time for a change?

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Clinical outcomes in intermittent claudication - time for a change?

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Efforts to treat intermittent claudication have inspired many interventions spanning surgery, pharmacology, medical devices and exercise therapy. These interventions are intended to relieve symptoms, particularly pain induced by walking. This has motivated the prioritisation of measures of walking performance as a primary outcome when examining treatment efficacy. However, considering the sequelae of intermittent claudication, the impact of impaired walking ability lies not in how far one can walk in discomfort but in how far one cannot walk comfortably. Its impacts are defined by what it deprives from a person's life rather than how far they can walk. The magnitude of this complex, individualised phenomenon is best quantified by measuring disease-specific quality of life (QoL). Fundamentally, QoL should be the primary endpoint in trials examining the efficacy of treatments for intermittent claudication.

Why is this not the case?

Historically, walking assessments are used in clinical practice both as a diagnostic tool and outcome measure. Walking assessments respond to interventions which address the presenting complaint and underlying pathophysiology whilst providing an objective measure of disease burden. The use of walking assessments for intermittent claudication trials predates the development of QoL instruments. Only recently have patient-reported outcomes been considered for achieving regulatory approvals for medical devices or pharmaceuticals. Despite the development of several QoL tools since, there has been disparate application of QoL instruments [1], leading to yet unmet calls for standardisation [2] and potential research waste.

Another barrier to choosing QoL as a primary outcome measure is resource. QoL measures can be less responsive than walking-based measures to conservative treatments [3] therefore

requiring larger sample sizes to detect a difference. Almost all trials powered using walking performance measurements have not been powered to detect changes in QoL. Exceptions include the SUPER trial [4] (which did not recruit to target) and the CETAC trial [5] (possibly the only adequately powered trial using QoL as a primary outcome in this field). Until trials are delivered which are powered to assess changes in QoL outcomes, we rely upon meta-analyses to determine the efficacy of interventions. This approach may conclude that the only effective intervention is a combination of angioplasty and supervised exercise.

Finally, some might assume that changes in walking performance are adequate surrogates for changes in QoL. Accepting this requires evidence to justify trial-level surrogacy; such evidence does not exist. Limited evidence supports only a weak correlation between changes in walking performance and changes in disease-specific quality of life [6]; most data concerning this relationship remains unpublished.

Accepting these conclusions implies there is uncertainty regarding the magnitude of efficacy and cost-effectiveness of many established interventions. There is a substantial remit to improve research practices in this field. Standardising of the use of QoL instruments will require international consensus – a laborious yet worthwhile endeavour. QoL as an outcome measure is no panacea. Decisions about treatment consider the magnitude and durability of potential gains in QoL alongside the costs of treatments and their mortality and morbidity related risks. As yet, there is no core outcome set for intermittent claudication to direct researchers to capture important outcomes in a standardised manner.

To evaluate whether changes in walking performance measures can act as trial-level surrogates for changes in QoL we should encourage analyses of existing unpublished data from major trials. Were sufficient evidence to emerge, the use of walking performance

measures as a primary outcome is justified. Should this relationship not hold; future trials may seek to re-evaluate existing interventions which may improve QoL irrespective of effects upon walking performance. Efforts to treat intermittent claudication are primarily efforts to improve QoL and our research choices should reflect this.

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