School of Physiotherapy

The effectiveness of pulsed electrical stimulation in the management of osteoarthritis of the knee

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Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Robyn Fary

Signature: …….

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Abstract

Osteoarthritis of the knee is a chronic disease leading to considerable burden on health. Pain, while not always present is the most prominent clinical feature and the cause of significant disability. There are a wide variety of treatment options available to patients, many with substantial side effects or contraindications for use. However, these options have modest effects at best and target symptoms rather than the disease.

Pulsed electrical stimulation (PES) is an electrotherapy treatment modality using capacitively coupled, pulsed, monophasic current with a frequency of 100Hz, delivered at sub-sensory intensity. It has been reported to produce positive outcomes for pain, function and physician global assessment in short-term randomised controlled trials (four and 12 weeks) and longer term longitudinal studies. It is relatively inexpensive, non-pharmaceutical, non-invasive and has few side effects. Despite all this its use is not widespread. In addition, PES has a putative disease-modifying action through its ability to stimulate chondrocyte activity and type II collagen formation.

The aim of this doctoral research was to investigate the effectiveness of PES in treating osteoarthritis of the knee by measuring pain, function, patient global assessment, quality of life and physical activity over a period of 26 weeks.

In order to do this, an initial pilot study using commercially available PES equipment was conducted. The aims of this small study following three participants over 16 weeks were to investigate whether reported improvement was maintained over the longer period of time and to pilot test the materials, process and equipment being considered for a subsequent randomised controlled trial. This study provided evidence to suggest that the longer term randomised controlled trial was warranted.

The next phase of this doctoral research centred around the development of the PES and placebo-PES equipment. Initial testing of the equipment that was made to replicate the parameters reported in the literature produced unacceptable adverse skin reactions. As a consequence, further consideration was given to electrical treatment parameters and a second prototype containing pulsed, asymmetrically biphasic current with a frequency of 100Hz was developed and tested.

A cross-sectional study of 25 healthy adults with no contraindications to electrotherapy was undertaken to compare the rate of adverse skin reactions after using the replicated monophasic device with that after using the asymmetrically biphasic device. These rates were also compared with the rates of adverse skin reactions cited in the PES literature. Thirteen (52%) participants experienced an adverse skin reaction after using the monophasic prototype device, while one (4%) participant demonstrated an adverse skin reaction after using the biphasic prototype device. Additionally, the rate for the monophasic prototype differed significantly from the reported rates in three of the four published studies ($p<0.04$). These results gave strong support for the use of the biphasic current in the proposed randomised controlled trial.

In order to investigate the effectiveness of PES in treating people with osteoarthritis of the knee, a double-blind, randomised, placebo-controlled, repeated measures trial was undertaken over 26 weeks. Seventy people were randomised to either the PES or placebo group. Outcome measures included pain, function, patient global assessment, quality of life, physical activity and global perceived effect. At the end of the study at 26 weeks, there was a statistically significant improvement in pain visual analogue scale ($p\leq0.001$) in both groups. However, there was no difference between the groups (mean change difference 0.9mm; 95% confidence interval -11.7mm to 12.5mm). Similarly no differences were found between the groups in any of the other outcome variables. These results conclude that in this particular sample of people with mild to moderate symptoms and impairment, and moderate to severe radiographic osteoarthritis of the knee, PES used over 26 weeks was no better than placebo.

Osteoarthritis of the knee is a chronic condition. People suffering pain and disability from the disease need to be able to make informed choices about best available treatment options. This doctoral research provides independent evidence of the effectiveness of PES. In doing so it adds to the body of evidence available to assist those with osteoarthritis and their health care providers in making treatment choices.

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List of publications

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Poster

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List of abbreviations

AC	Alternating current
AAS	Adjusted activity score
ACR	American College of Rheumatology
ATP	Adenosine triphosphate
BMI	Body mass index
BPES	Biphasic pulsed electrical stimulation
CONSORT	Consolidated Standards of Reporting Trials
DC	Direct current
E-PES	Effectiveness of pulsed electrical stimulation
GPES	Global perceived effect scale
HAP	Human Activity Profile survey
IFT	Interferential therapy
LCD	Liquid crystal display
MAS	Maximal activity score
MCII	Minimal clinically important improvement
MCS	Mental component summary
MPES	Monophasic pulsed electrical stimulation
MRI	Magnetic Resonance Imaging
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis

OAK	Osteoarthritis of the knee
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology Clinical Trials
PCS	Physical component summary
PEMF	Pulsed electromagnetic field
PES	Pulsed electrical stimulation
PGA	Patient global assessment
QoL	Quality of life
RCT	Randomised controlled trial
SF-36	Medical Outcomes Study Short-Form 36 Survey
TENS	Transcutaneous electrical nerve stimulation
TKR	Total knee replacement
VAS	Visual analogue scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

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Chapter 1: Review of the literature, rationale for thesis and study design

1.1 Introduction and overview of osteoarthritis of the knee

Osteoarthritis (OA) is a major cause of pain and disability in the community and OA of the knee (OAK) is one of the most common causes of musculoskeletal disability in the Western world (Walker-Bone et al. 2000). It contributes significantly to the worldwide burden of health (Felson et al. 2000; Walker-Bone et al. 2000; Symmons et al. 2003; Woolf and Pfleger 2003; Buckwalter et al. 2004; Buckwalter and Martin 2006; Sharma et al. 2006) and imposes a substantial financial cost on the Australian community (Segal et al. 2006; Access Economics 2007). The progressive and chronic nature of the disease exacerbates the forecasted health burden (Holt et al. 2010) so efforts to improve the long term management of the disease are therefore essential.

While pain is not always present with diagnosed OAK it is, when present, considered the most prominent clinical feature (Altman and Dean 1989; Woolf and Akesson 2001; Fernihough et al. 2004; Gwilym et al. 2008) and the most important determinant of disability (McAlindon et al. 1993; van Baar et al. 1998; Sharma et al. 2003; Torres et al. 2006; Somers et al. 2009). Pain is usually activity related, but may be present at rest in some patients, especially in more advanced disease (Sale et al. 2008).

Other clinical features include: bone and joint tenderness; crepitus; decreased range of joint motion; variable degrees of local inflammation with heat and swelling, which may be due in part to joint effusions; and loss of function (Altman et al. 1986; Symmons et al. 2003). People with OAK are also likely to demonstrate lower activity levels than those without OAK (Bennell et al. 2004; Farr et al. 2008).

The disease process itself is a complex one characterized by articular cartilage degeneration, but essentially affecting all joint structures. Common features include hypertrophy of bone (osteophytes and subchondral bone sclerosis), bone oedema, subchondral cysts, thickening of synovium and joint capsule, ligamentous laxity and

periarticular muscle weakness (Felson et al. 2000; Iannone and Lapadula 2003; Sarzi-Puttini et al. 2005; Brandt et al. 2006; Goldring and Goldring 2007).

The diagnosis of OAK may be based on clinical findings, for example, the combined presence of pain, crepitus on movement, bony tenderness and enlargement; on radiographic evidence, for example, decreased joint space width, presence of osteophytes, presence of subchondral bone sclerosis and cysts; or a combination of both clinical and radiographic findings (Altman et al. 1986).

A wide variety of effective treatment options that target symptoms and function are currently available. These include, but are not limited to: medication (predominantly non-steroidal anti-inflammatory agents and analgesics); nutritional supplements (glucosamine, chondroitin sulphate, fish oil), exercise and self-management programs, and surgery. Some physiotherapists also use various electrotherapy modalities such as ultrasound, transcutaneous electrical nerve stimulation (TENS) and interferential therapy to address pain, inflammation and swelling.

The variety of available treatment options reflects the diversity of clinical presentations and the heterogeneity of the disease. It also may reflect the modest effect sizes achieved with many of these options (Zhang et al. 2010) and that adverse effects and complications in the presence of co-morbidities commonly restrict use of pharmacological (Gislason et al. 2006; Solomon et al. 2006) and surgical treatments.

Pulsed electrical stimulation (PES) is a treatment modality that is reported to have significant effects in terms of pain management and improvement in function in the short term (Zizic et al. 1995; Garland et al. 2007). It is commonly grouped with TENS as evidenced in the Cochrane review on TENS use in OAK (Rutjes et al. 2009) because of its mode of delivery. The clinical guidelines developed by the Philadelphia Panel (Harris and Susman 2002), Osteoarthritis Research Society International (OARSI) (Zhang et al. 2010) and Royal Australian College of General Practitioner Osteoarthritis Working Group (March et al. 2010) all recommend TENS for treating OAK.

This modality is of particular interest as in vitro and animal studies suggest it also has disease-modifying potential (Lippiello et al. 1990; Wang et al. 2004; Brighton et al. 2006; Brighton et al. 2008). To date, only relatively short-term randomised

controlled trials (RCT) have been conducted to investigate its effectiveness. Therefore, whether symptomatic and functional benefits are maintained or whether they increase with ongoing use is unknown. Additionally, there are no data to address whether the putative disease-modifying effects occur in vivo in humans.

Given the encouraging published reports, apparent ease of use and the potential for OA disease modification, it is surprising that the use of PES is not more widespread. Limitations in the study designs and reporting of previous PES research may have contributed to this situation. Nevertheless it remains a modality of interest and worthy of further investigation. The aim of this thesis was therefore to investigate the capacity of PES to produce sustained improvement in symptoms and function in people with OAK over 26 weeks.

1.2 Pulsed electrical stimulation

1.2.1 Defining the pulsed electrical stimulation modality

Pulsed electrical stimulation treatment is the application of any electrical waveform that has an interrupted flow of current (Walsh 2008). That is, it may be an alternating (AC) or direct (DC) current with any wave shape but it must periodically cease flow and, in so doing, create pulses of current stimulation (Walsh 2008). Whilst this seems simple enough, the diversity of current sources and the variety of methods of application leads to terminology that can vary in ways that does not always seem logical.

In this thesis, the term PES will specifically refer to electrical stimulation delivered using capacitive coupling, meaning that the patient forms a part of the electrical circuit. This is in contrast to inductive coupling where the patient is not part of the circuit. Pulsed electromagnetic field (PEMF) treatment is one such modality. It is delivered using inductive coupling and has been extensively studied (Sharrard 1990; Trock et al. 1993; Trock et al. 1994; Thawer 1999; Pipitone and Scott 2001; van Nguyen and Marks 2002; Thamsborg et al. 2005). Two systematic literature reviews combine these two different interventions, PES and PEMF, citing the pulsed nature of the treatment (McCarthy et al. 2006) and the ultimate creation of an electrical field in the tissue (Hulme et al. 2002) as justification for the combined review. While there is merit in both these assumptions they ignore the fact that a pulsed TENS

application also fits these criteria yet TENS is excluded from these reviews. Additionally both reviews ignore the possibility that actual current flow through the tissue and the tissue being part of the circuit may both be important determinants of effectiveness.

Differentiating PES as a distinct treatment modality from other forms of capacitively coupled electrotherapy treatments commonly used in clinical practice, such as TENS and interferential, also raises questions. While there are specific electrical features that characterize each of these modalities (Johnson 2008; Palmer and Martin 2008), the major distinction between electrotherapy treatments like TENS and interferential on the one hand, and what is traditionally labelled PES in the literature on the other is that PES is delivered to patients at a sub-sensory intensity. That is, patients using PES should feel no electrical stimulation for the duration of treatment. This is in direct contrast to other capacitively coupled electrotherapy modalities where sensation of the electrical stimulation and hence stimulation of sensory nerves is an objective of the treatment (Roche and Wright 1990; Grimmer 1992; Osiri et al. 2000; Johnson 2001; Adedoyin et al. 2002; Cheing et al. 2003; Chesterton et al. 2003; Sluka and Walsh 2003; Law and Cheing 2004).

Another more recent systematic review of TENS use in OAK included PES papers (Rutjes et al. 2009). This lends weight to the proposition that capacitively coupled electrotherapy modalities share similar characteristics. The review by Rutjes et al. (2009) proved to be inconclusive citing small studies of questionable quality as the reason for such an outcome.

Adding further to confusion regarding nomenclature, the US federal agency Centers for Medicare and Medicaid Services, refers to the PES device reported in the literature as a transcutaneous electrical joint stimulation device system (Farr et al. 2006).

1.2.2 Pulsed electrical stimulation clinical trials

The first reported clinical trial using PES was a multi-centre, double blind, randomised, placebo-controlled study using PES over a four week period (Zizic et al. 1995). This was the only trial publication available at the time of developing this thesis. The PES equipment used for this early study was the commercially available

Bionicare® BIO-1000™ device *(BioniCare Medical Technologies Inc., Sparks, MD, USA)*. The manufacturer's technical specifications state that this device delivers a monophasic, exponentially decreasing, pulsed waveform with a frequency of 100Hz.

The Zizic et al. (1995) study enrolled 78 participants with OAK and reported positive outcomes for the variables pain, function, physician global evaluation (all 10cm visual analogue scales (VAS)) and duration of joint stiffness in the morning (minutes). Participants were asked to use PES for six to 10 hours per day for the duration of the study. Six participants withdrew (four from the placebo and two from the active group) and one participant was excluded from analysis because the treating physician did not have any other patients in the trial to act as a matched control. Reasons for withdrawing included the development of a rash (one placebo and one active), one moving away (placebo), one unwell with asthma (active) and two not wanting to continue (placebo). Of those who remained, good compliance was achieved with 78% active and 67% placebo achieving the target dose. The only adverse effects noted were skin rashes under the electrodes that occurred equally amongst those using the active device and those using the placebo (24% and 21% respectively). This led the authors to contend that the skin reaction was due to the gel used rather than the electrical current administered.

No mean data were published and outcomes were described as percentage improvements. These percentage improvements were statistically significant for the variables previously mentioned, but in the absence of the mean data, it was difficult to determine whether the improvements were of clinical significance.

Strengths of this study were the use of a credible placebo device and specification of primary outcome variables. However, while the study was reported to be a randomised trial, details of sequence generation and concealment were not provided. Moreover, it is not explicitly stated whether outcome assessors were blind to allocation and intention to treat analysis was not applied. Selective reporting of results was also evident with outcomes for walking time, tenderness and swelling as mentioned in the methods not included in results.

The discussion by Zizic et al. (1995) related the potential benefits of PES on articular cartilage to the study's outcomes. However, symptomatic improvement after four

weeks cannot reasonably be attributed to changes in the articular cartilage nor was this potential variable measured.

A second multi-centre, double blind, randomised, placebo-controlled trial of PES was reported by Garland et al. (2007). This study was published after research funding had been established and thesis development was well underway. Participants had moderate to severe OAK characterised by unequivocal radiological changes (Kellgren-Lawrence score of 3 or 4) and persistent pain despite non-steroidal anti-inflammatory drug (NSAID) and/or analgesic treatment.

The trial asked participants to use the same PES device as Zizic et al. (1995) for a 12 week period (six to 14 hours per day). It measured pain and other symptoms (0-100 VAS), pain (Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)), stiffness (WOMAC), function (WOMAC) and patient global assessment (PGA) (0-100 VAS). The randomisation to devices procedure was conducted, by an observer independent of the study, at a ratio of 2:1 (active:placebo) for the 58 participants. This meant that results were reported for 39 participants using the active device and 19 using the placebo. A further 42 participants, all from one clinic, who had been enrolled and randomised were excluded from analysis after it was reported that a number of those had been given other treatments in addition to the study treatment. Of the 58 whose results were analysed, 63.1% using the active device and 65.8% using the placebo achieved the minimum target dose of six hours per day. Adverse skin reactions occurred in 17.9% of those with the active device and 21.1% of those with the placebo.

As in Zizic et al. (1995) percentage changes from baseline were measured. Statistically significant differences were reported for all variables apart from pain measured by WOMAC. It is assumed that the stated clinically important improvements occurring in four of the five variables refers to the 20% improvement generally agreed by expert opinion as clinically meaningful (Bellamy et al. 2005; Clegg et al. 2006), though this is not explicitly stated. Mean data tables demonstrated substantial real differences between the two groups. However, only WOMAC function achieved the minimal clinically important improvement described by Tubach et al. (2005) and neither of the two key variables of pain or function achieved

the absolute mean change of 20 that is required to meet the primary OARSI responder criteria (Pham et al. 2004).

In addition to changes from baseline, the percentage of participants experiencing a 50% improvement in outcomes was compared between the groups. Significant differences were noted in three of the five variables – PGA, pain and other symptoms VAS and WOMAC pain – between the groups.

Once again, the use of a credible placebo device was a strength of this study. Adequate sequence generation and adequate concealment of allocation were reported. However, there were no explicitly specified primary outcomes and intention to treat analysis was not applied. Additionally, while ongoing analgesic use was allowed for all participants it is not reported whether use was similar between the two groups. No power calculations were presented and due to the small number of participants in the placebo group, it is difficult to determine the true meaning of the results. The exclusion of all 42 randomised participants from one clinic raises the risk of bias in the study. The WOMAC VAS function subscale has a score range from zero to 1700. However, Garland et al. (2007) cite this range as from zero to 850. This suggests that around half of the WOMAC function subscale questions were either excluded or not reported, or that a different scoring regime to that recommended was implemented. As a result, further risk of bias from selective reporting cannot be excluded. Finally, unsubstantiated claims were made about how long the effects tended to last after cessation of PES. No studies to support this claim have been found and none are cited in this paper.

Of particular note, the placebo changes in both studies (Zizic et al. 1995; Garland et al. 2007) were minimal. This is at odds with general reports in the OA literature where the placebo effect is usually observed to be considerable (Zhang et al. 2008) and consistently present across a range of modalities from neutraceuticals to arthroscopy (Moseley et al. 2002; Clegg et al. 2006). Apart from the potential risk of bias from excluding 42 participants and selective reporting there is no other indication from the published data why these two PES studies should have achieved the notable absence of a placebo response.

Two other clinical trials using the Bionicare® device have also since been reported. Mont et al. (2006) conducted a multi-centre, prospective, four year open label,

longitudinal study, that enrolled 157 participants and used PES for eight plus or minus two hours daily for an initial period of one year. After the first year, participants could elect to continue to use the device for a further year until the end of the study at four years duration. All participants had OAK to the extent that all had been given advice that a total knee replacement (TKR) was warranted. The primary aim of the study was to determine whether use of PES could defer the decision to have replacement surgery. Secondary aims were to determine changes in the outcomes of physician's global assessment, patient's pain and symptoms, and function (all using a 10cm VAS). A comparison group of patients treated with TKR some 10 years prior were included in the analysis.

Compared with the group from 10 years prior, there was a statistically significant difference in rates of TKR deferral in the group using PES. The difference in deferral rates was most significant for those people classified as having severe symptoms at baseline. Within the PES group those who chose to have a TKR at some point during the four year period experienced significantly less improvement in the three secondary outcome measures than those who deferred the surgery. Adverse skin reactions occurred in 45% of participants. This is a higher number than that reported in the two RCTs and may reflect the greater length of time of usage. It also may be due to the type of gel used but this was not reported.

While this study reported positive results with the use of PES, there are a number of issues that arise from using a comparison group from some 10 years prior. No data comparing medication between the two groups are cited. Data collected during usual medical care in the 10 year prior group may be affected by unknown confounding factors, for example different health professionals collecting the data. It may be that increasing health care costs influenced the PES participants' decisions to delay undergoing an expensive procedure rather than their responses to PES treatment alone. Finally, advancement in pain management strategies during the 10 year period cited (1983-1993) could well have led to improved medical and self-management control of the symptoms in the experimental group which in turn may have contributed to the decision to defer surgery.

Farr et al. (2006) investigated the use of PES in 288 people who had failed non-operative treatment for OAK symptoms. In a prospective, longitudinal study

conducted over a two year period, the relationship between hours of use and effect size was studied. A dose-response relationship was reported to exist. Those who used the device for more than 750 hours over the study period were found to demonstrate significantly better responses in the outcome measures of patient assessment of disease activity in the joint, patient assessment of pain and investigator assessment of disease activity, all measured on a five point Likert scale. Additionally, improvement in all these variables measured from baseline to end of the study was found to be statistically significant. Being a study where all participants knew they were receiving treatment there is a risk of expectation bias towards a positive outcome. This type of study is also open to selection bias. That is, those participants who are gaining improvement are more likely to continue to use the treatment and therefore artificially inflate the does-response relationship.

1.2.3 Pulsed electrical stimulation and articular cartilage

While clinical trials to date have focused on symptomatic effectiveness of PES, animal and laboratory studies have focused on its capacity to positively affect articular cartilage. In many ways it is this potential to modify the cartilage pathology in OA that has sparked much of the interest in the modality, and which has generated impetus to determine its symptomatic effectiveness. For articular cartilage changes to be confidently measured radiologically, a period of at least 12 months and preferably two years between measurements is warranted (Cicuttini et al. 2004). Consequently, compliance over such a period of time would likely be enhanced considerably if PES provided some symptomatic benefit to patients as well.

Hyaline articular cartilage absorbs load forces and facilitates smooth movement in joints. It is a metabolically active tissue that relies on external influences for nutrition in the absence of nerve and blood supply. Chondrocytes are sparsely scattered and embedded within an extracellular matrix. The matrix is made up of collagen fibres enmeshed with aggrecan (proteoglycan) aggregates. Negatively charged sulphate and carboxyl groups along the glycosaminoglycan chains of aggrecan molecules in the matrix provide the cartilage tissue with an endogenous electrical potential while dissolved electrolytes in solution in the matrix neutralise the sulphate charges (Mow et al. 1999) .

External forces, such as weight-bearing affect the flow of fluid through the matrix. This in turn breaks off the neutralising ions from the glycosaminoglycan chains and creates a streaming potential within the cartilage (Schmidt-Rohlfing et al. 2002) . It is thought that this electrical action stimulates chondrocyte activity and molecular activity (Kim et al. 1995). Brighton et al. (2006) postulate that there is a disruption to this normal flow in diseased cartilage with consequent interruption to the normal metabolic state of the cartilage.

The capacity of externally applied electric and electromagnetic fields to positively affect osteoblast and chondrocyte proliferation and extracellular matrix protein production in vitro and in animal studies has been well documented (Lippiello et al. 1990; Thawer 1999; Aaron et al. 2004). At present, the specific mechanisms whereby externally applied electric currents stimulate cartilage matrix production and chondrocyte activity are not fully understood. However, there is growing support that the mechanism through which this occurs relates to the ability of electrical stimulation to enhance chondrocyte differentiation and to up-regulate the expression of matrix genes and products (Ciombor et al. 2003; Wang et al. 2004; Brighton et al. 2006; Brighton et al. 2008).

Brighton et al. (2006; 2008) report results obtained after applying capacitively coupled electrical stimulation to both bovine articular and human articular cartilage explants in vitro. Explants were used as they are thought to more closely mimic the in vivo situation where chondrocytes are embedded within their native extracellular matrix. This is in contrast to earlier work where the stimulation was applied to foetal bovine chondrocytes in mass culture (Wang et al. 2004). In both studies, specific capacitively coupled electric fields resulted in significant up-regulation of the expression of selected extracellular matrix genes (aggrecan and type II collagen) as well as total proteoglycan and collagen production in the experimental specimens when compared to the controls. This work provides strong theoretical support for the use of electrical stimulation to maintain and repair articular cartilage in the clinical setting.

Interestingly, while specific electrical regimes for enhancing chondrogenesis were reported in the different laboratory studies, there was considerable variability among them. Lippiello et al. (1990) used direct current with frequency 100Hz while the

Brighton and Wang teams (Wang et al. 2004; Brighton et al. 2006; Brighton et al. 2008) used alternating current with frequency 60kHz. This raises the question as to how important is the specificity of current type, frequency and electrical field strength in achieving chondrogenetic effects?

1.2.4 Summary

Ambiguity in the PES terminology obviously exists, possibly as a result of companies trying to differentiate their product from others on the market. Essentially, PES, like TENS and interferential, is a transcutaneous electrical stimulation modality. While in the future it may be more informative to describe it thus, while still specifying its electrical properties and delivery characteristics, the term PES is used in this thesis to provide consistency with the current literature regarding sub-sensory, capacitively coupled stimulation.

With reference to the clinical trials reviewed here, it is of note that all were conducted with support from, and by several employees of, *BioniCare Medical Technologies Inc.* the company that manufactured the PES device tested. This introduces potential conflict of interest and bias into all of these studies. The rationale for use of PES in all of these studies was its potential for disease-modifying actions through its putative effects on articular cartilage, yet in none of these studies was assessment of the articular cartilage undertaken nor was there any attempt to explain how changes to cartilage could result in the rapid improvement of symptoms. Nevertheless, as all studies reported positive symptomatic outcomes there remained a strong need for an independent investigation into the effectiveness of this non-pharmaceutical, non-invasive treatment option.

The putative disease-modifying potential of PES is supported by sound laboratory and animal research but remains untested in vivo in humans. This aspect is not addressed in this thesis.

1.3 Pain

1.3.1 Pain mechanisms in osteoarthritis

While pain is one of the most commonly reported symptoms in OA (Altman and Dean 1989; Creamer 2000; Fernihough et al. 2004; Gwilym et al. 2008) the exact pain mechanisms in OA remain elusive (Felson 2005; Kidd 2006; Gwilym et al.

2008). The presence of an inflammatory process is a well-documented phenomenon and suggests a logical pain production pathway. Likewise there is much in the specific pathology of OA that can reasonably cause pain, while development of peripheral and central sensitization and the impact of psychosocial factors are also likely contributory factors in a disease where chronic pain is a common feature.

1.3.1.1 Inflammation

It is widely agreed that the pro-inflammatory mediators present in the osteoarthritic joint, which initiate the signalling cascade to sensory nerve endings via ion channels, contribute to the production of pain (Bhave and Gereau 2004). The widespread use and effectiveness of anti-inflammatory medication in treating pain in OAK supports this pain mechanism (Hochberg 2001; Sarzi-Puttini et al. 2005; Alvarez-Soria et al. 2008).

Inflammation within the synovium is reported to be an important cause of pain in those with OAK (Goldring 2009). Hill et al. (2007) showed an association between a change in synovial thickening measured using magnetic resonance imaging (MRI) and a change in pain measured on a VAS over periods of 15 and 30 months. However, while inflammation of the structures affected in OA is a likely contributor to pain production, Brenner et al. (2004) provide contradictory evidence stating that pain in OA is not primarily of inflammatory origin. They examined the concentrations of a variety of inflammatory markers (prostaglandin E_2, thromboxane B_2, nitric oxide, interleukins -6, -1alpha and -1 beta and tumour necrosis factor alpha) and enzymes (COX-2 and inducible nitric oxide synthase) in the synovial fluid and synovial membranes of patients with OAK undergoing arthroscopy. The authors compared these concentrations with measures of clinical features (pain VAS and WOMAC) and radiological disease severity (Kellgren-Lawrence scores). Their results showed that the concentration of inflammatory markers and enzymes generally reflected those found in synovial fluid and membrane in previous OA studies. However, the only significant relationship found was between prostaglandin E_2 and WOMAC scores once corrected for age and body mass index (BMI). This demonstrated that the presence of most inflammatory markers and enzymes were not related to the amount of pain, dysfunction and stiffness experienced, nor were they related to the radiological severity of the disease. A limitation of this study was the

restriction on the size of the synovial membrane collected that may have led to some synovial changes being missed.

Further studies using diagnostic ultrasound to investigate the relationship between synovitis, effusion and pain in OA have shown poor correlation (Conaghan et al. 2005; Keen et al. 2008; Song et al. 2008). These reports further support the contention that factors other than inflammation contribute significantly to pain production in OA.

1.3.1.2 Pathological changes

Because articular cartilage is aneural, its degeneration alone is unlikely to cause pain in OA. Other structural changes that may contribute to pain include: periosteal stretching associated with osteophytes; decreased cartilage volume; raised intraosseous pressure; subchondral bone microfractures; bone marrow oedema; ligament damage; capsular tension; and meniscal damage (Altman and Dean 1989). However, when comparing radiological findings of these features with reports of pain, the link between pathological features and pain remains unclear.

It is generally agreed there is discordance between the amount of pain reported and the radiographic features of the disease (Hedbom and Hauselmann 2002; Dieppe and Lohmander 2005; Bedson and Croft 2008). Davis et al. (1992) reported that up to 40% of people with severe radiographic change present symptom free.

Other research, described below, using a greater range of X-ray views describes some association between symptoms and radiographic findings. However, differences in the findings mean that full understanding of the relationship remains elusive.

Cicuttini et al. (1996) reported that the presence of osteophytes was the best radiological predictor of pain and reported a stronger relationship between osteophytes reported in skyline views of the knee and pain, than that between osteophytes found on antero-posterior and lateral views. Szebenyi et al. (2006) noted that people who had structural changes noted on X-ray in both the patello-femoral and tibio-femoral compartments were more likely to report pain than those who only had one compartment affected. More specifically, they noted that the greatest association existed when there was subchondral sclerosis present in both

compartments. These results contrast with those of Duncan et al. (2008) who, while acknowledging the importance of the patello-femoral joint, determined that it was the radiographic severity of the disease within a compartment rather than the specific compartment affected that was most related to symptoms.

More recently Neogi et al. (2009) reported a strong relationship between frequency, consistency and severity of pain, and Kellgren-Lawrence radiographic grades. Using a within-subject study design, Neogi et al. (2009) were able to reduce the confounding of pain responses that may occur with external influences such as psychosocial and cultural factors. However, the study sample from which the consistency and severity data were collected included those with knee pain present and who had specific risk factors for OAK. This limits the generalisability of the study. That is, while some confounding factors were well controlled through study design, other potential confounders, such as, selection by phenotype, may have been introduced (Pincus and Block 2009). Nevertheless, the results of this large scale study provide robust data for consideration.

Inconsistencies in the relationship between the presence of OA changes found on MRI and clinical symptoms are also reported (Link et al. 2003; Kornaat et al. 2006; Phan et al. 2006; Kornaat et al. 2007). Kornaat et al. (2006) noted associations between the MRI findings of patella osteophytes and pain and between a large joint effusion and both pain and joint stiffness. All other MRI findings, including subchondral cysts, bone marrow oedema and meniscal tears, among others, were not associated with clinical symptoms in this study. Phan et al. (2006) likewise found little relationship between changes in MRI findings (including the rate of cartilage loss and evidence of bone marrow oedema and ligamentous and meniscal pathology) and changes in WOMAC scores measured three times over a period of 2.4 (+/- 0.4) years.

The reasons for the apparent inconsistency between symptoms and radiologically reported changes may be due to the variety of tools used to measure symptoms and/or radiological procedures (Bedson and Croft 2008); study design factors such as between person confounding (Neogi et al. 2009) and subject selection procedures (Dekker et al. 1992); or because the pain producing mechanisms are just not visible radiologically (Dekker et al. 1992).

1.3.1.3 Mechanical changes

The structural and physiological changes within the OA joint often lead to biomechanical changes including reduced joint range of motion, periarticular muscle weakness and varus-valgus joint laxity.

Miura et al. (2009) found an association between pain and the presence of varus-valgus laxity but not with quadriceps strength. O'Reilly et al. (1998), van Baar et al. (1998) and Amin et al. (2009) on the other hand all found strong associations between pain and quadriceps strength. Whether quadriceps weakness is mainly a result of pain inhibition (Lewek et al. 2004); secondary to other joint structural changes such as ligamentous laxity or malalignment; or a primary risk factor for the development of OAK and knee pain (Slemenda et al. 1997) is yet to be fully determined. Maly et al. (2008) found that joint range of motion and BMI were related to pain levels but not to peak knee adduction moment, varus-valgus alignment, range of adduction-abduction during gait or quadriceps strength. Different methods were used to assess the variables in the studies. This undoubtedly contributes to seemingly contradictory outcomes. In the meantime, the relationship between biomechanical factors and pain production remains a complex one.

1.3.1.4 Nociception and neural sensitization

Studies that demonstrate decreased threshold for thermal and mechanical stimuli and increased background firing in people with OA suggest that some of the pain experienced in OA may be due to abnormal pain sensitivity (Hendiani et al. 2003; Bhave and Gereau 2004; Bradley et al. 2004; Dray and Read 2007; Kidd et al. 2007). McDougall (2006) went further stating that peripheral sensitization of afferent nerves within the joint was the main source of pain in arthritis. Bradley et al. (2004) noted that people with OA had abnormal pain sensitivity accompanied by greater sensitivity at sites away from the affected joint, while Felson (2005) suggested that impairment of noxious inhibition at the spinal cord level may also contribute to the pain of arthritis.

That both peripheral and central neural sensitization can occur in people with OAK (Dieppe and Lohmander 2005; Grubb 2009; Schaible 2009) is well documented and adds to the diversity of pain presentation in OA.

1.3.1.5 Psychosocial influences

Psychosocial factors can significantly influence pain perception in people with chronic joint pain (Davis et al. 1992; Creamer and Hochberg 1998; Ferreira and Sherman 2007; Gwilym et al. 2008) with anxiety, coping style, fear avoidance and possible depression being associated with pain and disability (Dekker et al. 1992; Rosemann et al. 2008). Psychological characteristics are associated with pain perception independent of radiographic presentation and mechanical factors such as muscle weakness (van Baar et al. 1998).

1.3.2 Pain mechanisms and electrical stimulation

It is clear that the causes of pain and pain mechanisms in OAK are multi-factorial and are modulated by psychosocial influences. This heterogeneity could explain the varied responses of different individuals to different interventions. Of particular interest to this study are those pain pathways that may be influenced by externally applied electrical stimulation.

1.3.2.1 Ion channels and receptor responses

There are many pain mediating receptors in the periphery that may theoretically be affected by an externally applied electrical input by virtue of their endogenous electrical potential and the role of polarization in receptor function and nociceptor stimulation (Wood 2006).

Ion channels that allow the passage of ion flow in and out of cells are regulated by changes in membrane potential (Schafers and Sorkin 2008) and inflammatory cytokines, commonly found in OA, modify ion channel function. In doing so, the cytokines contribute to changes in pain response and neuronal excitability. Seegers, et al. (2001) hypothesize that the cellular membrane proteins involved in signal-transduction may be affected by an applied electrical stimulation. Thus ion channel regulation is one possible mechanism whereby externally applied electrical stimulation could modify symptoms in OA.

Seegers et al. (2002) also demonstrated the capacity of monophasic, pulsed electrical stimulation to alter adenosine triphosphate (ATP) levels in vitro and in vivo, and postulated that altering ATP levels may affect pain sensation through P2-purinergic receptors. Their results however, demonstrated completely different ATP production

responses in vitro, where it increased, compared with in vivo, where it decreased. Hamilton and McMahon (2000) describe how ATP accentuates pain responses. If ATP is decreased in vivo as reported by Seegers et al. (2002) it provides an additional theory as to how electrical stimulation may act to relieve pain.

More specifically, voltage-gated ion channels located in primary afferent neurons determine the timing and extent of action potential firing by allowing the passage of charged ions in and out of cells in response to cellular membrane potential (Schulz et al. 2008). The initiation of increased sensory nerve signalling by inflammatory mediators enhances increased background firing and other features of peripheral sensitization (Bhave and Gereau 2004). The processes involved in gate activation and voltage sensing in these ion channels is complex (Tombola et al. 2006) but again, it is feasible that externally applied electrical stimulation may in some way influence their responses and subsequently a patient's pain perception.

Moderation of ion channel function and receptor activity is clearly an area where changes in electrical potential, secondary to externally applied electrical stimulation, may affect pain responses.

1.3.2.2 Inflammatory mediators

Grubb (2009) states that inflammatory mediators associated with joint damage sensitize afferent neurons by binding to receptors at the nerve endings. Two laboratory studies, investigating the effect of externally applied electrical stimulation on bovine articular cartilage explants and human articular cartilage (Brighton et al. 2006; Brighton et al. 2008), introduced the inflammatory mediator interleukin-1β into some of the cartilage cultures to simulate a disease state. Results showed that the electrical stimulation effectively inhibited the upregulation of metalloproteinases induced by the interleukin-1β. While these studies focused specifically on how cartilage explants responded to stimulation, the results provide the basis for an hypothesis that electrical stimulation may decrease pain by modulating inflammatory mediator activity.

1.3.3 Summary

Osteoarthritis is a heterogeneous disease in which the processes of pain production and perception of pain are very complex. There is conflicting evidence regarding the

relationships between the pathology and severity of the disease and pain perception. Irrespective of this discordance, there are clearly mechanisms whereby pain pathways may be influenced by electrical stimulation at a very local level in the periphery and this provides support for using electrical stimulation treatment at sub-sensory intensity.

1.4 Functional ability and quality of life

Pain is clearly a prominent clinical feature that is of significant concern to patients with OAK. It is also an important determinant of disability (McAlindon et al. 1993; Sharma et al. 2003; Torres et al. 2006; Somers et al. 2009). However, it is not the only determinant of disability. Similar to pain, there is discordance between disease severity measured radiologically, structural progression of OA and functional and quality of life (QoL) status (Salaffi et al. 2005; Rosemann et al. 2006; Felson 2009). As a consequence, the impact of OAK measured by a person's ability to carry out activities of daily living and participate in social interaction, as well as their general well-being, needs to be considered as well as their levels of pain. Indeed, patient perception of this impact is central to coping with chronic disease (Patrick and Deyo 1989; Carr 1999).

1.4.1 Functional ability and quality of life in the osteoarthritis population

Both function and QoL are concepts that reflect the health status of an individual or population. Limitations in health status contribute to overall disability in patients with chronic disease and OA is second only to cardiovascular disease in the western world as a cause of disability (Salaffi et al. 2005).

Functional ability, or perhaps more importantly, functional disability in OA is defined in a variety of different ways. These include describing difficulties with mobility and the physical effects of the disease (Maly et al. 2006; Rosemann et al. 2006; Dunlop et al. 2008) as well as its impact on a combination of work-related, recreational, social and self-care activities (Carr 1999; Cieza et al. 2009).

Osteoarthritis of the hip and knee frequently leads to considerable difficulty with mobility tasks such as walking and climbing stairs (Creamer et al. 2000; Felson et al. 2000) and greater dependence on family and friends for assistance with activities of daily living (Guccione et al. 1990; March and Bagga 2004). Jinks et al. (2002)

reported that a decrease in functional capacity measured on WOMAC was associated with increasing chronicity of disease. Functional disability of this magnitude has significant consequences for independent living in an ageing population (Guccione et al. 1990; March and Bagga 2004).

Quality of life may also be defined in various ways with ambiguity existing in the literature as the term is interchanged with 'health status', 'subjective well-being', 'life satisfaction' and 'functional disability' (Hickey et al. 2005). However, it is usually interpreted broadly encompassing such aspects as emotional well-being (Carr 1999; Hickey et al. 2005), relationships between family and friends (Carr 1999; Hickey et al. 2005), affect and mood (Ang et al. 2006) and physical ability (Ware et al. 2002).

Data from the generic QoL measurement tool, the Medical Outcomes Study Short-Form 36 Survey (SF-36) interpretation guide (Ware et al. 2002), show that normalised scores for the United States population with OA are consistently lower than those in the general United States population. This finding is reflected in the Australian population (Lapsley et al. 2001; March and Bagga 2004).

Carr (1999) reported that the impact of OA on QoL is substantial and needs to extend beyond functional disability to include emotional and psychological aspects. As important elements of health status and QoL, depressive symptoms and impaired psychosocial ability are also reported to be prevalent in the OA population (Creamer and Hochberg 1998; Sale et al. 2008).

Importantly, Maly et al. (2006) compared self-report measures of mobility (WOMAC physical function subscale) and QoL (SF-36) and noted that the relationship between the WOMAC physical function and SF-36 scores was a moderate one. That is, while closely related, difficulties with functional mobility and QoL cannot necessarily be interpreted interchangeably. This view is supported by other authors (Testa and Simonson 1996; Brazier et al. 1999; Salaffi et al. 2005) who also recommended using both disease-specific and generic tools to fully determine health status in OA.

1.4.2 Relationship between pain and disability in osteoarthritis

There is ample evidence that presence of pain in OA is related to decreasing functional ability and diminished QoL (McAlindon et al. 1993; Jordan et al. 1997; Creamer et al. 2000; Felson et al. 2000; Ang et al. 2006; Ferreira and Sherman 2007; Leveille et al. 2007; Hawker et al. 2008; van Dijk et al. 2010).

In a large cross-sectional study Ang et al. (2006) reported that there was a strong relationship between the severity of chronic pain and both physical and mental function measured using the SF-36. Hawker et al. (2008) examined the specific nature of pain experienced by people with hip or knee OA. They reported that different types of pain experience had different impacts on functional ability and QoL. That is, that people seemed to be able to manage a dull, chronic ache pain while shorter-lasting, but more intense pain, led to avoidance of both social and recreational activities. These results support the importance of optimizing pain management strategies in OAK in order to improve function and QoL. The full account of the relationship between pain and disability, however, is more complex.

Ferreira and Sherman (2007) described the mediating influences of social support and optimism on pain and well-being in OA. This means that perceptions of pain will be affected by both social circumstances and personality. A more optimistic and socially supported person with OA is likely to perceive their pain as less severe than someone who is socially isolated or more pessimistic in outlook independent of disease severity.

Other clinical features such as quadriceps and other muscle weakness (McAlindon et al. 1993; Slemenda et al. 1997; van Dijk et al. 2010), joint malalignment (Sharma et al. 2001), decreased joint range of motion (van Dijk et al. 2010), joint laxity and poor proprioception (Sharma et al. 2003), and BMI (Creamer et al. 2000; Sharma et al. 2003) are also important determinants of physical function and disability in OAK. Additionally, psychosocial aspects such as anxiety, depression, fear-avoidance attributes and lack of confidence in one's self-efficacy contribute substantially to disability in OAK (Creamer et al. 1999; Marks 2007). Importantly, these are also reported as determinants of and risk factors for pain in OAK.

It is also of interest to consider the bidirectional association between disability and OA features (Rosemann et al. 2008). That is, to what extent does decreasing functional ability contribute, for example, to pain, muscle weakness and depression thus creating a cyclical process of deteriorating health status?

1.4.3 Summary

The relationships between pain, pathological features of OAK, function, QoL and joint disease are complex. This means that when investigating the effectiveness of an intervention, a singular focus on just one of these dimensions is unlikely to deliver a comprehensive understanding of a person's condition. As such, during such investigations, it is essential that outcome measurements are meaningful to patients (Bijlsma 2005) and span a range of parameters. Consequently, the achievement of a combined improvement in pain, physical function and QoL should be sought. In other words, if a treatment improves pain but has significant side effects, is arduous to implement, or has negative consequences for general well-being it is less likely to achieve compliance with use. The impact that OAK has on function and QoL in an ageing population (March and Bagga 2004; Salaffi et al. 2005) means that measuring these aspects is essential.

1.5 Physical activity

Physical activity is widely acknowledged as being beneficial to good health and well-being (Macera et al. 2003; Cress et al. 2004; Haskell et al. 2007; Hunter and Eckstein 2009), as well as in slowing down the progress of disability in the elderly (Miller et al. 2000). In 1995, the Centers for Disease Control and Prevention and the American College of Sports Medicine, issued a consensus expert opinion statement recommending that every adult in the United States should accumulate 30 minutes or more of moderate-intensity physical activity on most, preferably all, days of the week in order to promote health and well-being (Pate et al. 1995). A more recent update of this recommendation for healthy adults (Haskell et al. 2007), a companion paper with recommendations targeting older adults (Nelson et al. 2007), and a physical activity guide for older Australians that incorporates the previously cited American recommendations (Brown et al. 2008) have continued to highlight the health benefits associated with physical activity.

Additional recommendations arising from the 2002 Exercise and Physical Activity Conference gave clear guidelines for aerobic exercise and neuromuscular rehabilitation for people with OAK (Minor et al. 2003). These recommendations, again based on consensus expert opinion, stated that people with OA of the hip and knee should accumulate 30 minutes of moderate intensity physical activity or exercise on at least three days per week as well as undertake combined strengthening, endurance, coordination/balance and functional exercise.

1.5.1 Defining physical activity

Physical activity is a broad concept that provides challenges for its accurate measurement. Caspersen et al. (1985) define physical activity as *any bodily movement produced by skeletal muscles that results in energy expenditure* (p.126). Three dimensions: frequency, duration and intensity are often used to enhance this definition (Macera et al. 2003). Exercise, a subcategory of physical activity, is considered to be more planned, structured and purposeful and aimed at improving fitness levels (Caspersen et al. 1985; Macera et al. 2003). Physical activity, while in some ways overlapping with, also needs to be considered separately from function, where movement is considered in the context of serving a specific task. For example, tasks being associated with activities of daily living. Cress et al. (2004) describe physical activity in the context of well-rounded programs in which endurance, strength, balance and flexibility are incorporated to enable achievement of general health and well-being. Depending on definition, levels of physical activity may be measured and interpreted in a variety of ways. For the purposes of this thesis, the definition put forward by Caspersen et al. (1985) is used as it more accurately reflects the usual physical activity likely to be undertaken by a cohort of people with OAK at work and during household and leisure time.

1.5.2 Physical activity in the osteoarthritis population

To compare levels of physical activity in a group with OAK and a matched group without OAK, Bennell et al. (2004) used a self-report survey, the Human Activity Profile (HAP). The HAP is a self-report questionnaire comprising 94 statements relating to whether a person continues to do an activity, has stopped performing the activity or has never done the activity (Fix and Daughton 1988). The higher the score, the more active the respondent is. Two scores are calculated. The maximal

activity score (MAS) represents the highest oxygen-demanding activity the participant is still able to perform. The adjusted activity score (AAS) provides a reflection of an individual's typical daily physical activities. The AAS also provides a descriptor for activity classification (Fix and Daughton 1988). Participants whose AAS is less than 53 are classified as impaired, those with AAS in the range of 53 to74 are moderately active and those with AAS greater than 74 are classified as active.

There was no difference found in MAS scores between the two groups studied by Bennell et al. (2004). However, there were significant differences between the groups based on their AAS with the group with OAK being generally less active than the control group without OAK.

In a large epidemiological study using a self-report survey and including all people with doctor-diagnosed arthritis of any sort, Shih et al. (2006) reported that people with arthritis are less physically active than those people without arthritis. These findings reflect those found by Bennell et al. (2004) in the OAK population.

Farr et al. (2008) measured physical activity levels in 255 patients with early OAK and low mean pain scores (88.5 ± 72.2 out of a possible 500) using an accelerometer worn for at least eight hours per day for at least six consecutive days. Seventy percent of patients did not meet the minimum level of physical activity required to enhance health outcomes in adults as recommended by Pate et al. (1995). More importantly, 62% failed to meet the Exercise and Physical Activity Conference recommendations specifically formulated for people with OAK (2003).

1.5.3 Joint pain, function and physical activity

Joint pain is considered a major determinant of physical activity levels with increasing pain leading to decreasing activity (van Dijk et al. 2010). It is also the most significant correlate with exercise adherence (van Gool et al. 2005). Shih et al. (2006) reported a significant association between presence of severe pain and inactivity in men. While not reaching significance, there was also a definite trend towards this relationship in women. Conversely, engagement in physical activity and exercise is reported to improve pain and function in people with OA (Roddy et al. 2005; Roddy et al. 2005; van Gool et al. 2005; Dunlop et al. 2008) and is

recommended in clinical guidelines as an important treatment option for managing OAK (Vignon et al. 2006; Conaghan et al. 2008; March et al. 2010; Pisters et al. 2010; Zhang et al. 2010).

Physical inactivity in people with OA is also associated with the development of co-morbidities such as muscle de-conditioning and obesity (Shih et al. 2006), while a lack of regular vigorous physical activity is a major predictor in worsening levels of function (Dunlop et al. 2005).

1.5.4 Summary

Despite general consensus regarding the benefits of physical activity, people with OAK undertake less physical activity than recommended and thus remain at risk of developing co-morbidities. Compliance with structured physical activity programs is low despite the longstanding activity level recommendations, specific targeting of activity in treatment management plans, and evidence regarding the healthful benefits of exercise. Consequently, physical activity measurement is another important parameter to consider when investigating the effectiveness of interventions that target pain as a treatment strategy.

1.6 Rationale for thesis

The burden of OA in the community is high (Felson et al. 2000; Walker-Bone et al. 2000; Symmons et al. 2003; Woolf and Pfleger 2003; Buckwalter et al. 2004; Buckwalter and Martin 2006; Sharma et al. 2006). With healthcare costs also high it is essential that cost-effective options for disease management are explored (Segal et al. 2004). The published reports concerning PES for OAK (Zizic et al. 1995; Farr et al. 2006; Mont et al. 2006; Garland et al. 2007) suggest that it has the capacity to provide a low risk (adverse skin reactions notwithstanding), cost-effective treatment option for OAK that could be implemented more widely than it currently is. Consequently it was felt that a longer duration, independent investigation into its effectiveness was warranted. In order to achieve this, preliminary work was conducted in order to develop the protocol for a RCT. The following sections 1.6.1 through 1.6.7 describe the detailed rationale for the RCT protocol.

1.6.1 Study design

A randomised, placebo-controlled repeated measures trial conducted over 26 weeks using valid and reliable outcome measures to evaluate the effectiveness of pulsed electrical stimulation (E-PES) was planned.

The E-PES trial was designed to ensure a valid, unbiased assessment of the effectiveness of PES. Key methodological criteria such as independent randomisation processes, allocation concealment, a priori power calculations, adequate and maintained blinding using a robust placebo, and sufficient follow-up (Guyatt et al. 1993; Herbert 2000; Nuesch et al. 2009) were included. Having one investigator dealing with all participants through all stages of the study was planned to eliminate any bias associated with different clinical styles. Additionally the full trial protocol was published (Fary et al. 2008).

The study design ensured that reporting of results would conform to the Consolidated Standards of Reporting Trials (CONSORT) statement (Begg et al. 1996; Moher et al. 2001) and comply with the recommendations of the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group for phase III clinical trials of less than one year duration (Bellamy et al. 1997). This meant the inclusion of pain, PGA and function in the outcome measures. Additional outcome measurements of joint stiffness, QoL, physical activity and an overall perception of improvement were also considered to be important inclusions. All outcome measures had previously been reported to be reliable and valid in a population of people with OAK.

Repeated outcome measure assessments were planned to occur at baseline, four, 16 and 26 weeks. These time frames were chosen to include the only previously published RCT time frame (four weeks) available during the thesis development stage (Zizic et al. 1995). Sixteen weeks was then planned as the intermediate time point as it gave a more even distribution of data collection throughout the trial.

Participants were to be included if they had a diagnosis of osteoarthritis confirmed using the ACR modified clinical classification system (Altman et al. 1986). For diagnosis of OAK, this classification requires that a patient experiences knee pain and, in addition, presents with four of the following six criteria: aged over 50 years; stiffness that lasts for less than 30 minutes in the morning; crepitus on knee joint

movement; bony tenderness; bony enlargement; and no palpable warmth. The ACR modified clinical classification method of diagnosis has a specificity of 89% and a sensitivity of 84% (Altman et al. 1986) compared with the combined clinical radiographic classification where specificity is 86% and sensitivity 91% (Altman et al. 1986).

Additionally, for inclusion in the E-PES trial, pain had to have been persistent and stable for the previous three months. This was defined as not getting worse or better overall despite short-term fluctuations. The three month prior time-frame was chosen as it ensured that the study was not biased toward recruitment of patients who were either progressively improving or deteriorating with respect to pain intensity. The third inclusion criterion was a minimum baseline score on the pain VAS of 25mm. This allowed for any achievement of a clinically relevant improvement of 20mm (Pham et al. 2004; Tubach et al. 2005) to be accurately measured and reported.

Participants were to be excluded if they presented with co-existing inflammatory arthropathies as this could have confounded the results; contraindications to electrical stimulation as the device could not be used; skin disorders in the vicinity of the knee to be treated so that any adverse skin reaction would be recognised and attributed to use of the device; a TKR scheduled during the study period as that would introduce a contraindication to device use and confound the results; and/or insufficient English to follow instructions and complete forms as all outcome measures other than accelerometers were to be paper-based. For maintenance of safe device use it was vital that participants were able to fully understand the written instructions.

Statistical analysis was planned to report outcomes of clinical significance to ensure that any results were meaningful to patients. Ethical approval from the Curtin University Human Research Ethics Committee was sought and approved (HR122/2006) and the trial was registered with the Australian Clinical Trials Registry (now Australian and New Zealand Clinical Trial Registry, 12607000492459) prior to commencement.

1.6.2 Measurement of pain

The primary outcome of the E-PES trial was chosen to be change in pain measured on a 100mm VAS over 26 weeks (Appendix 5a). The reliability of the VAS has previously been demonstrated (Melzack and Katz 1999) and it is regularly used in research studies in this population.

An incidental measurement of pain was also included with the use of the full WOMAC Likert format 3.1 questionnaire (Appendix 5e). The WOMAC is a disease-specific, self-administered measure of health status assessing pain, stiffness and function. Higher scores denote worse health status. The WOMAC Likert format 3.1 for pain has a maximum score of 20. It is a valid and reliable tool for use in this population (Bellamy 2004).

Pain was to be measured at baseline, four, 16 and 26 weeks.

1.6.3 Measurement of patient global assessment

This outcome measure asks a patient to consider how their condition is affecting them at the time of assessment. That is, it is a time-specific outcome measure. The PGA chosen for use in this study was a 100mm VAS described by Ehrich et al. (2000) (Appendix 5a). Respondents were to consider all the ways in which their arthritis was affecting them at each data collection point. The left hand anchor of the VAS was marked as *Very Well* and the right hand anchor as *Very Poorly.*

Patient global assessment was to be measured at baseline, four, 16 and 26 weeks.

1.6.4 Measurement of health status - function and quality of life

As reported beforehand, the inclusion of separate measures for functional ability and QoL was warranted to give a more comprehensive assessment of health status.

WOMAC is recommended by OMERACT as the instrument of choice for measuring function in OA of the lower limbs (Bellamy et al. 1997). WOMAC Likert format 3.1 was chosen for use in this study (Appendix 5e). A maximum score of 68 is available from answering the 17 questions about functional ability with higher scores reflecting worsening function.

The total WOMAC score, an aggregation of pain, stiffness and function scores (maximum 96), provides a disease-specific measure of health status for people with OA of the knee or hip. However, it does not provide information about the social or emotional consequences of the disease.

The SF-36 has eight subscales reflecting both physical and mental health status as well as two physical and mental component summary measures (Appendix 5b). Comprised of 36 questions it is, like the WOMAC, a self-administered questionnaire. It is a well studied, valid and reliable outcome measure that has become a valuable tool as a generic, rather than disease-specific, measure of disease burden (Ware 2000; Ware et al. 2002). It is widely used and considered a valid psychometric tool in OA studies (Kosinski et al. 1999). Raw scores for each subscale and the two summary measures are normalized to scores out of 100 where higher scores reflect better general well-being and a score of 50 is the general population mean.

There are limitations to using only self-report methods when measuring some variables. Stratford and Kennedy (2006) and Maly et al. (2006) report that pain change is the most important determinant of change in self-reported function with the WOMAC. Stratford and Kennedy (2006) state further that progress measured with WOMAC is often not reflected by actual performance measures post arthroplasty. This is supported by Maly et al. (2006) who found that self-report and performance measures seem to measure different things in people with OAK. Additionally, Stratford et al. (2003) advise that clinicians and researchers need to consider closely the tool for measuring function to ensure that the right tool is used in the right circumstance. For example, if the goal for task achievement requires particular timing for completion then performance measurement would be better than self-report. Conversely, Steultjens et al. (1999) report that very similar information is gained when using both self-report and performance measures and state that consideration needs to be given to what is to be gained with the different measures.

Later work by Steultjens et al. (2001) demonstrated, in a cohort of people with OA of the hip or knee, that there was no difference between responsiveness of self-report measures of disability and of performance measures. Further they added that because of the advantages of using questionnaires (ease of use, time-effectiveness and

minimal subject burden) over extended performance based measures, self-report outcome measures were preferable.

In deciding which specific outcome measures to use, the substantial commitment required of participants during a 26 week trial was considered an important factor. Additionally, it is acknowledged that pain and perception of pain improvement is critical to patients (Patrick and Deyo 1989). These two factors combined with the work of Steultjens et al. (1999; 2001) led to the decision that use of self-report measures alone for function and QoL was appropriate.

Both WOMAC and QoL were to be measured at baseline, four, 16 and 26 weeks.

1.6.5 Measurement of joint stiffness

As the WOMAC health status instrument was being used for pain, function and overall health status, it was decided that its third component, joint stiffness, should also be measured at the same times and reported independently. The maximum score for stiffness is eight (Appendix 5e).

1.6.6 Measurement of physical activity

Accelerometers provide an accurate, objective measurement of ambulatory physical activity (Ainsworth and Coleman 2006), are recommended for use in physical activity research (Ward et al. 2005) and have been validated for use in the older population (Brandon et al. 2004). However, they have their limitations. They are relatively expensive and require equipment and software to support their use (Ainsworth 2009). They do not measure activities such as swimming or bicycling, nor do the dual-axis versions distinguish between steps taken up a flight of stairs and those taken on level ground. Additionally, Hendelmann et al. (2000) report that accelerometer count data and metabolic equivalent (MET) calculations may not correlate very well as upper body use and load carriages are underestimated. Therefore, while providing a direct measurement of ambulatory activity, the accelerometer may underestimate the amount of health enhancing activity that people are engaging in.

Self-report questionnaires are also commonly used to measure physical activity, are often valid and reliable, and are often the method of choice in large scale epidemiological studies (Fix and Daughton 1988; Brown et al. 2004; Ainsworth and

Coleman 2006; Shih et al. 2006). Whilst inexpensive and easy to use, they are also subject to recall bias and require a certain degree of literacy on the part of the person completing the questionnaire. Vigorous activity is likely to be overestimated by questionnaires while activities of daily living more likely to be underestimated (Ainsworth 2009).

For the E-PES trial, both accelerometer (Actigraph GT1M) and self-report (HAP) (Appendix 5d) data were to be collected at baseline and 16 weeks. Participants were to wear their accelerometers, held secure in a nylon pouch positioned over the anterior superior iliac spine, on a belt around their waist during waking hours for eight consecutive days. This duration was to ensure collection of six full days of data. Accelerometers were to be taken off only for showering and water-based activities. A data reduction program developed by the Actigraph manufacturer was to be used to determine the number of minutes spent per day in four categories of activity intensity level (resting, light, moderate and vigorous). The cut off points for these categories described by Swartz et al. (2000) were chosen as they more closely reflected usual daily activity tasks in this population.

Resource constraints meant that collecting follow up physical activity data at multiple time points was not possible. Consequently, sixteen weeks was chosen as it was considered that fewer people would have dropped out at 16 weeks than at 26 weeks thus giving access to larger numbers for analysis.

1.6.7 Measurement of overall perceived improvement

Measuring individual aspects of disease presentation is necessary to tease out relationships that may exist between each parameter and to provide a more complex overview of an intervention's effectiveness. However, it is also essential to ascertain how each person feels about their overall progress. For this reason, the global perceived effect scale (GPES)(Appendix 5c) was included in the array of outcome measures to be used in this thesis.

The GPES was to give participants the opportunity of saying whether they felt better, the same or worse by varying degrees since entering the study. An 11-point scale as reported by Pengel et al. (2004) ranging from -5 (vastly worse) to +5 (completely

recovered) with zero point being unchanged was chosen to be administered at both 16 and 26 weeks.

1.6.8 Thesis plan

The preliminary work conducted to prepare for the E-PES trial forms the content of Chapters 2, 3 and 4. Chapter 2 describes, by way of published paper (Fary et al. 2009), a pilot study conducted to ensure familiarity with equipment use, provide experience with subject recruitment and retention in the study, assist with the E-PES trial protocol development, and develop an understanding of outcome measures, equipment use compliance and any adverse effects from its application. This study used the commercially available Bionicare® BIO-1000™ device.

Equipment was a crucial component of this thesis. Initial negotiations with the *BioniCare Medical Technologies Inc.* to use the Bionicare® BIO-1000™ device and the placebo equipment used in the previous RCTs (Zizic et al. 1995; Garland et al. 2007) were positive. However, changed financial circumstances of the company meant that by the time this trial was to commence, the equipment was no longer available. Chapter 3 describes the equipment development process undertaken to ensure equipment was available to continue with this research. A positive consequence of this situation was that the E-PES trial would be conducted completed independently of commercial interests. Additionally, some concern had been expressed by *BioniCare Medical Technologies Inc* about the robustness of its placebo device. Developing our own equipment meant that this concern could be addressed as well.

Chapter 4 describes, by way of paper, E-published ahead of print (Fary and Briffa 2010), the process undertaken for and the results of testing the new equipment developed. It provides clear support for the type of current chosen for investigation in the main study of this thesis.

The published protocol for the E-PES trial (Fary et al. 2008) is the subject of the fifth chapter.

Chapter 6 describes, by way of paper submitted, the results of the E-PES trial.

Finally, chapter 7 provides a summary of the thesis, a discussion of its main findings and the significance and clinical implications of these findings.

Supporting documentation not available in the forthcoming chapters is available in the following appendices.

Appendix 1: Participant information forms

Appendix 2: Participant informed consent forms

Appendix 3: E-PES trial administrative checklist

Appendix 4: E-PES trial telephone screening form

Appendix 5: Paper-based outcome measure forms

Appendix 6: Instructions for use of PES equipment

Appendix 7: Medication and hours of use diaries

1.7 Summary and significance

As a non-pharmaceutical, non-invasive, relatively inexpensive modality with few reported side effects, PES has the potential to provide an effective, more widely used treatment option for OAK, a condition presenting a substantial worldwide health burden. The previous studies into the modality cited in this literature review were all conducted with support from, and by several employees of, the manufacturers of the commercially available product Bionicare® BIO-1000™ , *BioniCare Medical Technologies Inc.* (Zizic et al. 1995; Farr et al. 2006; Mont et al. 2006; Garland et al. 2007). As a consequence, these studies were open to bias and conflict of interest. The two RCTs of four and 12 weeks were also relatively short-term (Zizic et al. 1995; Garland et al. 2007).

The purpose of this thesis is to provide an independent, long-term evaluation of the effectiveness of PES for managing symptoms of OAK. Specific aims were to determine the influence of PES on pain, function, QoL, physical activity levels and overall perceived effect measured at baseline, four, 16 and 26 weeks.

Chapter 2: Pilot study of pulsed electrical stimulation

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Effectiveness of pulsed electrical stimulation in the management of osteoarthritis of the knee: Three case reports

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This report examines the symptomatic and functional changes associated with subsensory threshold, pulsed electrical stimulation (PES) treatment for osteoarthritis of the knee in three patients. Two females and one male over age 60, with radiologically diagnosed osteoarthritis of the knee, were treated with PES. The intervention was delivered for eight hours daily at home using a portable, battery-operated unit over 16 weeks. Treatment outcome data were collected at three time points with results plotted for visual examination. Pain, function, patient global assessment, quality of life, global perceived effectiveness, and ambulatory activity levels were measured. The device was well tolerated with adherence levels of 63%, 83%, and 102% of target dose. Perceived global effectiveness of treatment was high for two of the three patients (+3 and +4.5 out of 5), but the third patient reported no change. Scores for pain, global assessment, function, and ambulation were internally consistent with global treatment effect. It is concluded that the PES device was well tolerated, and subsensory PES may provide an effective nonpharmaceutical, noninvasive addition to the management of osteoarthritis of the knee over 16 weeks.

Introduction

Osteoarthritis of the knee (OAK) is a major cause of pain and disability and is among the most common causes of musculoskeletal disability in the Western world (Walker-Bone, Javaid, Arden, and Cooper, 2000). It is a disease associated with aging, characterized by progressive resorption of the articular cartilage (Baker and Ferguson, 2005) and is expected to pose a greater burden on future health care.

Existing management options largely focus on symptom relief and maintenance of function. Pharmacotherapy is often associated with adverse effects (Gislason et al, 2006; Jick, Kaye, Russmann, and Jick, 2006; Solomon et al, 2006), whereas the

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decision for surgical intervention may be complicated by the presence of comorbidities, particularly among the elderly.

Physical therapists use a range of nonpharmaceutical, noninvasive treatment options to manage OAK. These options include a variety of electrotherapeutic modalities, such as transcutaneous nerve stimulation (TENS) and interferential current, with varying degrees of reported effectiveness (Adedoyin, Olaogun, and Fagbeja, 2002; Aubin and Marks, 1995; Cheing, Tsui, Lo, and Hui-Chan, 2003; Ng, Leung, and Poon, 2003; Roche and Wright, 1990).

In general, electrical stimulation modalities are applied at intensities above sensory threshold as pain modulation appears to be due to the action of the applied electrical stimulus on peripheral sensory nerve fibres and the stimulation of endogenous opiates (Sluka and Walsh, 2003). The effectiveness of high frequency (110 Hz), high intensity (to tolerance) electrical stimulation via TENS units when compared with low frequency (4 Hz), low intensity (strong but comfortable) electrical stimulation was reported by Chesterton et al (2003). They suggested that the physiological mechanisms that explained their outcomes were a result of spinothalamic tract cell inhibition or peripheral blocking of A-alpha and A-delta nerve fibres.

There has been some reported use of transcutaneous pulsed electrical stimulation (PES) delivered at subsensory levels for the management of OAK. One four-week randomized placebo-controlled trial (Zizic et al, 1995) found capacitively coupled, subsensory threshold PES to be effective in providing relief in pain, improving function, and decreasing joint morning stiffness. Because the mechanisms for effectiveness reported by Sluka and Walsh (2003) and Chesterton et al (2003) require nerve stimulation, it is very unlikely that they contribute to the effectiveness of subsensory stimulation, thus suggesting other mechanisms also at work.

The mechanism through which subsensory PES achieves its outcome is, at present, speculative. However, there are many pain-mediating receptors in the periphery that may hypothetically be affected by an externally applied electrical field by virtue of their endogenous electrical potential and the role of polarization in receptor function and nociceptor stimulation (Wood, 2006).

The capacity of monophasic, pulsed electrical stimulation to alter adenosine triphosphate (ATP) levels has also been demonstrated by Seegers et al (2002). It was postulated by this group that altering ATP levels may affect pain sensation through P2-purinergic receptors. More work is needed to identify those pain-mediating receptors that exist within the osteoarthritic joint and how their action may be affected by both subsensory and above sensory threshold externally applied electrical stimulation.

Although Zizic et al (1995) focused on symptomatic relief, Zizic also contended that this particular type of stimulation might have a disease-modifying effect. This assertion is yet to be fully tested. Using PES and electromagnetic fields to augment bone healing is well documented (Aaron, Ciombor, and Simon, 2004; Brighton and Pollack, 1985; Mandracchia et al, 2004; Thawer, 1999), and laboratory and animal studies show strong theoretical support for chondrogenesis (Brighton, Wang, and Clark, 2006; Lippiello, Chakkalakal, and Connolly, 1990; Wang et al, 2004).

While specificity of responses to particular electrical parameters was reported in these chondrogenesis studies, variability exists between them. Brighton, Wang, and Clark (2006) reported best outcomes in bovine explants after using very high frequency (60 kHz) current at 20 mV/cm using a pattern of continuous stimulation followed by a pulsed duty cycle, whereas Lippiello, Chakkalakal, and Connolly (1990) demonstrated improved cartilage healing in rabbits using pulsed direct current (100 Hz) with a peak value of 2 μAmps delivering an electric field within the tissue of 20 40 mV/cm^2. These types of responses are yet to be demonstrated clinically. However, given that no current treatment modality addresses the disease process itself, these laboratory findings provide a clear direction for further clinical investigation. For cartilage changes to be demonstrated clinically, modality use would ideally be extended over a period of at least 12 months for radiological cartilage changes to be measured. For this to occur though, the modality needs to be symptomatically effective and easy to use in the long term for patients to be compliant with its use.

The few clinical trials that have been reported have been of short duration, thus leaving a gap in knowledge regarding the effectiveness of PES over a longer time frame.

The purpose of this series of case reports was twofold: primarily to examine whether the short-term symptomatic results previously obtained using PES were maintained over 16 weeks and secondarily to determine patient compliance and comfort with its use.

Case descriptions

Three patients aged over 60 years and with radiologically diagnosed OAK agreed to try the PES stimulation. Because the device is not in routine clinical use, ethical approval was obtained from the Human Research Ethics Committee at Curtin University of Technology. All patients gave prior written informed consent. Patients were recruited by word of mouth, two having recently completed a self-management program for people with OAK.

None of the patients had coexisting inflammatory arthropathies, contraindications to electrical stimulation or was scheduled to have a total knee replacement within the treatment period. The two patients with bilateral OAK were asked to select their most symptomatic knee for treatment.

The first patient (Patient X) was an active 61-year-old woman with a keen interest in sewing who often cared for her younger grandchildren. She had had osteoarthritis symptoms in her right knee for three years and had mild to moderate degenerative changes in the medial joint compartment on X-ray. Tasks that included getting up and down from sitting and using stairs were the most functionally challenging for her. She was the most overweight of the three patients with a body mass index (BMI) of 36, was on medication for hypertension, and used anti-inflammatory medication to manage her osteoarthritis pain.

The second patient (Patient Y) was a 73-year-old retiree with multiple lower limb joint osteoarthritis, a BMI of 34.2, and a medical history that included hypothyroidism for which she was taking thyroxine. On X-ray she had early to moderate osteoarthritic changes in both hips, moderate to severe changes in both patello-femoral joints, early changes in medial and lateral compartments of both knees, and severe changes in her right midtarsal joint. Her right foot was giving her the greatest problems. Like patient X, she reported having severe difficulty with activities such as getting up and down from sitting and using stairs. Her lifestyle was less active than the other two patients, although she also regularly cared for her grandchildren. Patient Y regularly took prescribed anti-inflammatory medication for her arthritis and supplemented this with glucosamine, omega 3, and multivitamin tablets.

The third patient (Patient Z) was a 72-year-old retired builder who remained very actively involved in major family building and renovating projects. He and his wife regularly provided care for their great-grandson. He reported having had bilateral osteoarthritis symptoms for 10 years, with his left knee more troublesome than the right. His X-ray reports described bilateral moderately advanced degenerative changes in the medial tibio-femoral compartments. He regularly took glucosamine for his OA but was not using any prescribed medications or over-the-counter analgesics. While his initial pain report was 37/100, he was most troubled by the stiffness in his knees because that made it more difficult to climb ladders and return to standing after working on his knees or playing with his great-grandson on the floor.

All three patients were asked to continue their normal background medical management during the treatment period with a diary used to track any changes.

Intervention

Each patient agreed to wear the PES for 16 weeks. Measurements of pain, function, quality of life, and ambulatory activity were documented pre- and post-PES treatment to monitor treatment effectiveness.

The whole treatment process was undertaken over 18 weeks, comprising one week when the patients wore an accelerometer to measure ambulatory activity; 16 weeks of treatment with PES; and one additional week of accelerometer use. Contact with all three patients was maintained throughout this period by telephone, mail, e-mail, and clinic visits.

Equipment

The PES was delivered to the patients using the same commercially available, portable,

battery-operated device, the Bionicare® BIO-1000™,[1] used by Zizic et al (1995) in their four-week study that showed symptomatic and functional improvements. The manufacturers report that this device delivers pulsed, monophasic, exponentially declining electrical stimulation with a pulse width of 2 ms at a frequency of 100 Hz. These parameters are similar to those described by Lippiello, Chakkalakal, and Connolly (1990) that produced enhanced quality of cartilage repair in osteochondral defects in rabbits. The only adjustable parameter on the device is the intensity.

Skin surface electrodes, each with a contact area of 170 cm^2, were used with electrode gel at the skin-electrode interface. The cathode was placed anteriorly over the patella of the knee while a second electrode (the anode) was placed anteriorly on the thigh above the knee. The position of the electrodes was predetermined by the neoprene wrap supplied with the stimulation device. This positioning was that reported as being used in the previous trial and allows maintenance of skin contact with the large electrodes during knee movement while still targeting the knee joint itself. Color-coded Velcro attachments for the individual electrodes aided with consistent electrode positioning. Once the electrodes were secure, patients turned up the intensity until they felt pins and needles or a tingling sensation. Once achieved, the intensity was turned down until the sensation was no longer felt. The treatment was consequently delivered at a subsensory threshold level.

The patients were trained in using the device by a physiotherapist and were given written instructions and an educational video to take home. The patients were advised to use the device for at least eight hours per day during the treatment period. All patients wore it at night for convenience. A timer built in to the control unit recorded the cumulative amount of time that PES was used over the 16 weeks.

Evaluation

Repeated measures of pain, function, patient global assessment, and quality of life were recorded at the beginning of treatment and then at four and 16 weeks. Ambulatory activity levels were measured at the beginning and at 16 weeks and the 11-point global perceived effect scale at 16 weeks only.

Pain experienced during the previous 48 hours was measured by using a 100-mm visual analogue scale (VAS). The reliability of the VAS has previously been demonstrated (Melzack and Katz, 1994) and is regularly used in this population.

Function was measured by using a written questionnaire consisting of 10 questions (Likert scale format) about activities that are generally considered to be clinically relevant to patients with OAK. These included activities of daily living such as getting in and out of a chair, going up and down stairs, and dressing activities where knee movement is required. A maximum score of 100 signified very poor functional capacity.

Patient global assessment was measured by using a 100-mm VAS recommended for use in patient assessment forms by the American College of Rheumatology (2006). The patients were asked to consider all the ways in which illness and health affected them at the time of assessment and were asked to make a vertical mark on the VAS (from *very well* to *very poorly*).

Quality of life was measured by using the Medical Outcome Short-Form 36 survey (SF-36). The SF-36 has eight subscales reflecting both physical and mental status. It is composed of 36 questions, is self-administered, and can be completed in less than 15 minutes. All estimates of score reliability, from 14 separate studies, for each of the eight subscales of the SF-36 exceeded accepted standards for measures used in group comparisons (Ware, Kosinski, and Gandek, 2002). The SF-36 has been validated for use in Australia (Sanson-Fisher and Perkins, 1998).

An 11-point global perceived effect scale described by Pengel, Refshauge, and Maher (2004) was used to provide the patients' overall perception of the PES effectiveness to determine clinical relevance of any changes found. The scale ranged from −5 (vastly worse) to +5 (completely recovered). The midpoint of zero signified no change to symptoms.

Accelerometry is now considered the preferred method of measuring physical activity (Ward et al, 2005) because it provides data that allow individual examination of ambulatory activity frequency, intensity, and duration. For this study a Computer Science and Applications monitor, the most widely accepted accelerometer

[1]BioniCare Medical Technologies, Inc., Sparks, MD, USA.

in research, was used (Welk, 2002). The matchbox-size accelerometer was attached to a belt that the patients wore for a period of seven consecutive days at both the beginning and end of the treatment period.

The treatment outcomes measured before and at the conclusion of treatment were completed during scheduled visits to Curtin University of Technology. The four-week measures were completed by the patients at home, and the forms were returned to the physiotherapist by mail.

Outcomes

Two of the three patients reported being considerably better after the 16-week period of treatment. Patients X and Z scored +3 and +4.5, respectively, on the global perceived effect scale where a score of +5 equated to being completely recovered. Patient Y scored zero on the same scale, meaning that she experienced no overall change in her condition with the intervention.

There was an improvement in pain, patient global assessment, and function at each time point in patients X and Z, but patient Y did not change (Figure 1). Patients X and Z also demonstrated a trend toward improvement for each individual SF-36 scale at each time point, whereas patient Y demonstrated no change (Table 1). In particular, patient X showed improvements greater than one standard deviation according to the norms for a population with osteoarthritis (Ware and Kosinski, 2001) in six of the eight scales measured. Of particular note, these findings from pain, function, patient global assessment, and quality of life

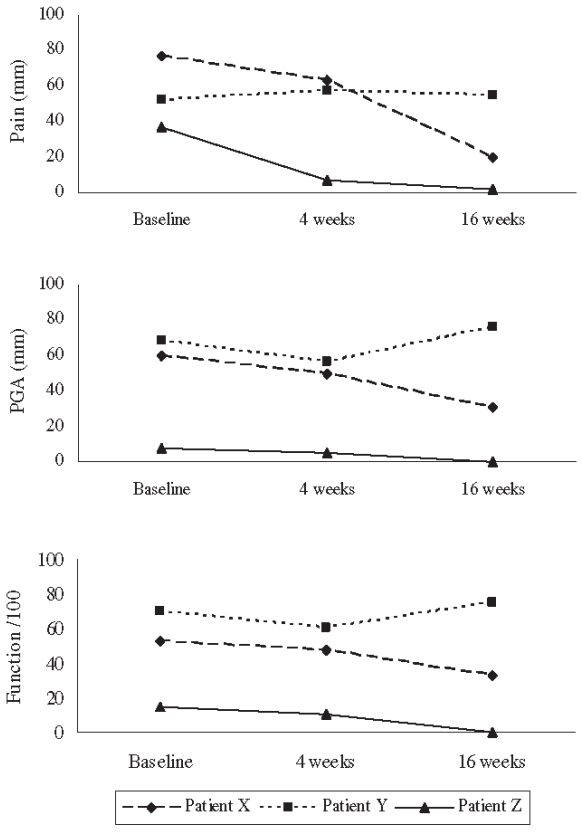

Figure 1. Plotted raw data for pain, patient global assessment (PGA), and function.

Table 1. Norm-based values of Medical Short-Form 36 scores at each measurement point in the study.

	[1]Osteoarthritis population mean	[1]Osteoarthritis population standard deviation	Patient X[2]			Patient Y[3]			Patient Z[4]		
			Baseline	4 weeks	16 weeks	Baseline	4 weeks	16 weeks	Baseline	4 weeks	16 weeks
Physical functioning	38.97	12.75	26.98	[5]**44.20**	**50.66**	24.83	29.14	26.98	48.51	46.36	54.97
Roles - physical	41.2	11.96	26.96	26.96	**55.6**	26.96	26.96	26.96	48.48	55.66	55.66
Bodily pain	40.77	9.86	27.88	35.53	**52.84**	31.50	31.50	35.53	52.84	52.84	59.28
General health	42.99	10.7	50.09	50.09	50.09	36.82	34.37	34.37	62.37	55.00	62.37
Vitality	45.31	10.07	45.21	50.26	**57.85**	17.39	22.45	24.98	60.38	60.38	62.91
Social functioning	43.69	12.54	34.27	45.49	**56.70**	39.88	39.88	39.88	56.70	56.70	56.70
Roles - emotional	45.57	12.72	24.13	**55.23**	**55.23**	34.49	34.49	34.49	55.23	55.23	55.23
Mental health	47.56	10.64	40.58	50.01	47.65	38.22	38.22	38.22	59.45	57.09	61.80

[1]Ware and Kosinski (2001).
[2]Patient X demonstrates improvement from baseline well above one standard deviation for this population in six of the eight scales.
[3]Patient Y scores below the mean for this population at baseline and effectively shows no changes over the study.
[4]Patient Z has baseline scores above the mean for this population in all of the eight scales while in six of the eight scales his baseline scores are higher than the mean (50). of the total general population. This suggests that he is likely to be showing a ceiling effect in subsequent measurements. Together with his high function scores these outcomes highlight his tolerance for managing his underlying OAK.
[5]Overall positive change from baseline measure of greater than one standard deviation for the population in bold.

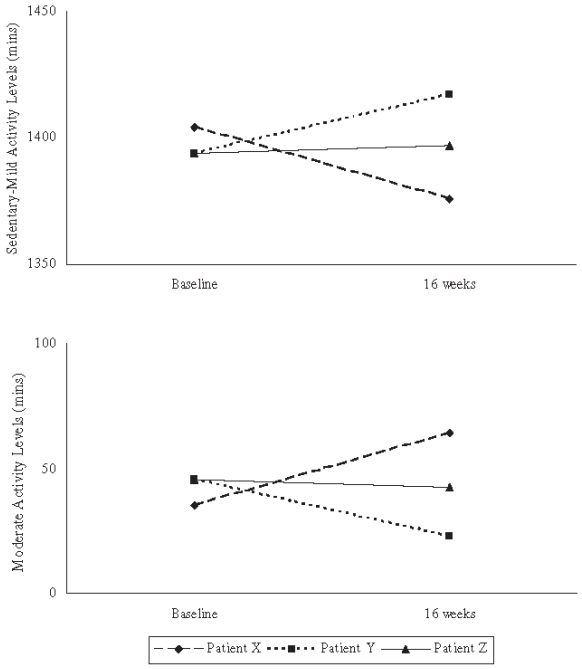

Figure 2. Plotted raw data for accelerometer measurements.

outcome measures reflected those of the global perceived effect scale.

Similar trends were noted in ambulatory activity (Figure 2). Patient X demonstrated the largest change with a 29-minute per day shift of sedentary/light activity to moderate activity levels. Patient Y became more sedentary with a shift of 22 minutes per day from moderate activity to sedentary/light activity levels, whereas activity levels for patient Z remained the same; however, both patients Y and Z had higher baseline moderate activity levels (45.71 minutes per day) than patient X (35.14 minutes).

PES was used for 562, 734, and 915 hours in the 16-week period (patients X, Y, and Z, respectively). There was no change in medication use for any of the patients. Feedback from patients on ease of use and self-perceived effectiveness was very positive. Comments included: "I definitely benefited from it"; "I can climb ladders now"; "It took time to get used to sleeping with it but after that it was just a matter of five minutes to put it on in the evening"; and "People have commented on the decrease in my limp."

Discussion

The use of electrotherapy by physical therapists is not new. However, these cases describe a novel approach of using subsensory stimulation with long duration of use over an extended period of time.

These three patients were asked to use the PES for a total of 896 hours over 16 weeks. All patients found the device easy to use and were essentially compliant with its use. Lower application times for patients X and Y were related to minor problems with their device leads, resulting in reduced application time. Nonetheless, patient X achieved the largest positive response overall. These results suggest PES is well tolerated by patients and continued use with good compliance is feasible.

Another factor critically important in maintaining long-term compliance with use is the patient's perspective on the effectiveness of a treatment modality. The effects of interventions need to be relevant to patients, and it has been recommended that this perspective should be

included in ongoing research endeavors (Wells et al, 2001). With this in mind, each patient's view of the effectiveness of the device was assessed by using the global perceived effect scale. Clear relationships between changes in pain, function, quality of life, and activity, and each patient's individual perspective of their response to the treatment were achieved. This reinforces the earlier suggestion that good compliance could be expected with longer term use of this modality.

All three patients showed internal consistency in responses across all outcome measures. These results provide some confidence that although the number of cases is too small to draw conclusions, the effects may be associated with the use of PES. Nonetheless, without control patients, the effects equally may have been due to a placebo effect or other factors.

With regard to physical activity, patient X clearly showed an increase in moderate activity, showing that she became less sedentary over the 16 weeks. Conversely, patient Y, who reported no symptomatic improvement, became more sedentary. Although there was little change in patient Z's activity measures, his self-reported scores in function and quality of life indicated that he was already functioning at a high level of capacity, suggesting that in his daily routine there was little room for improvement. These outcomes suggest a relationship in these patients between pain, function, and perceived effectiveness outcomes and level of ambulatory activity.

Accelerometry provides an objective measure of intensity and duration of ambulatory activity. However, in an older population accelerometers may not be responsive to more subtle changes, such as the ease with which ambulatory activity is conducted, nor are they sensitive to changes in nonambulatory activity, such as cycling and swimming (Matthews, 2005). Incorporation of other activity measures, such as a self-reported activity measure to complement the accelerometer data, may have revealed additional changes.

Conclusion

This series of case reports conducted with patients in Australia suggests that subsensory threshold PES may provide an effective nonpharmaceutical, noninvasive device for managing the symptoms of OAK. Treatment outcomes indicate that symptomatic changes could be sustained for at least16 weeks and that PES is likely to be easily tolerated in the target population for continued use. Longer randomized controlled studies are needed to determine ongoing symptomatic relief and the additional disease-modifying potential of the modality.

Acknowledgments

The three PES devices (Bionicare® BIO-1000™) used for treatment were supplied by the Australian distributor of the product. We thank Sophie Coleman for assistance with recruitment of patients.

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Chapter 3: Development of pulsed electrical stimulation equipment

3.1 Introduction

When developing the project for this thesis *BioniCare Medical Technologies Inc.*, the company that produced the BioniCare® BIO-1000™ used in the previous chapter's pilot study (Fary et al. 2009), expressed considerable interest in providing the equipment for the ongoing research. So much so that in early January, 2007, written confirmation of support, by way of equipment provision for the project, was received. By March that year, the financial circumstances of the business had changed meaning that the equipment was no longer available for use. As no other commercially available devices contained the specific parameters described by the previous PES reports (Zizic et al. 1995; Farr et al. 2006; Mont et al. 2006; Garland et al. 2007), it was necessary to develop our own equipment with these parameters. While this added a substantial extra component to the thesis, it also resulted in a study conducted completely independent of commercial concerns. This can only be seen in a positive light.

Research conducted under the auspices of commercial entities may be open to bias and conflict of interest (Wynia and Boren 2009). Meta-analyses comparing results from industry-funded drug trials with those conducted without industry funding have shown that there are substantially increased odds of finding favourable results in reports from industry-funded research (Bekelman et al. 2003; Lexchin et al. 2003). The E-PES trial protocol associated with this thesis incorporated key research elements to reduce bias. Nevertheless, had it remained supported by a commercial entity, perception of bias or conflict of interest may have existed. Being completely independent meant that this perception would be eliminated and is one of the strengths of the study.

Verbal communication with *BioniCare Medical Technologies Inc.* had also highlighted some concern with the placebo device used in the Garland et al. (2007) and Zizic et al. (1995) RCTs. It was stated that while the current flow cut out after three minutes, it could easily be restarted by unlocking the device and turning up the

intensity. This could potentially have led to people in the placebo group receiving more than the three minutes of stimulation intended if they were to adjust the intensity during the treatment duration. Developing our own equipment meant that this concern could also be addressed.

The Department of Medical Technology and Physics at Sir Charles Gairdner Hospital in Nedlands, Western Australia, was approached to source the expertise required for the development of the PES equipment and a robust placebo device. As a result, Senior Biomedical Engineer, Mr Chris Tingley, provided advice, the technical expertise, practical application and safety assurances to produce the equipment for the study.

3.2 Choice of equipment

Commercially available TENS units were chosen for modification as they provided convenient casing and controls and were similar in size to the BioniCare® BIO-1000™ units. They were also readily available without prescription and relatively inexpensive to purchase.

Initially the Metron Pro-10s unit (*Ausmedic Australia, Hilton, WA Australia*) was chosen as it provided a continuous treatment option and a physical guard over the control dials to prevent inadvertent changes to intensity or waveform parameters. Unfortunately it did not offer a 100Hz frequency and even with alternative commercially available crystals (electronic resonators that set frequency) substituted into the electronic circuit, the closest frequency obtainable was 94Hz.

The Metron Digi-10s (*Ausmedic Australia*) was then investigated as a possible alternative. This unit was slightly more expensive but had the advantage of having a digital display of parameters, a locking button to ensure no inadvertent changes to intensity or treatment parameters occurred, and was able to deliver an exact frequency of 100Hz. It also provided a continuous treatment option which was necessary for prolonged treatment duration.

3.3 Electrical stimulation waveforms

The electrical parameters of the BioniCare® BIO-1000™ are described by Zizic et al. (1995) as pulsed, monophasic current with a frequency of100Hz, and a spiked, exponentially decreasing wave form. These parameters were replicated within the Metron Digi-10s casing.

This was achieved by inserting a diode into the circuit to cut off half of the existing biphasic current wave form. Unfortunately, early testing of this device produced unacceptable, significant, adverse skin responses under the electrodes. This was unexpected given it was an exact replication of the Zizic et al. (1995) current and adverse skin reactions were not a major feature in the BioniCare® literature. However skin irritation and even chemical burns are considered common side effects of monophasic current (Hooker 2001) so in that context, the adverse skin reactions occurring were not that surprising.

Subsequent to this early testing of the monophasic current, another prototype was developed. The BioniCare® BIO-1000™ wave shape, pulsed nature and frequency parameters were maintained but instead of a monophasic current type, an asymmetrically biphasic current type was incorporated (Figure 3.1). Because of the alternating flow of current with a biphasic waveform there is less likelihood of a chemical build up occurring under the electrodes and therefore less likelihood of adverse skin reactions. Early attempts to produce the desired waveform caused the device to draw too much current from the battery for the intended durations of use. Through experimentation it was found that a small 0.47ufd capacitor installed into the output circuit would produce the correct waveform without consuming excessive battery power.

3.4 Placebo device

The placebo device was constructed to also produce the asymmetrically biphasic wave form. This ensured that in the initial stage of turning on and setting the device, the same type of current was delivered to all participants. Doing so was to protect blinding within the study as the overall sensation produced by the current would be the same for all participants. An additional three-dimensional, three minute timing component was developed for insertion into 35 of the devices (Figure 3.2).

The timing component cut off the electrical stimulation after three minutes to replicate the time used in the placebo in the RCTs by Zizic et al. (1995) and Garland et al. (2007). By then the treatment was being delivered at the sub-sensory intensity so the participants were unaware that the current flow had stopped. There was no change to the liquid crystal display (LCD) screen so the device still appeared to be delivering current flow. Unlike the *BioniCare Medical Technologies Inc.* placebo device, current could not be recommenced by simply adjusting the intensity of the current flow up. The whole device needed to be turned off and then back on again. This meant that the possibility of regularly receiving bursts of PES treatment was eliminated.

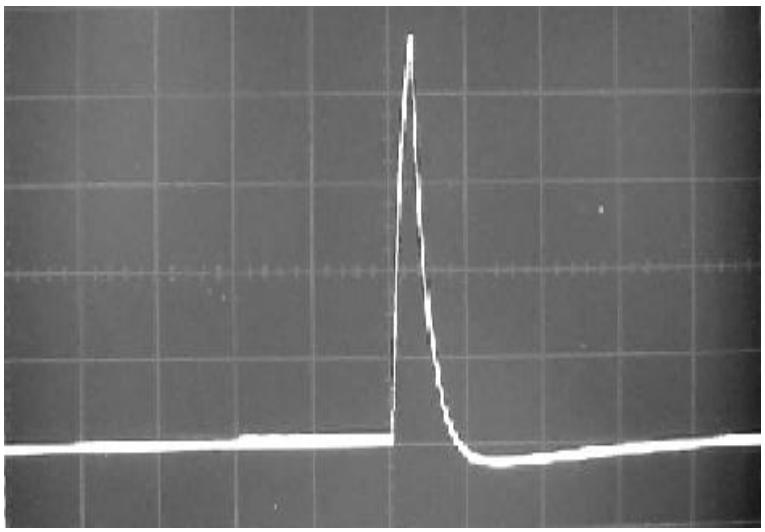

Figure 3.1 Asymmetrically biphasic experimental waveform as viewed on the oscilloscope through 500 ohms resistance

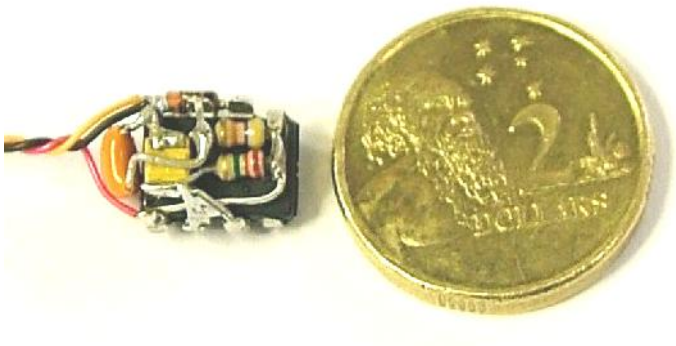

Figure 3.2 Placebo circuit

3.5 Electrodes and mechanism for capacitive coupling

Consistent with the aim of replicating previous reported use of PES, the method of application was also replicated. Neoprene wraps based on the wrap-around, three point Velcro securing system used with the BioniCare® devices were manufactured (Figure 3.3).

Figure 3.3 PES equipment as used by participants

Colour-coded Velcro anchors (red and black) were stitched to the inside of the wrap to ensure constant electrode placement (Figure 3.4).

Figure 3.4 Neoprene wrap showing colour-coded Velcro attachments, electrodes, electrode pockets, electrode wires and PES control box

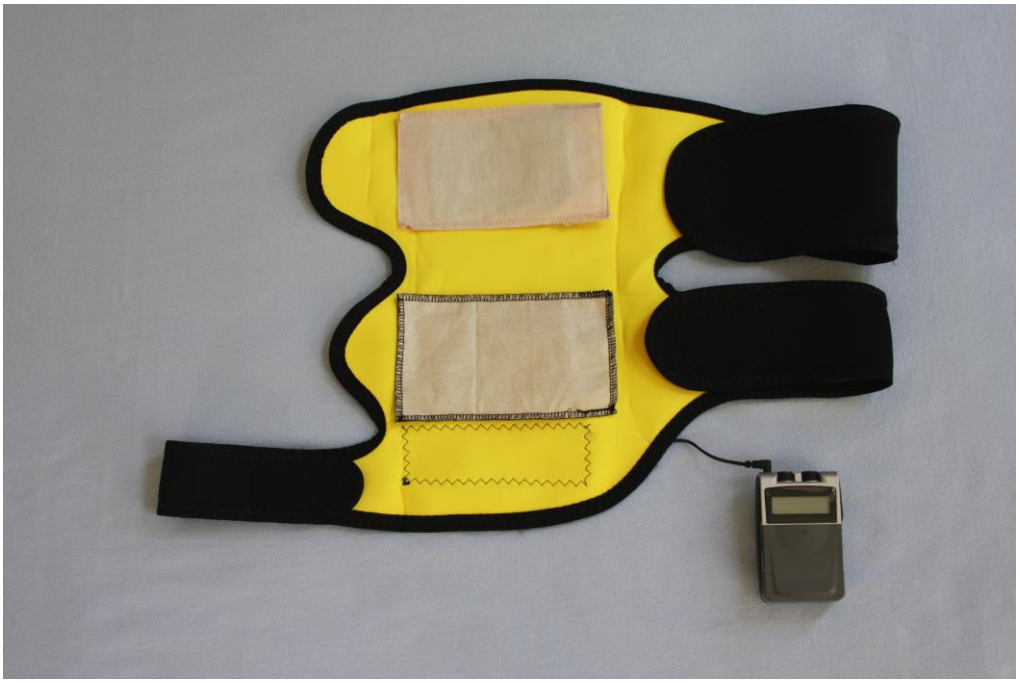

Figure 3.5 Neoprene wrap with electrode pockets attached internally via Velcro

Multiple use, conductive, silicone electrodes measuring 120 mm long and 80 mm wide were used. These were chosen rather than self-adhesive ones because of the duration of skin contact with treatment and cost. This size of electrode was the largest available at the time yet it was still smaller than the flexible electrodes used in the BioniCare® system.

Electrode pockets made of calico material and measuring 175 mm long and 100 mm wide were made to extend the area of the electrical field (Figure 3.5). This size closely resembled the size of electrodes used in previous studies. Additionally, impedance testing demonstrated that increasing the size of the electrode contact surface decreased the impedance. This in turn decreased the electrical field density at the skin-electrode interface – an important factor to consider with the treatment duration proposed.

3.6 Coupling gel

As previous PES studies had concluded that adverse skin reactions were likely to be caused by response to conductive gel (Zizic et al. 1995; Garland et al. 2007), a salt free hypoallergenic gel, Spectra 360 (*Parker Laboratories Inc., Fairfield, New Jersey, USA*), was chosen for this study.

3.7 Batteries

Rechargeable batteries were used because the duration of treatment time (minimum of seven hours per day) meant that it was both economically and environmentally unfeasible to use non-rechargeable batteries.

Early biphasic waveform development attempts drew current from the battery at a rate of 50 milliAmps/hour (mA/h). This meant that a battery would need a capacity of at least 350mA to be able to provide power for the seven hours required and that even with high capacity batteries, the current draw needed to be reduced. By altering the way the wave form was produced, that is by inserting the 0.47ufd capacitor, the current draw was reduced to a maximum rate of 20 mA/hour.

Rechargeable, Powerex brand, 9 volt, nickel metal hydride batteries (*Maha Energy Corp., City of Industry, California, USA*) with a capacity of 300 mA hours were sourced for the study (Figure 3.6). A bench test of these batteries was conducted using the experimental PES device at a discharge rate of 20 mA/h across a resistance of 1,000 Ohms. Results demonstrated that the battery would continue to provide enough power for continuous treatment for up to nine and a half hours. This was clearly sufficient for the study requirements.

3.8 Instruction manual

An instruction manual was developed so that important issues such as a summary of the study requirements; warnings about use; what to do should any adverse events occur; care of equipment; step by step instructions for use; and contact details for the main investigator were readily available to participants (Appendix 6).

Figure 3.6 Battery and charger

3.9 Summary

Having completed the development phase, it was necessary to formally test the PES equipment. In particular, the monophasic waveform equipment was to be compared with the biphasic one for both adverse skin reaction and comfort. It was anticipated that the rate of adverse skin reaction after use of the biphasic prototype would be less than that after use of the monophasic one. Additionally, the rates were to be compared with those previously cited (Zizic et al. 1995; Farr et al. 2006; Mont et al. 2006; Garland et al. 2007).

Results demonstrated that the slightly biphasic current was comfortable to use and had an acceptable rate of adverse skin reaction. The rate of adverse skin reaction noted after use of the monophasic prototype was unacceptably high. These data are presented in Chapter 4 as a paper, E-published ahead of print (Fary and Briffa 2010) and provide justification for the specific electrical parameters chosen for use in the E-PES trial.

Chapter 4: Prototype equipment testing study

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CLINICAL TECHNICAL NOTE

Monophasic electrical stimulation produces high rates of adverse skin reactions in healthy subjects

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ABSTRACT

Monophasic pulsed electrical stimulation (PES) has been reported to improve pain and function in osteoarthritis of the knee with few side effects. This use of monophasic current is contrary to conventional thinking where it is often associated with adverse skin reactions. The objectives of this study were to compare the rates of adverse skin reactions, using independently developed subsensory monophasic PES in healthy subjects, with those described in previous studies and compare the rate of adverse skin reactions after using the monophasic PES with that after using the same shaped electrical waveform that is asymmetrically biphasic. Healthy subjects (n=25) with no contraindications to electrical stimulation were administered subsensory, monophasic, and biphasic PES sequentially to the knee region for approximately 10 minutes each. Stimulation intensities; duration of stimulation; description of sensation reported; skin condition after intervention; and duration of skin reaction were all recorded. Fifty-two percent of subjects experienced adverse skin reactions using monophasic PES. This was significantly different from the reported rates in three of the four previous studies (p<0.04). Only one subject (4%) using the biphasic current demonstrated an adverse skin reaction. Results support the caution advised in the electrotherapy literature when using monophasic electrical stimulation.

INTRODUCTION

Monophasic (direct current) electrical stimulation has been widely used to enhance wound (Griffin et al, 1991; Houghton et al, 2003) and bone (Aaron, Ciombor, and Simon, 2004; Mandracchia et al, 2004) healing as well as in the management of edema (Robertson, Low, Ward, and Reed, 2006). It is also used for iontophoresis to enhance the transport of material (e.g., anti-inflammatory medication) across the skin into subcutaneous tissue (Hamann, Hodges, and Evans, 2006). In addition, animal and laboratory studies suggest that monophasic current has a role in modifying the disease process of osteoarthritis through its positive effect on cartilage cells (Baker, Spadaro, Marino, and Becker, 1974; Lippiello, Chakkalakal, and Connolly, 1990). Consequently, it is a modality of considerable interest.

Several clinical trials and one series of case reports have reported that monophasic, pulsed electrical stimulation (MPES) is effective in treating symptoms of osteoarthritis of the knee (Farr et al, 2006; Fary, Briffa, and Briffa, 2009; Garland et al, 2007; Mont et al, 2006; Zizic et al, 1995). MPES in these trials is defined as the subsensory, capacitively coupled delivery of a pulsed, exponentially decreasing shaped current with a frequency of 100 Hz. These trials have used the BioniCare Stimulator, Model BIO-1000 (Murray Electronics Associates, Hunt Valley, MD, USA) to deliver this specific type of electrical stimulation. MPES was used for lengthy durations

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(average protocol use of 8 hours per day) over periods of 4 weeks (Zizic et al, 1995) up to greater than 3 months (Farr et al, 2006; Mont et al, 2006).

In all the MPES studies, the device was used at a subsensory intensity. This means that for the duration of the treatment patients were not aware of any sensation like the tingling or prickling often associated with electrotherapeutic modalities such as TENS and interferential. This is an interesting method of electrical stimulation delivery. However, it is hypothesized that pain pathways may be influenced at a very local level in the periphery by externally applied electrical stimulation moderating ion channel function (Seegers, Engelbrecht, and Papendorp, 2001) and inflammatory mediator responses (Brighton, Wang, and Clark, 2006; Brighton, Wang, and Clark, 2008). For these actions, sensory stimulation is not necessary.

It is well recognized that one possible side effect of monophasic electrical current is skin irritation and chemical burns (Hooker, 2001). Damage can occur because the unidirectional flow in the circuit can lead to an alkaline buildup at the positive electrode and an acidic one at the negative electrode. If the concentrations of either are great enough, a chemical burn may result (Robertson, Low, Ward, and Reed, 2006). With pulsed current the skin behaves as a capacitor so that when the current flow stops, the skin discharges the current in the opposite direction (Robertson, Low, Ward, and Reed, 2006). This finding suggests that MPES is less likely to produce adverse skin reactions than monophasic continuous current being dependent on the amount of reverse current flow achieved. Biphasic current is even less likely to produce adverse skin reactions because the alternating direction of current flow largely avoids the chemical buildup at the electrode/skin interface.

Frequency of adverse skin reactions to MPES in the clinical osteoarthritis trials, reported as rashes under the electrodes, were 15% (Farr et al, 2006), 18% (Garland et al, 2007), 45% (Mont et al, 2006), and 24% (Zizic et al, 1995). Similar reaction rates of 21% (Garland et al, 2007) and 21% (Zizic et al, 1995) were reported for the placebo devices used in the two randomized controlled trials. The similarity in reaction rates in the active and placebo groups lead the investigators to conclude that the adverse skin reactions were related to the gel-coupling medium rather than the current.

This current study tests the assumption that the gel was the cause of the adverse skin reactions. To do this, we developed a device to deliver the MPES parameters as defined by the previous clinical studies to healthy subjects. For comparison purposes, another device that delivered an electrical current with the same parameters except for being slightly biphasic (BPES) was also developed.

The experimental hypothesis was that the incidence of mild, transient adverse skin reaction after using our MPES equipment would be comparable to that reported in previous trials citing use of the same current (Farr et al, 2006; Garland et al, 2007; Mont et al, 2006; Zizic et al, 1995).

A secondary hypothesis was that there would be a higher proportion of subjects developing an adverse skin reaction to MPES than to the biphasic stimulation. No adverse skin reaction was expected with the use of BPES.

An additional aim was to assess the comfort of their use. It was hypothesized that subsensory, transcutaneous use of both of the experimental devices would provide no discomfort to subjects.

METHODS

Subjects

Twenty-five healthy individuals (15 male) with average age of 42 years were recruited to participate in this cross-sectional study. Subjects presented with no contraindications to electrical stimulation in at least one knee nor with any existing skin disorders that could have interfered with interpretation of the results. All subjects were able to discriminate between sharp and dull sensation stimuli in the area to be tested and all subjects were Caucasian, which allowed skin responses to be easily identified. All subjects gave prior written informed consent. Ethical approval was obtained from the Human Research Ethics Committee at Curtin University of Technology (Approval number PT0090).

Equipment

Metron Digital TENS (Ausmedic Australia, Hilton, WA, Australia) devices were selected for modification as the circuitry was readily altered to deliver the desired MPES as defined by the previous clinical MPES trials (i.e., monophasic, pulsed, exponentially decreasing current at a frequency of 100 Hz (Farr et al, 2006; Fary, Briffa, and Briffa, 2009; Garland et al, 2007; Mont et al, 2006; Zizic et al, 1995). Modifications were made by a senior biomedical engineer working in the Medical Technology and Physics Department at Sir Charles Gairdner Hospital, a tertiary level hospital in Perth, Western Australia. The BPES device delivered a waveform with the same shape and frequency but, being offset below the zero line, delivered an asymmetrical biphasic current.

Two conductive silicone electrodes per device were used. The electrodes, 120 mm long and 80 mm wide, were applied to the subject's anterior thigh and anterior knee. Capacitive coupling was achieved by wetting two Chux (Clorox Australia, East Doncaster, VI, Australia) open-weave cloths with room temperature water. The cloths were each folded to size, 160 mm long and 100 mm wide, 12 layers thick. One Chux pad was then placed between each electrode and the skin. Water was used as the conduction medium to eliminate the possibility of any skin reactions noted being a response to gel application. The electrodes and conduction media were secured by a Handycrepe (Smith & Nephew, West Perth, WA, Australia) hospital quality wrinkled cotton bandage.

Procedure

The two devices were tested simultaneously (one on each knee) except for one instance where the subject had metal screws in the left knee as a result of previous surgery. This excluded the left knee from testing. In this case the BPES equipment was tested first on the right knee. Because there was no adverse skin reaction to BPES, the MPES was then applied after a period of five minutes' rest.

Once the electrodes were secured, the intensity control on one device was turned up until a tingling/prickling sensation was felt under one or both of the electrodes. The intensity was then turned down until there was no longer any sensation or until the intensity had been decreased to a minimum of three on the display screen. This level ensured current flow continued throughout the testing time. Both the intensity of first sensation detection and the intensity at which the sensation disappeared were recorded. Once the timer had been set for the first device the process was repeated for the second device. There was no specific sequence with regard to which device was activated first.

Once the intensity was set, the subject used the device for between 10 and 15 minutes. Initially, the duration for testing was planned to be 15 minutes because pilot testing of the MPES device during development produced an adverse skin reaction within this time period. However, three of the first five subjects tested for 15 minutes sustained an adverse skin reaction after using MPES. In one of these cases, the reaction was significant with a large area of redness that took 120 minutes to resolve. In light of these results a decision was made to decrease the testing time to 10 minutes. It was felt that this stimulation duration was long enough to test the hypothesis.

During the testing time subjects were asked to report any sensations under or around the electrodes. If any sensation was noted, the device was turned down again until the sensation disappeared. The absence of sensation was not achievable when using MPES with five of the subjects. With these subjects the device was turned down to between three and five on the display screen where, with each subject's explicit verbal consent, a very mild prickle sensation was intermittently reported for the rest of the testing duration. The decision to allow continuation of testing in these circumstances was made with due consideration. There was no pain or discomfort reported; at current flow intensities of three to five out of a possible 80, there was no risk of harm to the subject; use at above sensory thresholds is well within normal use for this type of electrical stimulation device; the length of time of use was minimal; and the outcome to be measured related to the current exposure itself and not to the subsensory component of the treatment.

At the end of each respective testing time, the devices were turned off, the electrodes removed, and the skin beneath the electrodes inspected for any signs of reaction. All skin outcomes were recorded, including where there were no skin reactions.

Adverse skin reactions were described as absent, mild, moderate, or significant. A mild adverse skin reaction was defined as being patchy, light red coloring (less than 50% electrode area affected) under at least one electrode. A moderate adverse skin reaction as being a consistent, light red coloring (between 50% and 90% surface area affected) under at least one electrode. A significant response was noted when there was obvious redness (greater than 90% area affected) under at least one electrode. When an adverse skin reaction was noted, the degree of response was recorded and subjects were then asked to make a note of how long the reaction lasted. Those subjects were then contacted 24 hours after the testing was completed and the duration of the skin reaction was recorded.

Outcome measures

The outcome measures recorded were 1) intensity (mA) at which the first prickling/sensation occurred; 2) maximal intensity (mA) at which sensation was subsensory; 3) verbal descriptions of sensation during use of the device; 4) presence and severity of adverse skin reaction; and 5) where applicable, the duration of skin reaction.

Data analysis

All data were entered into a spreadsheet and analyzed by using SPSS version 16.0. Means for intensity

measurements and for the number and duration of adverse skin reactions from both MPES and BPES were calculated. The rates of adverse skin reactions occurring in this study from MPES were compared with rates reported for MPES in previous studies (Farr et al, 2006; Garland et al, 2007; Mont et al, 2006; Zizic et al, 1995) using chi-square testing. Descriptions of stimulation current comfort were analyzed qualitatively.

RESULTS

Monophasic pulsed electrical stimulation

Of the 25 subjects tested, 13 (52%) demonstrated adverse skin reactions with the use of MPES. The majority of reactions were classified as mild to moderate with only three producing a very red reaction under the entire positive electrode. Adverse skin reactions from MPES were reported as lasting from approximately 15 minutes up to 2 hours (Table 1).

The mean intensity measured at first sensation noted for MPES was 32 mA (range 7 mA to 80 mA, with 80 mA being the upper limit of the intensity control) and the mean testing intensity (i.e., the intensity at which subsensory conditions were achieved) was 11.6 mA (range 3 mA to 54 mA) (Table 1). There was no relationship between the testing intensity level and skin reaction.

A range of sensory descriptions were used with MPES being described most commonly as being prickling (16 subjects). Other descriptions were itching (five subjects); tingling (four); pins and needles (one); insects crawling (one); acupuncture-like (one); and pressure (one). Four subjects used two sensation descriptions. For example, one subject reported a sensation of feeling insects crawling under the positive electrode and itching under the negative one.

TABLE 1 Subject test parameters and skin reactions for each device

	Monophasic device n=25 Mean (SD)	Biphasic device n=25 Mean (SD)
Intensity first sensation (/80 mA)	32 (18.8)	52.3 (13.8)
Intensity subsensory achieved (/80 mA)	11.6 (13.6)	41.8 (16.8)
Test duration (minutes)	11.4 (2.3)	11.4 (2.3)
Number of adverse skin reactions	13	1
Duration of adverse skin reaction (minutes)	49.2 (32.1)	15

Of particular note, MPES behaved in a way that was unexpected in that subjects occasionally reported that the sensation returned after the intensity had been turned down to a level where they had not been able to feel it. For nine subjects, this led to several downward alterations of intensity during the testing time. Five of these subjects were not able to achieve a subsensory state. Of those five who maintained some sensation of the electrical stimulation, only one developed a skin reaction.

Comparison with adverse skin reaction rates reported in previous studies

Because the previously published MPES studies reported subsensory treatment use, only those who achieved subsensory level stimulation with the study MPES device were included in this analysis (n=20). There was a significant difference noted between the counts of adverse skin reactions from the MPES device used in this study and those reported by three of the four previous studies ($p<0.02$) (Farr et al, 2006; Garland et al, 2007; Zizic et al, 1995) (Table 2). Only Mont et al (2006) reported similar adverse skin reactions rates (45% Mont; and 60% current study; $p=0.31$) (Table 2).

Biphasic pulsed electrical stimulation

Only one subject demonstrated any adverse skin reaction (a mild response under the negative electrode) after using BPES. This reaction was reported to have lasted for approximately 15 minutes. The mean intensity measured at first sensation noted for BPES was 52.28 mA (range 26 mA to 73 mA), and the mean

TABLE 2 Adverse skin reaction rates occurring with the study monophasic device achieving subsensory stimulation compared with previous MPES studies

	Adverse skin reaction[1] Number (percentage)
Study monophasic device[2]	12 (60%)
Farr et al (2006)	44 (15%)[3]
Garland et al (2007) (active device)	7 (18%)[3]
Mont et al (2006)	71 (45%)[4]
Zizic et al (1995) (active device)	9 (24%)[3]

[1]Raw numbers calculated from sample sizes and reaction rates cited in previous papers.
[2]Comparison using only those in the sample who achieved subsensory stimulation (n=20).
[3]$p<0.02$ compared with study monophasic device
[4]$p=0.31$ compared with study monophasic device.

testing intensity was 41.84 mA (range 10 mA to 69 mA) (Table 1). Subjects variously described the BPES as tingling (12 subjects), prickling (five), pins and needles (three), pulsing (two), buzzing (one), tickling (one), and tension-like (one).

Comparison of study MPES and BPES adverse skin reaction rates

There was a significant difference noted between the type of current used in the two study devices and the rates of skin reaction ($p=0.001$) with MPES producing the higher rate. In general, subjects found the sensation from the BPES device more comfortable and less coarse than the MPES one.

DISCUSSION

MPES clearly resulted in a substantial rate of adverse skin reactions. Although most of the responses were classified as mild to moderate, this must be considered in the context of the very short exposure time. Even mild reactions after only 10–15 minutes of exposure are cause for concern.

The parameters of the MPES current in the device used for this study replicated those cited in the previous literature (Farr et al, 2006; Garland et al, 2007; Mont et al, 2006; Zizic et al, 1995). However, there were differences in the conditions of use. MPES in previous studies was used for lengthy durations. This study limited the time to 10–15 minutes. Gel was previously used as the coupling agent, and the presence of adverse skin reactions was attributed to gel use. This study used water as the coupling agent. However, even with decreased stimulation duration and the absence of gel, a high proportion of adverse skin reactions were produced. Our data are therefore not consistent with gel being the sole cause of the adverse skin reactions or with duration of use being a factor. If gel or duration were major factors in adverse skin reaction development, there should have been fewer skin reactions noted when using the replicated MPES. Our data are consistent with the electrotherapy literature that states that monophasic current may be associated with adverse skin reactions (Hooker, 2001; Robertson, Low, Ward, and Reed, 2006).

One possible explanation for the difference between our rates of adverse skin reactions and those reported in the previous studies using BioniCare (Farr et al, 2006; Garland et al, 2007; Mont et al, 2006; Zizic et al, 1995) may be that there were other characteristics about the current used in the BioniCare device not identifiable in publication. Terminology ambiguity within the field of electrotherapy and frequent lack of documentation of stimulation parameters makes replicating studies difficult (Walsh, 2008).

There was also a clear difference between adverse skin reaction rates occurring after using the MPES and BPES devices studied here. This outcome confirmed expectations that the BPES device would produce fewer adverse skin reactions than the MPES one. Of note was that even with higher mean intensities for the duration of testing (Table 2), there were far fewer adverse skin reactions following BPES use compared with MPES use.

No reports of discomfort were made with use of either of the waveforms though BPES was generally considered to be more comfortable than MPES. It is difficult to explain why subsensory treatment with the MPES device was not able to be achieved by five participants. All those who reported continued sensation with MPES achieved a subsensory level with BPES.

It is possible that there was a gradual decrease in skin-electrode impedance throughout the testing time with this waveform that resulted in increased current flow with time. This could perhaps have resulted in more sensory neurons being stimulated and also explained the return of the sensation of the stimulation felt by some of the subjects. However, it does not satisfactorily explain why a subsensory state could not be achieved by five of the subjects. Nor does it explain why this only occurred with MPES.

Limitations of the study

The duration of testing was reduced from 15 to 10 minutes during implementation of the study. However, because both knees in each individual received the same duration of testing, this change would not have increased within subject bias and should not have influenced the finding of a difference in rates of adverse skin events between BPES and MPES.

The investigator conducting the testing was not blind to the type of device being applied, and the same investigator inspected the skin site and graded the response. Independent confirmation of the presence of adverse skin reactions though came from the participants who were required to monitor the duration of the response and report back to the investigator 24 hours after testing. That they were able to do this demonstrates that the skin reactions were unambiguously present.

Five participants using MPES were unable to achieve subsensory use of the device. These data were included in the initial analysis of the rate of adverse skin reaction and description of the current. They were also included in the comparison analysis with the BPES device. This was done because skin

response and comfort of use were the variables of interest. However, these data were excluded from the comparison with published papers. This was to provide consistency in the comparison as the MPES published papers (Farr et al, 2006; Garland et al, 2007; Mont et al, 2006; Zizic et al, 1995) all reported subsensory stimulation delivery.

CONCLUSION

Replicating the MPES stimulation parameters described in previously published papers has produced an adverse skin reaction rate clearly different to those previously reported. However, this study's rate is very consistent with the general electrotherapy literature. Consequently, it reinforces the substantial risk to the skin generally associated with using monophasic current and raises concern about the use and reproduction of the previously reported modality parameters for clinical practice. This must be considered both in short- and long-term use, particularly for chronic conditions such as osteoarthritis where long-term and recurrent use would be expected.

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Declaration of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Chapter 5: The effectiveness of pulsed electrical stimulation (E-PES) trial research protocol

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Study protocol

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The effectiveness of pulsed electrical stimulation (E-PES) in the management of osteoarthritis of the knee: a protocol for a randomised controlled trial

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Abstract

Background: Osteoarthritis (OA) of the knee is one of the main causes of musculoskeletal disability in the western world. Current available management options provide symptomatic relief (exercise and self-management, medication and surgery) but do not, in general, address the disease process itself. Moreover, adverse effects and complications with some of these interventions (medication and surgery) and the presence of co-morbidities commonly restrict their use. There is clearly a need to investigate treatments that are more widely applicable for symptom management and which may also directly address the disease process itself.

In two randomised controlled trials of four and 12 weeks duration, pulsed electrical stimulation was shown to be effective in managing the symptoms of OA of the knee. Laboratory and animal studies demonstrate the capacity of externally applied electric and electromagnetic fields to positively affect chondrocyte proliferation and extracellular matrix protein production. This latter evidence provides strong theoretical support for the use of electrical stimulation to maintain and repair cartilage in the clinical setting and highlights its potential as a disease-modifying modality.

Methods/Design: A double-blind, randomised, placebo-controlled, repeated measures trial to examine the effectiveness of pulsed electrical stimulation in providing symptomatic relief for people with OA of the knee over 26 weeks.

Seventy people will be recruited and information regarding age, gender, body mass index and medication use will be recorded. The population will be stratified for age, gender and baseline pain levels.

Outcome measures will include pain (100 mm VAS and WOMAC 3.1), function (WOMAC 3.1), stiffness (WOMAC 3.1), patient global assessment (100 mm VAS) and quality of life (SF-36). These outcomes will be measured at baseline, four, 16 and 26 weeks. Activity levels will be measured at baseline and 16 weeks using accelerometers and the Human Activity Profile questionnaire. A patient global perceived effect scale (11-point Likert) will be completed at 16 and 26 weeks.

Discussion: This paper describes the protocol for a randomised, double-blind, placebo-controlled trial that will contribute to the evidence regarding the use of sub-sensory pulsed electrical stimulation in the management of OA of the knee.

Trial registration: Australian Clinical Trials Registry ACTRN12607000492459.

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Background

Osteoarthritis is a major cause of pain and disability in the community and OA of the knee is one of the most common causes of musculoskeletal disability in the Western world [1]. As prevalence increases it is expected to pose an increased burden on health care in the future.

Management options such as medication, exercise, self-management programs and surgery largely focus on providing symptom relief and maintenance of function, but do not, in general, address the disease process itself. Moreover, adverse effects and complications with some of these interventions (medication and surgery) and the presence of co-morbidities commonly restrict their use.

In recent years considerable effort has been directed towards investigating the effectiveness of putative disease-modifying OA drugs such as glucosamine, chondroitin sulfate, doxycycline and diacerein [2-5]. There is also interest in the use of pulsed electrical stimulation and electro-magnetic fields as potential OA disease modifying modalities. Laboratory work and animal studies provide theoretical support for the use of electrical stimulation to maintain and repair articular cartilage in the clinical setting [6-10]. However, there are limited studies examining the effects of pulsed electrical stimulation in humans.

Two randomised, placebo-controlled trials have reported using capacitively coupled pulsed electrical stimulation (PES) delivered via skin surface electrodes [11,12]. In both trials, outcome measures focussing on symptom relief and functional capacity have been the variables of interest.

The first of these trials [12] randomised 78 subjects to placebo or PES treatment with a monophasic, spiked signal at 100 Hz delivered by the Bionicare® BIO-1000™. PES was applied for between six and 10 hours per day at an intensity just below the sensory threshold for four weeks.

Response to intervention was better for the active device than the placebo for the outcome measures of pain, physical function, physician global assessment and duration of joint stiffness in the morning ($p < 0.05$) [12]. No statistically significant difference was observed for range of knee joint motion, joint tenderness, joint swelling, knee circumference and 50 feet walking time.

The second PES trial [11] examined 58 subjects using the same stimulation device in the same manner over 12 weeks. In this trial significant and clinically meaningful results were reported in patient global assessment, a pain and symptom visual analogue scale, WOMAC function and stiffness and overall WOMAC score. Only WOMAC pain change between the placebo and active groups did not reach statistical significance.

No randomised, controlled trials studying this particular modality over a longer time period have been found.

The modality being investigated is neither invasive nor pharmaceutical. As the majority of those with OA of the knee are likely to be elderly, they are also more likely to have co-morbidities such as heart and lung disease which increase the anaesthetic risk associated with invasive surgery. Similarly, there is increasing awareness of the adverse side effects of many of the medications that are used to manage OA of the knee [13-15]. Consequently, in a climate where patients are seeking different options in their disease management strategies, the potential for PES to provide an effective, safe alternative that is acceptable to the community is very high.

This research proposes to investigate the longer term effectiveness of PES and to determine the sustainability of responses in subjects with symptomatic knee OA.

Methods/Design

Study design

A double-blind, randomised, placebo-controlled, repeated measure trial will be conducted over 26 weeks. Participants will be assessed, prior to the commencement of treatment (baseline), and after four, 16 and 26 weeks of treatment (Figure 1).

Aims and hypothesis

The primary aim is to investigate for a period of 26 weeks, the effectiveness of transcutaneous PES in the treatment of symptomatic knee OA. A secondary aim is to determine whether effects, if any, are influenced by gender, age and/or baseline pain levels.

The experimental hypothesis is that PES will produce a clinically important and sustained improvement in pain, function, patient global assessment, global perceived effectiveness, quality of life and activity levels when compared with placebo treatment in individuals with symptomatic OA of the knee.

Participants

Seventy participants with primary OA of the knee will be recruited.

Inclusion criteria

- Primary knee OA diagnosed in accordance with the American College of Rheumatology (ACR) modified clinical classification criteria (sensitivity 84%, specificity 89%) [16,17]. This classification system has been shown to be a valid tool for OA knee diagnosis [18].

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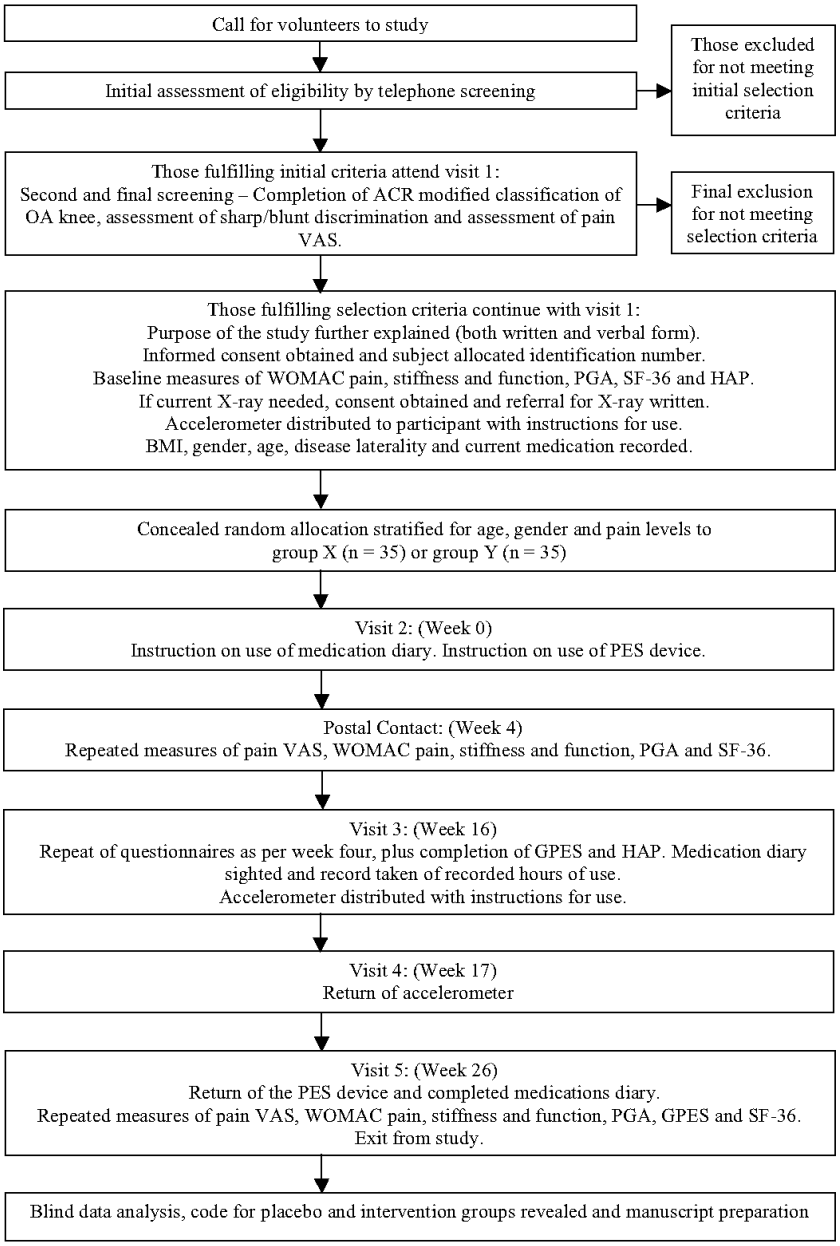

Figure 1
Summary of study procedure. ACR – American College of Rheumatology; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; PGA – Patient Global Assessment; SF-36 – Medical Outcomes Study 36-item Short-Form Survey; HAP – Human Activity Profile; GPES – Global Perceived Effectiveness Scale.

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• Persistent, stable pain for a minimum of three months.

• Pain score of at least 25 mm on a 100 mm visual analogue scale (VAS).

Exclusion Criteria

• Co-existing inflammatory arthropathies.

• Contraindications to electrical stimulation (pregnancy, decreased sensory perception, presence of metal in the field of application, or any implanted electrical stimulation device).

• Skin disorders in the treated knee area.

• Scheduled to have a total knee replacement within six months of entering the trial.

• Not able to read or understand English.

Procedure

Recruitment

Potential volunteers will be recruited through community-based rheumatology and general practices, rheumatology outpatient clinics in teaching hospitals in the Perth metropolitan area, the Arthritis Foundation of Western Australia and promotion through media outlets.

Determining eligibility and baseline assessment

Initially volunteers will be telephone-screened to check for obvious exclusion criteria.

At a screening visit, diagnosis according to the ACR modified clinical classification will be made, sharp/blunt sensory discrimination will be tested and the pain VAS completed. Eligible participants who present with bilateral OA of the knee will be asked to nominate which knee they consider to be the most symptomatic and that knee will be treated.

Subjects who meet eligibility criteria will receive further information concerning the trial. In particular, the aims and methods will be explained in detail following which, written consent to participate will be sought. This trial has been approved by the Curtin University Human Research Ethics Committee (HR122/2006). Following consent, participants will be assigned an identification number and will be asked to complete baseline measures of WOMAC pain, stiffness and function, patient global assessment, quality of life and the Human Activity Profile (HAP) test, while details regarding body mass index (BMI), age, gender, laterality of joint disease, disease severity (if X-ray available) and current medication will be recorded. Participants who have not had a plain X-ray within the past two years will be referred for X-ray. Participants who are unwilling to have X-rays taken will not be excluded from the trial. Available X-rays will be graded according to the Kellgren and Lawrence radiological grading system. All outcome measurements will be taken and all instructions provided by an experienced musculoskeletal physiotherapist at Curtin University of Technology. At this first visit participants will also be provided with an accelerometer to collect seven days of ambulatory activity, after which it will be returned in person.

In the interim, participants will be randomly allocated into groups. Upon returning the accelerometer, they will be fitted with the PES device and given detailed verbal and written instructions regarding its use. They will also be provided a medications diary and relevant instructions.

Randomisation and blinding

An administrator, not otherwise involved with the trial, will allocate the participants to groups using computer-generated block randomisation combined with stratification. Groups will be stratified with regard to gender, age (<60, 60–75 and >75), and intensity of pain (VAS scores 25–40, 41–60 and 61–100). The administrator will dispense an appropriate device using a list, provided by the senior biomedical engineer who modified the devices, that matches the device serial numbers to active or placebo. Participant identification will be added to the list at the time of randomisation so, should the need arise, the investigators will be able to determine the nature of the device provided to a participant without risk of becoming aware of assignment for any other participants (Figure 2). The measurer though will remain blinded to assignment throughout.

The group-to-device-to-intervention code will remain in the possession of the equipment dispensary (protected by password) until after the data analysis has been completed.

Trial intervention

A commercially available transcutaneous electrical nerve stimulator (Metron Digi-10s) has been adapted by a senior biomedical engineer to produce either a pulsed, exponentially declining waveform with a frequency of 100 Hz or a placebo device identical in appearance. Participants will be advised to use the device at a sub-sensory level, to replicate the conditions in the previous randomised controlled trials, for a minimum of seven hours per day. It will be recommended that they wear the device overnight. There is a locking mechanism on the device so that once the treatment intensity has been set there can be no inadvertent intensity change during the course of treatment. The instructions given to participants by the physiotherapist, who remains blind to the nature of the device, will be

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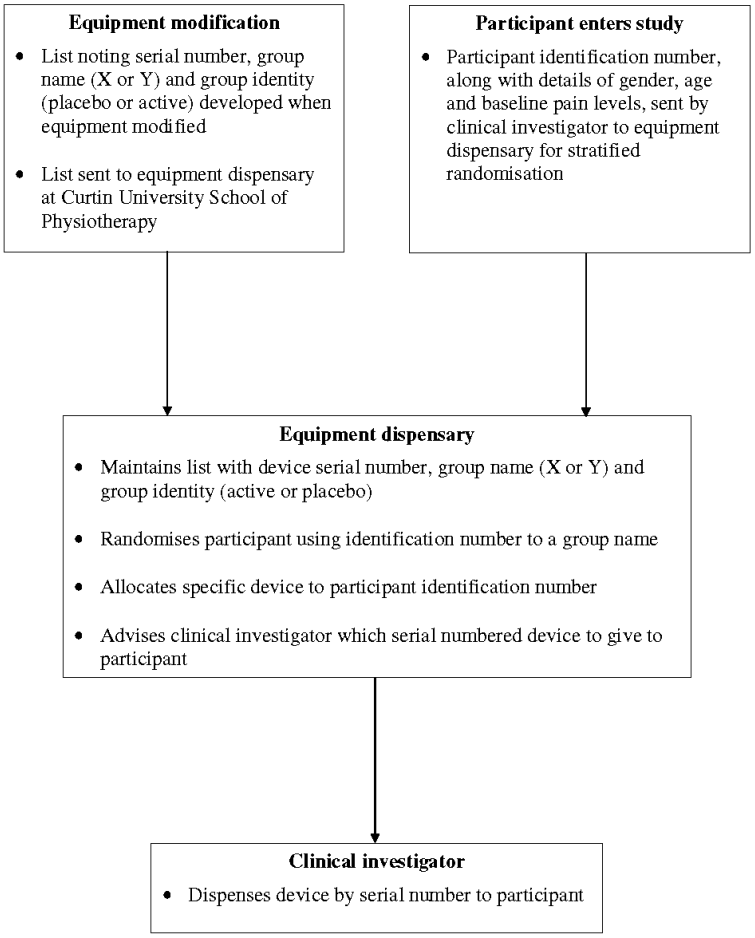

Figure 2
Process for stratified randomisation and concealed allocation.

exactly the same regardless of which device participants are using.

Background therapy

Participants will be asked to continue their normal background medical management during the trial period. A medications diary will be used to alert the investigators to any changes in medication usage. Each subject's managing doctor will be informed by letter of their patient's participation in the trial. Doctors will be requested to refrain from changing OA management during the period of the trial if at all possible.

Compliance

Participants will be asked to keep a record of their daily PES use. This will be maintained within the medications diary booklet. Intermittent questioning about PES use via regular phone calls during the trial period and a review of the booklet at 16 weeks will occur.

Safety monitoring and adverse events

Participants will be encouraged to contact the investigators should any questions arise during the trial. Correspondingly, they will be asked open-ended questions by the physiotherapist during the scheduled phoned calls to determine any adverse effects from using the device. The

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only adverse reaction that is expected is mild skin irritation. This occurred in both the placebo and intervention groups in both randomised controlled trials in approximately equal proportions (range 17.9–24% active and 21 – 21.1% placebo) and responded favourably to topical therapy, a temporary halt in use and/or change in the conduction gel [11,12]. Any participant reporting skin irritation will be asked to stop using the device and to return to the Curtin University School of Physiotherapy for assessment at the first available opportunity. Should there be pain, swelling or more than a five centimetre diameter area of redness after desisting for 48 hours, a medical opinion will be obtained before proceeding further.

Outcome measures

Outcome measures include the core set of primary efficacy variables recommended by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group for phase III clinical trials in OA [19] and recommended for inclusion in OA clinical trials by the Cochrane Collaboration [20].

The three *primary efficacy variables*, to be measured at baseline, four, 16 and 26 weeks, are:

• Pain (100 mm VAS and Western Ontario and McMaster Universities Osteoarthritis Index -WOMAC Likert format 3.1). Two measures for pain will be included as this mirrors standard practice in much of the OA literature and it will provide internal validity for this important outcome measure. The reliability of the VAS has previously been demonstrated [21] and is regularly used in this population. WOMAC measures health status and assesses pain, physical function and stiffness in patients with OA of the hip or knee. The WOMAC questionnaire is self-administered and can be completed in less than five minutes. Two major validity studies have shown that WOMAC pain, physical function and stiffness subscales are valid and that the questionnaire is reliable and sensitive enough to detect changes in health status following a variety of interventions [22].

• Patient Global Assessment (100 mm VAS as described by Ehrich et al [23]). Participants are asked to consider all the ways in which their arthritis is affecting them at the time of the assessment and indicate by marking the VAS how they are doing. The left hand anchor of the VAS is *Very Well* while the right hand anchor is *Very Poorly*.

• Physical function (WOMAC Likert format 3.1). Likert values from 17 questions of the WOMAC are summed to generate a score for physical function with a higher score indicating worse function.

Secondary outcome measures

• Quality of life (Medical Outcomes Study 36-item Short-Form Survey version 2 – SF-36). The SF-36 has eight subcomponent scales reflecting both physical and mental status. It is comprised of 36 questions, is self administered, and can be completed in about 15 minutes. All estimates of score reliability, from 14 separate studies, for each of the eight scales of the SF-36 exceeded accepted standards for measures used in group comparisons [24]. The SF-36 has been extensively validated in many English speaking countries of the world including Australia [25]. The rationale for using both WOMAC and the SF-36 for this trial is that a combined approach using both generic quality of life and knee specific health status measures is considered likely to prove best for knee-related problems [26]. Quality of life measurements will be taken at baseline, four, 16 and 26 weeks.

• Joint stiffness (WOMAC Likert format 3.1) measured at baseline, four, 16 and 26 weeks.

• Global perceived effect scale (GPES) measured using an 11-point scale ranging from -5 (vastly worse) to +5 (completely recovered) with the zero point being unchanged as reported by Pengal et al [27]. This will be measured at 16 and 26 weeks.

• Physical activity will be determined using the HAP questionnaire plus accelerometers measured at baseline and 16 weeks.

◦ The HAP is self-administered. It incorporates 94 activities listed in ascending order of oxygen cost. Respondents are asked to indicate whether they are able to perform the activity unassisted; whether they have ever performed the activity and whether they have stopped performing the activity [28]. In a cross-sectional study, the HAP has been found reliable and sufficiently sensitive for use in people with OA of the knee [29]. This study demonstrated that people with OA of the knee are in fact less active than their healthy counterparts and that there was a relationship between HAP scores and participants' pain and function scores. The proposed trial offers the potential to determine whether improvement in pain and function result in a spontaneous increase in the level of physical activity.

◦ Accelerometry is now considered the preferred method of objectively measuring physical activity as it provides data that allows individual examination of ambulatory activity frequency, intensity and duration [30]. However, to our knowledge accelerometers have not been validated for use in people with OA of the knee. For this trial an Actigraph GT1M (formerly Computer Science and Applications monitor), the most widely accepted accelerometer in research, will be utilised [31]. The match-box size acceler-

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ometer will be attached to a belt that the participants will be asked to wear for a period of seven consecutive days at both the baseline and 16 week data collection points.

The benefits of physical activity are well known and include reduced risk of cardiovascular disease, diabetes, some forms of cancer, osteoporosis, falls and fractures. Physical activity interventions have also been shown to assist with weight control and to improve physical functioning and mental health. The impact of physical activity on OA remains unanswered. Osteoarthritis of the knee is often associated with considerable knee pain that suggests that people with knee OA may curtail their physical activity. Although most studies of OA of the knee measure changes in function, few measure physical activity levels so there is limited evidence to demonstrate whether or not this is the case. Moreover whether treatments that reduce pain result in an increase in physical activity is yet to be determined.

Sample Size Calculations

The primary outcome measure will be defined as an improvement in the absolute pain VAS score of 20. This is the minimum absolute change necessary for classification as a responder in the Osteoarthritis Research Society International (OARSI) response criteria [32,33]. Assuming no change in the placebo group, it has been calculated that a sample size of 70 (35 in each group allowing for 20% withdrawals) will be sufficient to detect this 20 point change as well as differences equal to the absolute minimal clinically important improvements of 19.9 (Pain VAS), 18.3 (PGA) and 9.1 (WOMAC function) described by Tubach et al [34] with a power of 80% using a two-tailed test with alpha level of 0.05. Calculations were based on standard deviations data from Garland et al [11] (Pain VAS and PGA) and Raynauld et al [35] (WOMAC function).

Statistical Analysis

All analyses will be performed on an intention to treat basis while the investigators remain blind to treatment groups. Change in pain between baseline and 26 weeks will be compared between groups using the independent t-test. To test for the fixed effect of treatment while adjusting for any differences in the baseline measures, repeated measures analysis using a linear mixed model will also be performed for pain VAS, patient global assessment, WOMAC function, stiffness and pain, and QOL measurements taken at four, 16 and 26 weeks. There will be no adjustment for multiple comparisons as all comparisons have been determined a priori and, while adjustment maintains study wise error, it may preclude detection of clinically important differences [36].

Change in activity level between baseline and 16 weeks will also be analysed using the independent t-test. Secondary analyses such as the proportion of participants achieving minimal clinically important improvements in pain, function and patient global assessment at each observation time will be compared using the Chi-square test. GPES at 16 weeks and 26 weeks will be compared between groups using unpaired t-tests.

Ethical considerations

A placebo control is being used in this trial. However, as subjects are not being asked to change their usual treatment regimen, no subject will be disadvantaged by using the placebo.

Data Quality

Data will be entered into a specifically designed database with pop-up value lists, value ranges, data type and field complete validations. Random scrutiny by co-investigators of at least ten percent of all data entered will be conducted throughout the trial to ensure accuracy and completeness.

Timelines for E-PES trial

Patient recruitment and initial phone screening began in July 2007. Final screening and data collection commenced in October 2007 with final exit data expected to be collected in February 2009.

Discussion

This paper describes the rationale and protocol for conducting a double-blind, randomised, placebo-controlled trial that will investigate the use of pulsed electrical stimulation in the management of OA of the knee. It incorporates features designed to minimise bias [37] and uses valid outcome measures that will facilitate comparability with other research in the area.

This trial will contribute to the evidence regarding the use of a non-pharmaceutical, non-invasive modality in managing symptoms of OA of the knee. Given the modality's simple technology and ease of use (patients can readily use it at home), it has huge potential to provide a safe, effective treatment option for clinicians.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

All authors were responsible for identifying the research question and contributing to drafting the trial protocol. Robyn Fary has been responsible for the drafting of this paper, although all authors have provided substantial

input, providing comments on the drafts and have read and approved the final version.

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Chapter 6: The effectiveness of pulsed electrical stimulation (E-PES) in the management of osteoarthritis of the knee: results of a randomised controlled trial

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ABSTRACT

Objective To determine the effectiveness of sub-sensory, pulsed electrical stimulation (PES) in the symptomatic management of osteoarthritis of the knee.

Methods A double-blind, randomized, placebo-controlled, repeated measures trial in 70 participants with clinical and radiologically diagnosed osteoarthritis of the knee who were randomized to either PES or placebo. The primary outcome was change in pain over 26 weeks measured on a 100mm pain VAS. Other measures included pain (WOMAC), function (WOMAC), patient global assessment (100mm VAS), joint stiffness (WOMAC) quality of life (SF-36), physical activity (Human Activity Profile; accelerometer) and global perceived effect (11-point scale).

Results Thirty-four participants were randomized to PES and 36 to control. Intention to treat analysis showed a statistically significant improvement in pain VAS over 26 weeks ($p \leq 0.001$) in both groups, but no difference between groups (mean change difference 0.9mm; 95%CI -11.7mm to 12.5mm). Similarly no differences existed between groups for changes in WOMAC pain, function and stiffness scores [-5.6 (-14.9 to 3.6); -1.9 (-9.7 to 5.9); 3.7 (-6.0 to 13.5) respectively], SF-36 physical and mental component scores [(1.6 (-1.5 to 4.8) and 1.2 (-2.9 to 5.4) respectively], patient global assessment [-2.8 (-13.9 to 8.4)] or activity measures ($p > 0.16$).

Fifty-six percent of the PES group achieved a clinically relevant 20mm improvement in pain VAS at 26 weeks compared with 44% of controls (95%CI -11% to 33%).

Conclusion In this sample with mild to moderate symptoms and moderate to severe radiographic osteoarthritis of the knee, 26 weeks of PES was no more effective than placebo.

Electrotherapy is often used to manage symptoms of osteoarthritis (OA). It is a relatively inexpensive, non-invasive, short-term treatment option, which is recommended in evidence-based clinical guidelines (1-4). One electrotherapy treatment, pulsed electrical stimulation (PES), has been reported to significantly decrease pain and improve function in knee OA (5-8). Anecdotal evidence however and our personal observations suggest that PES is not widely used.

PES is delivered through capacitive coupling using surface electrodes and conduction gel. While often being grouped with transcutaneous electrical nerve stimulation (TENS) (9), it does differ from TENS and interferential therapy (IFT) in its specific electrical current parameters and its proposed method of action (6). In particular, it is delivered at sub-sensory intensity. That sub-sensory electrical stimulation is reported to be effective in managing pain suggests a local mechanism of action. This mechanism is at present poorly understood. However, there are many pain mediating receptors in the periphery that may be affected by an externally applied electrical field by virtue of their endogenous electrical potential and the role of polarization in receptor function and nociceptor stimulation (10). It is possible that externally applied electrical stimulation interferes with this process and thus reduces pain perception.

PES is also reported to be a potential disease modifier through its capacity to up-regulate chondrocyte activity (11-14). This assertion is yet to be tested in humans, mainly because long-term effectiveness and compliance with use has yet to be established.

As OA of the knee is a chronic disorder, we considered the earlier randomized controlled trials of PES of four (8) and 12 (6) weeks duration to be relatively short.

Additionally, Farr et al. (5) in a prospective, longitudinal study referred to a dose-response relationship suggesting that increasing PES use results in better pain management. This assertion has not been tested in an independent randomized controlled trial.

As current treatment options have moderate effect sizes at best (15) and are often limited in use by contraindications and co-morbidities (16, 17) we wanted to examine whether the reported improvements with PES use continued beyond 12 weeks. By doing so we aimed to determine whether PES could provide a useful, low risk addition to OA management with a view to studying its potential as a disease-modifier.

The primary aim of this study was to determine whether PES decreased pain in OA knee over 26 weeks. Other outcomes included function, patient global assessment (PGA), quality of life, physical activity and overall perceived effect.

PATIENTS AND METHODS

The full protocol of this double-blind, randomized, placebo-controlled, repeated measure trial is published elsewhere (18). The trial was approved by the Curtin University Human Research Ethics Committee (HR122/2006) and all participants gave written informed consent. All recruitment tasks, screening, measurements and instructions for use of the device were completed by the same experienced musculo-skeletal physical therapist (RF).

Participants

Seventy participants (mean age 70 years, 53% male) were enrolled between September 2007 and April 2009. Diagnosis of OA of the knee was in accordance with the American College of Rheumatology (ACR) modified clinical classification

system (19). Plain X-rays available for 64 participants confirmed the diagnosis. Persistent and stable pain (defined as not getting worse or better overall despite short-term fluctuations) for a minimum of three months prior to study entry was confirmed in all participants by phone interview. All participants had a baseline pain score of at least 25mm on a 100mm visual analogue scale (VAS). Volunteers were excluded if they had co-existing inflammatory arthropathies; contraindications to electrical stimulation; skin disorders in the vicinity of the knee to be treated; total knee replacement scheduled during the study period; and/or insufficient English to follow instructions and complete forms.

Recruitment occurred through notices in published newsletters of community organizations, letters to medical general practices and word of mouth. Data were collected in person at the University and by mail.

Randomization and blinding

Allocation, stratified by gender, age (<60, 60-75 and >75 years), and baseline VAS pain scores (25-40, 41-60 and 61-100mm), was performed independently by an administrator, not otherwise involved in the study, using computer generated randomisation in blocks of six. Following the randomization process, the administrator provided the serial number of an appropriate device (placebo or active) and the device was then dispensed to the participant. This process ensured that all study investigators and participants remained blind to allocation until analysis was complete.

Intervention

A commercially available TENS stimulator (Metron Digi-10s) was modified by a biomedical engineer to deliver PES current parameters as follows: pulsed,

asymmetrically biphasic, exponentially decreasing waveform with a frequency of 100Hz and pulse width of 4ms. Current was delivered via 120 x 80mm multiple use conductive silicone electrodes inserted into larger calico pockets (175 x 100mm) to increase the contact surface area and reduce current density. Electrodes, positioned over the anterior distal thigh (anode) and anterior to the knee joint itself (cathode), were coupled to the skin using hypoallergenic conduction gel and secured with specially made neoprene wraps. The placebo device was identical in appearance and method of use, however, the current flow was programmed to turn off after three minutes. Being a sub-sensory treatment, this change was not detectable by participants.

Identical written instructions were provided to all participants. They were asked to wear the device seven hours daily, preferably overnight, for 26 weeks. Specifically, participants attached the device and turned the intensity up until they could feel pins and needles or a prickling sensation under one or both electrodes. After achieving sensory output, participants were instructed to turn the intensity down until they could no longer feel any electrical stimulation. At this stage a built in locking mechanism that prevented subsequent adjustment of intensity without restarting the device was engaged.

Participants kept a log (hours) of device use over 26 weeks. At exit, they were asked to indicate whether they thought their device was PES or control.

Background therapy

Participants were advised to continue their usual treatment for OA throughout the study, including prescribed medications, health professional interventions such as

exercise programs, and complementary therapies. However, they were counseled against starting any new treatments. A medication diary was kept by all participants.

Outcome measures

The primary outcome was change in pain over 26 weeks measured on a 100mm pain VAS. Participants responded to the following instruction: *Consider the amount of pain that you have experienced due to arthritis in your treated knee over the past 48 hours. Please make a vertical mark crossing the line below at a point that you consider indicates how severe your pain has been.* The left side anchor of the line was marked as *no pain* and the right side anchor as *extreme pain.*

In addition, physical function (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] Likert format 3.1) and PGA (100mm VAS (20)) were measured to complete the core set of three primary efficacy variables, recommended by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group (21). Administration of the WOMAC provided an incidental pain score. These outcomes were measured at baseline, four, 16 and 26 weeks.

Other outcome measures included: quality of life (Medical Outcomes Study 36-item Short-Form Health Survey version 2 (SF-36)) and joint stiffness (WOMAC 3.1) measured at baseline, four, 16 and 26 weeks; physical activity (Human Activity Profile (22) and Actigraph GT1M accelerometers worn for seven consecutive days) measured at baseline and 16 weeks; and an 11-point global perceived effect scale (GPES) (23) administered at 16 and 26 weeks.

Two measures of physical activity were administered to enhance measurement precision. The Human Activity Profile (HAP) is a valid and reliable self-report

questionnaire but is subject to information bias (24). Accelerometers provided a direct measure of ambulatory physical activity.

Licence agreements for the WOMAC 3.1, SF-36 and HAP were obtained pre-study.

Sample size

A priori calculations for sample size were based on published pain VAS (6), PGA (6) and WOMAC function (25) data.

It has previously been proposed that the minimal clinically important improvement (MCII) in OA knee pain is 19.9mm on a 100mm pain VAS (26). Further, a change of 20mm has been defined as the minimum required for classification as a primary responder by Osteoarthritis Research Society International (OARSI) (27, 28). Accordingly, we deemed that an improvement in the PES group of 20mm greater than that achieved in the placebo group would constitute a clinically meaningful and important difference. Allowing for 20% withdrawals, it was determined that a sample of 70 would be sufficient to detect a between group difference of 20mm in change of pain VAS, as well as differences in change equal to MCII of 9.1 points for WOMAC function and 18.3mm for PGA (26). Calculations specified a power of 80% and a two-tailed test with alpha level 0.05.

Data analysis

Analyses were performed on an intention to treat basis using the Statistical Package for the Social Sciences, version 17.0. The last-observation-carried-forward method was applied for participants who completed at least one set of follow up data. Differences between groups at baseline, and changes between baseline and 26 weeks were examined using independent t-tests. To test for the fixed effect of treatment, repeated measures analysis using a linear mixed model was performed for pain VAS,

PGA, WOMAC scores and SF-36 at each follow-up. Between group comparisons of GPES scores at 16 and 26 weeks were analysed using independent t-tests. In secondary analyses, chi-square was used to compare proportions achieving MCII in pain, function and PGA and proportions reporting improvement in GPES scores in each group at all follow-ups. Differences were interpreted as significant if <0.05.

RESULTS

Characteristics of participants

From September 2007 to November 2008, a total of 120 participants were provisionally vetted by telephone and 85 given appointments for formal screening and baseline assessment where appropriate. Seventy participants were randomized in the study (Figure 1).

Baseline characteristics were comparable between groups with the exception of a lower BMI in controls (p=0.04) (Table 1). Of the sample, 37 (53%) were male, mean BMI was 28.1 and 48 (69%) had Kellgren-Lawrence radiographic scores of 3 or 4. Symptoms were mild to moderate in severity. Overall, mean baseline pain VAS score was 52mm with only 20 (28%) participants scoring above 60 mm. By comparison, WOMAC pain scores were generally lower with only five (7%) scoring above 60/100 on the normalized scale. WOMAC function scores also suggested low levels of disability.

Participants were physically active with 51 (73%) classified as moderately active or active according to their HAP adjusted activity score. Similarly, accelerometer data showed the average daily time spent in moderate level activity (3-6 metabolic equivalents) exceeded the 30 minutes per day, five days per week recommended by Haskell et al (29) to gain health benefits (Table 1).

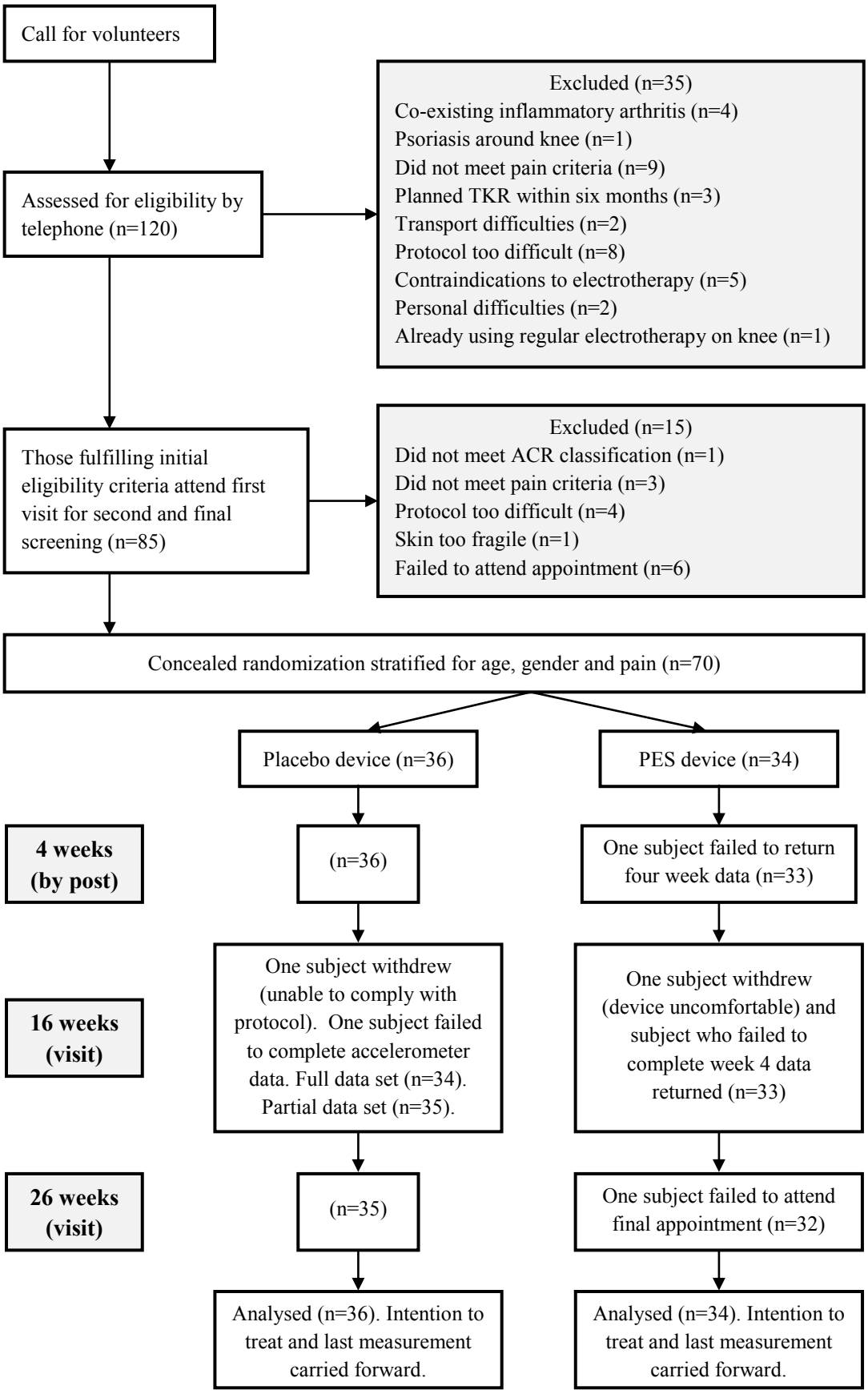

Figure 1. Flow of participants through the trial

Abbreviations: TKR – total knee replacement, ACR – American College of Rheumatology, PES – pulsed electrical stimulation.

Table 1. Baseline characteristics of the participants

Characteristic *(mean (SD)) unless otherwise indicated*	Control (n=36)	PES (n=34)
Age (years)	68.9 (11.4)	70.7 (8.9)
Male gender (%)	56	50
BMI ($kg.m^{-2}$)	26.8 (4.3)*	29.4 (5.9)*
Duration of symptoms (years)	11.4 (7.8)	12.6 (12.7)
Time since osteoarthritis diagnosis (years)	9.4 (10.3)	6.9 (7.4)
Kellgren-Lawrence radiographic grade (number) †		
1	3	1
2	5	7
3	10	14
4	13	11
Clinical features of osteoarthritis (number (%))		
Stiffness < 30 minutes in morning	31 (86.1)	30 (88.2)
Crepitus	33 (91.7)	31 (91.2)
Bony tenderness	21 (58.3)	25 (73.5)
Bony enlargement	25 (69.4)	30 (88.2)
No palpable warmth	36 (100.0)	32 (94.1)
Osteoarthritis laterality		
Bilateral (%)	47	56
Right side treated (%)	50	62
Medication use (number using (%)) ‡		
Complementary (glucosamine and fish oil)	19 (54)	15 (52)
Analgesic	18 (51)	10 (34)
Non-steroidal anti-inflammatory	15 (43)	13 (45)
Pain (VAS mm)	52 (18.2)	51 (17.2)
Patient global assessment (VAS mm)	47 (24.5)	44 (19.3)
WOMAC score (all normalized/100)		

Pain subscale	36 (18.1)	35 (16.3)
Stiffness subscale	41 (18.7)	45 (20.9)
Function subscale	34 (16.5)	35 (17.6)
Total score	34 (14.6)	36 (16.8)
SF-36 measures		
Physical component summary	36.5 (9.1)	37.0 (8.5)
Mental component summary	53.7 (11.2)	52.7 (11.0)
Human Activity Profile score		
Maximum activity	77 (8.2)	73 (9.6)
Adjusted activity	63 (12.4)	61 (13.7)
Accelerometer score		
Number of days of use	6 (0.3)	6 (0.4)
Daily accelerometer counts	178,181 (82,192)	211,250 (98,574)
Daily resting time in minutes	992 (90.5)	972 (94.8)
Daily light activity in minutes	333 (78.6)	345 (78.3)
Daily moderate activity in minutes	105 (56.8)	122 (63.6)
Daily hard activity in minutes	0.1 (0.3)	0.2 (0.6)

∗p=0.04; † control (n = 31), PES (n = 33); ‡ control (n = 35), PES (n = 29); Abbreviations: PES - pulsed electrical stimulation; SD – standard deviation; BMI – body mass index; VAS – visual analogue scale; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; SF-36 – Medical Outcomes Study 36-item Short-Form Survey version 2.

Participants used a variety of non-steroidal anti-inflammatory and analgesic medications, as well as combinations of fish oil and glucosamine. At baseline, while there was a trend to less analgesic use in the PES group, there were no statistical differences between the groups in use of either prescribed or complementary medication (Table 1). Over the 26 weeks, there was little variation noted in either the type of medication used or the dosage in either group. Six participants failed to

complete their medication diary while seven who did complete their diary were not using any medication for OA.

Device use, adverse effects and blinding

At 26 weeks, 20 (59%) of the PES group and 13 (36%) of the controls achieved 100% or greater target usage (p=0.03). However, effective device use defined as achieving 80% of the prescribed target did not differ significantly between groups (PES 25 (74%), control 22 (61%), p=0.11). The decision to define 80% of the prescribed target as effective device use closely reflected the minimum end of the accepted device use range of six hours per day reported in previous studies (5, 6, 8).

Twelve participants had adverse skin reactions in the form of rashes that were localized and mild. There was no difference between groups in the proportion of participants affected (6 (18%) PES, 6 (17%) control, chi sq = 0.1; p=0.9). Affected participants were advised to desist from device use until the rash had settled, after which they were able to resume treatment. Two participants from the control group used the device intermittently because of recurring skin reactions.

Thirty-one participants believed they knew whether their device was active or not but their ability to identify their group correctly did not differ from chance (6 (50%) PES, 10 (53%) control, Kappa = 0.02, p = 0.9). Thirty-five participants (19 PES, 16 control) did not know whether their device was active or inactive and four others did not complete the question. Thirteen of the 15 participants who believed they had used the active device reported feeling better on the GPES. Conversely, of the 16 who believed theirs was inactive, 13 reported no change or worse on the GPES (Kappa = 0.68, p<0.001). This suggests that blinding of participants was successfully maintained as participants' opinion on which device they had been allocated was largely influenced by their outcome.

Pain and function

For pain, PGA and function, there were statistically significant within subject changes in each group over 26 weeks except for WOMAC pain and function in the PES participants. However, between group mean differences in change for pain VAS 0.9, (CI -11.7 to 13.4); WOMAC pain -5.6, (CI-14.9 to 3.6), PGA -2.8, (CI -13.8 to 8.4) and; function -1.9, (CI -9.7 to 5.9) were not significant (Table 2). Interestingly, mean change in pain VAS over 26 weeks approached MCII, unlike PGA or function scores (Table 2). There were no between group differences for changes in pain, PGA or function at any of the earlier time points (Figure 2).

The proportion of participants achieving MCII for pain VAS at 26 weeks did not differ significantly between groups (19 (56%) versus 16 (44%) for PES and control respectively; 95% CI -11% to 33%; p=0.47) (Table 3).

Quality of life and activity

The SF-36 physical component summary measures (PCS) were slightly below and the mental component summary measures (MCS) slightly above the OA population norm (Table 1) (30). Only small improvements in PCS and MCS occurred over 26 weeks with no statistical differences between groups (Table 2). Patterns of change observed in the subscale scores were similar to those in the summary scores (Table 4).

Changes in both HAP and accelerometer physical activity measures at follow-up were small with no significant differences between groups (Table 2).

Table 2 Changes from baseline in outcome variables*. Data represent change at 26 weeks unless otherwise indicated.

	Control Mean change (SD)	PES Mean change (SD)	Between group mean change difference (95%CI)	Between group p-value
Pain VAS (mm)	18.7 (31.1)	19.6 (20.7)	0.9 (-11.7 to 13.4)	0.89
Patient global assessment VAS (mm)	14.1 (28.0)	11.3 (17.9)	-2.8 (-13.9 to 8.4)	0.62
WOMAC (all normalized/100)				
Pain subscale	10.1 (18.4)	4.5 (20.4)	-5.6 (-14.9 to 3.6)	0.23
Stiffness subscale	4.7 (19.3)	8.5 (21.5)	3.7 (-6.0 to 13.5)	0.45
Function subscale	6.9 (16.2)	4.9 (16.5)	-1.9 (-9.7 to 5.9)	0.62
Total score	6.8 (15.5)	5.5 (16.0)	-1.3 (-8.8 to 6.3)	0.74
Medical Outcomes Study SF-36				
Physical component score	-2.6 (7.3)	-1.0 (5.6)	1.7 (-1.5 to 4.8)	0.30
Mental component score	-2.4 (8.1)	-1.2 (9.3)	1.2 (-2.9 to 5.4)	0.55
Human Activity Profile†				
Maximum activity score	1.1 (7.9)	-1.0 (6.8)	-2.0 (-5.6 to 1.5)	0.26
Adjusted activity score	0.5 (8.8)	0.2 (6.2)	-0.3 (-4.0 to 3.3)	0.86
Accelerometer†	(n=34)	(n=33)		
Accelerometer counts – daily average	-5,419 (52,488)	12,600 (52,409)	18,020 (-7,566 to 43,607)	0.16
Daily resting time in minutes	-11.8 (88.7)	-27.6 (85.5)	-15.8 (-58.3 to 26.7)	0.46
Daily light activity in minutes	18.8 (67.6)	16.5 (65.2)	-2.3 (-34.7 to 30.1)	0.89
Daily mod activity in minutes	-0.4 (36.3)	11.1 (41.2)	11.5 (-7.4 to 30.4)	0.23
Daily hard activity in minutes	-0.2 (1.0)	-0.01 (0.7)	0.1 (-0.3 to 0.6)	0.51

*Negative mean change values for SF-36, HAP, accelerometer counts, calories, moderate and hard activity all represent improvement. For all other variables, a positive change values represents improvement.
†Physical activity measurement changes from baseline to 16 weeks. Abbreviations: PES – pulsed electrical stimulation; SD- standard deviation; CI – confidence interval; VAS – visual analogue scale; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; SF-36 – Medical Outcomes Study 36-item Short-Form Survey version 2; mod - moderate.

Global perceived effect scale

Similar to most other indices, GPES scores at both 16 and 26 weeks did not differ between groups (16 weeks mean difference 0.11, 95% CI -0.83 to 1.04; 26 weeks 0.78, -0.22 to 1.78).

Adjustment for covariates including sample characteristics, baseline measures and amount of device use did not alter any of the findings for any of the variables.

Table 3. Results from secondary analysis. Number (percent) of participants achieving 20mm change in pain VAS and minimal clinically important improvements (MCII)* in PGA and WOMAC function at 26 weeks

Outcome measure	Control	PES	Between group proportion differences 95%CI	Between group p-value
Pain VAS	16 (44)	19 (56)	-11% to 33%	0.47
PGA	16 (44)	13 (38)	-28% to 16%	0.78
WOMAC function	14 (39)	13 (38)	-22% to 22%	1.00

*MCII for PGA = 18.3; WOMAC function = 9.1 (17) Abbreviations: VAS – visual analogue scale; PGA – patient global assessment; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; PES – pulsed electrical stimulation; CI – confidence interval.

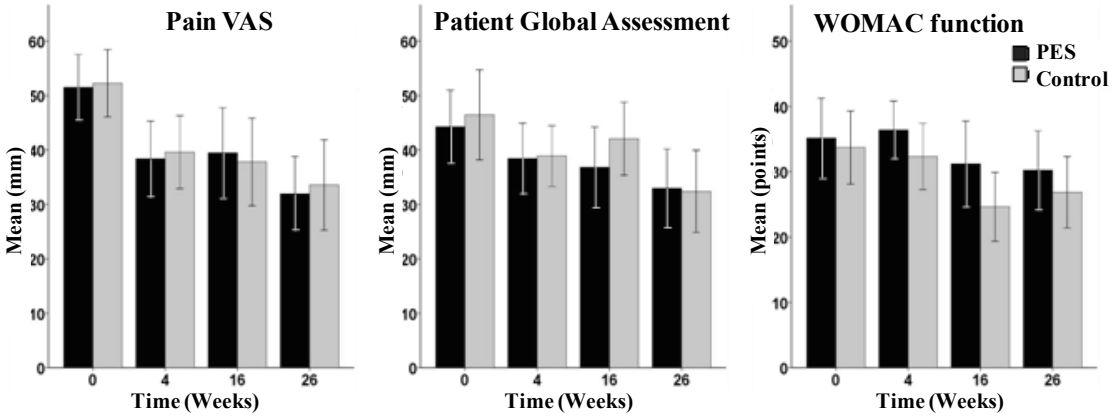

Figure 2 Scores for pain VAS, patient global assessment and function at each time point.

Error bars indicate 95% CI. There were no between group differences in change over time for any of these variables.

Table 4 Mean normalized values of Medical Outcomes Study Short-Form 36 survey subscale and component summary scores by time

SF-36 subscales and component scores	*OA population norms mean(SD)	Control				PES			
		Base	4/52	16/52	26/52	Base	4/52	16/52	26/52
PF	38.97(12.75)	33.71	33.12	36.34	36.34	34.07	34.07	36.05	34.94
RP	41.20(11.96)	39.17	39.71	40.46	41.48	39.78	41.41	41.37	41.66
BP	40.77(09.86)	40.07	42.07	42.27	45.86	40.74	43.28	42.59	44.92
GH	42.99(10.70)	49.44	48.52	50.70	49.43	46.91	46.30	46.63	44.89
V	45.31(10.07)	48.28	48.19	50.70	50.62	48.51	49.34	49.70	48.79
SF	43.69(12.54)	46.85	47.61	49.73	49.43	48.19	48.67	47.87	48.35
RE	45.57(12.72)	45.41	48.00	48.43	49.62	45.03	46.51	45.26	46.62
MH	47.56(10.64)	51.73	51.65	52.82	53.37	49.59	50.75	52.24	51.99
PCS	38.85(11.81)	36.47	36.33	38.28	39.12	36.96	37.70	38.28	37.95
MCS	48.72(10.98)	53.65	54.81	55.84	56.07	52.68	53.76	53.43	53.85

*Ware and Kosinski (21) Abbreviations:SF-36 Medical Outcomes Study Short-Form 36 Survey; OA - osteoarthritis; PES - pulsed electrical stimulation; Base – baseline; PF – physical function; RP – roles physical; BP – bodily pain; GH – general health; V – vitality; SF – social functioning; RE – roles emotional; MH – mental health; PCS – physical component summary; MCS – mental component summary

DISCUSSION

In patients with OA of the knee, PES treatment over 26 weeks was no better than placebo for reducing pain and improving physical function. Our results were consistent across all time points and outcome measures. Importantly, individual outcome results were reflected by the participants' overall perception of their response to treatment in the GPES. An unacceptably low proportion of participants using PES achieved the MCII for pain, PGA and function. Moreover, the control group responses were comparable.

Comparison with other studies

Previous randomized controlled trials of PES, conducted under the auspices of Bionicare®, the commercially available equipment, have reported favourable responses to PES compared with placebo (6, 8). Our results are clearly different.

Both our PES and placebo electrical parameters and method of application were comparable to Bionicare® in frequency (100Hz) and wave form (spiked, exponentially decreasing shape). Zizic et al (8) and Garland et al (6) described their current as monophasic but ours was slightly biphasic to avoid skin irritation (31). Comparison of our 16 week mean change data with the 12 week data reported by Garland et al (6) reveals strikingly similar 'PES treatment group' outcomes. The mean change for pain VAS in our study was 12.0 (22.6) mm whilst that reported by Garland et al was 14.7 (23.1) mm. However, while our placebo device response is consistent with that expected in osteoarthritis clinical trials (32) with a mean change of 14.4mm (SD 27.44), the placebo group in Garland et al changed very little with a mean change of 2.3mm (SD 21.95). This comparison was consistent across the three primary efficacy variables of pain, PGA and function and indicates that the difference in study outcomes appears to be due to differences in placebo responses, rather than differences in PES characteristics or equipment.

The possibility that the three minutes of placebo treatment could be therapeutic should be considered. However, as the placebo device used by Zizic et al (8) and Garland et al (6) also delivered three minutes of treatment and did not show a therapeutic effect, this is unlikely to be the case.

A comparison between the sample characteristics reported by Garland et al (6), Zizic et al (8) and amongst the participants in our study is limited by the different outcome

measures used and characteristics reported. However, in both the Garland et al (6) and Zizic et al (8) studies, higher scores in function at baseline were recorded meaning that OA was impacting on the health status of their participants to a greater extent than it was on participants in our study. Additionally, while the pain VAS scores reported by Garland et al (6) were similar to ours, their WOMAC pain scores were higher. Where reported, age and years since diagnosis were similar, while Garland et al's (6) participants had higher BMI scores and a higher proportion of females (66% versus 47% respectively). It is unlikely that these differences account for the contrasting results.

Placebo effect

A therapeutic response to placebo treatment is well documented in the OA literature (32, 33). A number of characteristics of our study have previously been noted to contribute to a robust placebo response (32, 34-36). Blinding was apparent throughout and the level of commitment required to participate was considerable and over an extended period of time. Furthermore, pain was the primary outcome. Participants had also been informed that previous trials of the modality had produced encouraging results so their expectations concerning improvement, along with their desire to contribute in an affirmative way, may have contributed to the positive response to the placebo control device.

Sample characteristics

Men accounted for just over 50% of the sample, whereas OA of the knee is usually more prevalent in women in the age group represented by this sample (37, 38). The mild to moderate baseline pain scores, mild levels of disability and high physical activity levels are also not typical. Thus the sample may not be representative of the OA population.

It may be that PES is more effective in some subgroups of people with OA. It is well recognised that OA is a heterogeneous disease (39-41) and that causes of pain and pain mechanisms in OA are multi-factorial (42-44). PES may be a more appropriate treatment modality in those patients in whom local pain mediators, which rely on membrane ion channels that may be affected by externally applied electrical stimulation, are the main cause of pain. In contrast, those in whom biomechanical changes or psychosocial factors are the main contributors to pain production may be less responsive. These latter factors were not measured in this study.

Therefore, while the outcome of this study is decisive, it may not be possible to generalize the results to the wider OA population.

Physical activity

Both accelerometer and HAP scores confirmed moderate levels of activity of the cohort at baseline. This may have limited the scope for further improvement and suggests that study participants were managing the functional impact of their disease quite well. However, as accelerometer data were recorded and reported cumulatively, determining whether moderate physical activity was performed in blocks of at least 10 minutes as recommended by Haskell et al (29) for general health improvement was not possible.

Strengths and limitations

The study was designed so that reporting of results conforms to the CONSORT statement (45). Both the sub-sensory nature of PES and robust allocation concealment meant blinding was a major strength of this study. All participants were screened, assessed and managed over 26 weeks by one experienced musculo-skeletal physical therapist thus avoiding investigator bias.

The recruitment of highly motivated volunteers may have resulted in a sample with characteristics different from the OA population in general. Additionally, the strong sense of commitment and desire to please noted in these participants may have enhanced the placebo response. It is unknown what influence these sample characteristics have had on the overall study outcome.

A priori calculation of sample size based on the achievement of a 20mm improvement in the PES group over that achieved by the placebo group had the potential to limit results interpretation given that a minimum baseline pain VAS score of 25mm was an inclusion criterion for the study. That is, if a substantial number of PES group participants were to achieve a final pain VAS score of zero mm and a similar number in the placebo group were to achieve pain VAS scores less than 20mm, the capacity to detect a 20mm difference between the two groups would have been compromised. However, as only one person in the whole sample (a PES group participant) achieved a pain VAS score of zero mm at 26 weeks, a true difference between the groups was able to be calculated and reported.

So as not to disadvantage those in the control group over such a lengthy period, participants were instructed to continue with their usual OA management. Apart from medication no concurrent treatments were recorded. Consequently there may have been unknown confounding factors that may have influenced the outcome.

CONCLUSION

In this sample with mild to moderate symptoms and moderate to severe X-ray evidence of osteoarthritis of the knee, PES was no more effective than placebo in achieving improvements in pain, function, quality of life or physical activity. Results of this study therefore do not support more widespread use of this modality.

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Dr Ritu Gupta, Statistician, Curtin University of Technology contributed to the statistical analysis in the study design phase and developed the computer- generated randomisation software used in the study.

Dr Richard Parsons, Statistician, Curtin University of Technology assisted with statistical analysis of data collected.

Competing interests

All authors state that they have nothing to declare.

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Trial registration

Australian New Zealand Clinical Trials Registry ACTRN12607000492459.

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Chapter 7: Summary and main findings

7.1 Introduction

Osteaorthritis of the knee is a chronic disease contributing considerably to worldwide health burden (Felson et al. 2000; Walker-Bone et al. 2000; Symmons et al. 2003; Woolf and Pfleger 2003; Buckwalter et al. 2004; 2006; Sharma et al. 2006). Currently the only treatments readily available target symptoms (Altman et al. 2000; Jordan et al. 2003; Sarzi-Puttini et al. 2005) and have moderate effect sizes at best (Jordan et al. 2003). Further, available treatments are often limited in their use because of side effects or because co-morbidities restrict their use (Gislason et al. 2006; Solomon et al. 2006).

Physiotherapists use a variety of modalities to treat people with OA including, but not limited to, exercise prescription, muscle strengthening programs, manual therapy, and electrotherapy modalities. One such electrotherapy modality, PES delivered at sub-sensory intensities, has previously been reported to be effective in managing the symptoms of OAK (Zizic et al. 1995; Farr et al. 2006; Mont et al. 2006; Garland et al. 2007; Fary et al. 2009). All previous studies were conducted with varying degrees of support from the company that produced the equipment, and both RCTs (Zizic et al. 1995; Garland et al. 2007) were of only short duration (four and 12 weeks respectively).

PES is relatively inexpensive, non-invasive, non-pharmaceutical and has few side effects. Consequently, independent verification of its effectiveness was warranted in order to determine if it was a viable treatment option for OAK. The aim of this thesis was therefore to explore, independent of device manufacturers, the effectiveness of PES in treating symptoms of OAK over 26 weeks. This chapter provides a summary of the steps required and the research undertaken to achieve this aim. It discusses the findings, outlining strengths and weakness, of each step. Finally, the overall implications of this research are discussed.

7.2 Pilot study of pulsed electrical stimulation

Prior to commencement of this part of this initial doctoral research project there was only one published report on PES. This was a randomised, placebo controlled trial conducted over a period of four weeks (Zizic et al. 1995). Outcome measures in that study included: pain, patient assessment of function, and physician global assessment, all measured on a 10cm VAS; patient assessment of duration of morning stiffness in the knee (minutes); knee range of motion (goniometer); joint tenderness on palpation and swelling (both 4-point Likert); knee circumference (inches); and 50 foot walking time (seconds). Improvements in pain, function, physician global assessment, and joint morning stiffness duration were reported.

Only two of the three primary efficacy variables of pain, function and PGA now recommended for use in clinical trials of OA were included (Bellamy et al. 1997; Hulme et al. 2002) with PGA not being used. In addition, only the VAS used to assess pain would currently be considered a measurement tool of choice.

The pilot study of this thesis (Fary et al. 2009) was undertaken to develop familiarity with use of the BioniCare® BIO-1000TM PES equipment, assist with the development of the protocol for the E-PES trial, provide experience with subject recruitment and retention, and develop an understanding of compliance with use of equipment and any adverse effects that may arise. In doing so it provided the opportunity to evaluate the effectiveness of PES over 16 weeks using a greater variety of outcome measures. All three recommended primary efficacy variables were included (pain VAS, function using OAK specific questions and PGA VAS). Additionally, QoL (SF-36), physical activity (accelerometer) and GPES (11-point Likert) were measured.

The equipment was well tolerated with adherence being 63%, 83% and 102% of target dosage and there were no adverse skin reactions. This was promising given that the proposed E-PES trial was to continue for 26 weeks duration. There was a trend towards improvement in the measures of pain, function, PGA and ambulation with this trend being reflected in two of the three patients who recorded an overall improvement in the global perceived effect scale. The third reported no change on the global perceived effect scale.

Limitations of this study included:

- the very small number of patients reported; and
- the use of accelerometers alone, while being valid and reliable measurements of ambulatory activity, did not measure other activities beneficial to health such as cycling and swimming.

The case studies provided valuable experience with the research process and the expanded range of outcome measures. While having its limitations, the largely positive response to PES was consistent with previous reports (Zizic et al. 1995; Farr et al. 2006; Mont et al. 2006; Garland et al. 2007) and suggested that the modality may be an effective treatment option over 16 weeks for people with OAK. This provided further support for conducting a RCT of longer duration.

7.3 Development of pulsed electrical stimulation equipment

As the BioniCare® BIO-1000TM devices were not available for the proposed E-PES trial, it was necessary to develop appropriate equipment for the study to continue. The major consequence of this was that the E-PES trial would be the first fully independent investigation into PES to be conducted.

Metron Digi-10s TENS units were sourced and modified to exactly replicate the parameters reported in the PES literature (Zizic et al. 1995; Farr et al. 2006; Mont et al. 2006; Garland et al. 2007). These parameters were described as a pulsed, 100 Hz frequency, monophasic current with a spiked, exponentially decreasing wave form. It has to be said that it is unusual for monophasic current to be used in this manner because a common side effect of its use is skin irritation and chemical burns (Hooker 2001). Being pulsed monophasic rather than continuous monophasic partially alleviated concerns about this current type. This is because pulsing allows the skin to act as a capacitor and discharge current thereby limiting chemical build up under the electrodes (Robertson et al. 2006). Nevertheless, it was not entirely surprising when initial testing of our pulsed monophasic prototype produced unacceptable adverse skin reactions with short durations of use.

These initial responses to the monophasic prototype led to the development and comparative testing of a biphasic PES device. The other current parameters of

pulsed, 100 Hz frequency and spiked, exponentially decreasing wave form remained the same. Biphasic current was chosen as it is even less likely than pulsed current to produce adverse skin reactions. This is because the changing direction of current flow means there is little opportunity for chemical build up to occur under the electrodes.

Comparative testing of the monophasic and biphasic prototypes was conducted and reported in chapter 4.

Another critical element of the E-PES trial was the placebo device. The placebo used by Zizic et al. (1995) and Garland et al. (2007) delivered three minutes of PES prior to ceasing current flow. Consequently, a placebo device that delivered three minutes of biphasic PES prior to ceasing current flow was constructed. As the current was delivered at a sub-sensory intensity and the LCD screen on the device did not alter, the cessation of electrical stimulation went unnoticed. Importantly, there was no way of recommencing current flow in this placebo unless the on-off switch was turned off and the procedure for re-setting the intensity was undertaken. This feature meant that it would be unusual for participants in the placebo group to get more than three minutes of the active PES treatment each day.

The method of application of PES described in the literature (Zizic et al. 1995; Farr et al. 2006; Mont et al. 2006; Garland et al. 2007) was also replicated. Neoprene wraps using a three point Velcro securing system were made to encase the electrodes. Electrode placement was the same with the anode on the distal third of the anterior thigh and the cathode positioned anterior to the knee joint while anti-allergenic coupling gel was used on electrode pockets constructed to match the size of the electrodes used with the BioniCare® BIO-1000TM.

At the end of the equipment development phase all aspects, except for the substitution of biphasic for monophasic current, of application of the modality had been faithfully replicated and a robust placebo device constructed.

7.4 Prototype equipment testing study

Twenty-five healthy subjects were recruited to test the rate of adverse skin reactions using both the monophasic and biphasic current device prototypes. This study (Fary and Briffa 2010) confirmed that the monophasic device produced unacceptable rates

of adverse skin reactions (52%) in healthy subjects and that these rates differed significantly from those reported in three of the four previously published PES studies (Zizic et al. 1995; Farr et al. 2006; Garland et al. 2007). Only Mont et al (2006) reported a similar adverse skin reaction rate (45%). By contrast, the slightly biphasic prototype was well tolerated and produced an adverse skin reaction in one subject.

This study supported the caution generally advised in the electrotherapy literature regarding the use of monophasic current while contradicting the assertions made by the authors of previous PES papers (Zizic et al. 1995; Farr et al. 2006; Mont et al. 2006; Garland et al. 2007) that conduction gel was the main cause of the adverse skin reactions reported.

There were key differences in the application of PES in the prior literature when compared to the monophasic PES prototype testing (Fary and Briffa 2010). All previous clinical trials had reported PES use for lengthy durations and had used gel as the coupling agent. The prototype testing limited use to a maximum of 15 minutes and water was used as the coupling agent. If either gel or duration of use were a major cause of adverse skin reaction, the rate of adverse skin reactions in the monophasic prototype testing should have been less than the previously reported rates.

Whether there were particular electrical parameter characteristics not articulated, or not identifiable, in the previous PES publications is unknown. What is known is that exact replication of the reported current characteristics, by a senior biomedical engineer with considerable experience in this area, produced unacceptable rates of adverse skin reactions.

Limitations of this study included:

- A change in protocol from 15 minutes testing to 10 minutes testing during implementation of the study as a result of three of the first five subjects sustaining an adverse skin reaction after use of monophasic PES. This change was accepted on the basis that a shorter testing duration was long enough to test the hypothesis and would be safer for the participants in the study.

- The absence of investigator blinding to the type of device used on each knee and the same investigator reporting on adverse skin reaction rates. However, where adverse skin reactions were evident, independent confirmation was provided by participants being required to report on duration of the response 24 hours after the testing.

- The inability of five participants to achieve a sub-sensory state with the monophasic prototype. These results were included in absolute rates of adverse skin reaction reports but were excluded from comparison with published literature because all published literature reported use of PES at a sub-sensory level.

The results derived from this comparative testing of the monophasic and biphasic PES prototypes provided justification for using a biphasic current in the E-PES trial rather than a pure monophasic one.

7.5 Effectiveness of pulsed electrical stimulation trial research protocol

Despite the limitations of the PES literature discussed in chapters 1 and 3, the consistently positive results reported by Farr et al. (2006), Fary et al. (2009), Garland et al. (2007), Mont et al. (2006) and Zizic et al. (1995) and the putative capacity of PES to act as a disease modifier (Lippiello et al. 1990; Wang et al. 2004; Brighton et al. 2006; Brighton et al. 2008) provided strong support for further research.

A double blind, randomised, placebo-controlled, repeated measures trial design was chosen as it provided the best opportunity to objectively assess the effectiveness of PES. Key methodological elements described by Herbert (2000) were included in the protocol. Computer-generated block randomisation combined with stratification was conducted by a person independent of the trial. A successful randomisation process and allocation concealment ensured that potential bias within the trial was reduced (Beller et al. 2002; Nuesch et al. 2009). Because all devices looked the same, and were applied and used in the same manner, blinding of both the investigators and the participants to device allocation was maintained until after data were analysed.

Outcome measures that were all valid and reliable for the target sample were chosen (Sanson-Fisher and Perkins 1998; Brazier et al. 1999; Melzack and Katz 1999; Ehrich et al. 2000; Ware et al. 2002; Welk 2002; Bellamy 2004; Bennell et al. 2004;

Pengel et al. 2004; Ward et al. 2005) while the three primary efficacy variables (pain, function and PGA) recommended for use in arthritis trials by the OMERACT group were included. Physical activity was measured in addition to function because of its important contribution to health and well-being (Haskell et al. 2007). Two measures were used to determine this outcome because of the known difficulties with measurement precision. The HAP is a valid and reliable self-report questionnaire (Fix and Daughton 1988). However, it is subject to the limitations associated with self-report activity measurements including recall bias (Ainsworth and Coleman 2006). Consequently, accelerometers that provide a direct measure of ambulatory physical activity were used to complement the HAP.

As OA is a chronic disease, treatment needs to be effective in the long term. A period of 26 weeks was chosen to reflect disease chronicity and was 14 weeks longer than the longest previous RCT published during the development of the research for this thesis (Garland et al. 2007). In addition, this period of time allowed for assessment of the ease of, and compliance with, use of the device. These latter aspects were considered to be important if, in the event of effectiveness being demonstrated, further research into effects on cartilage were to be undertaken.

The interim data collection time points of four and 16 weeks were chosen to allow comparison with previous publications while also considering burden on participants. The four week time point reflected the end point in the 1995 trial by Zizic et al. Four and 16 week data collection points were used in the pilot study undertaken for this thesis (Fary et al. 2009). The pilot study provided research experience with the time frames and indicated that participants would manage the time distribution well.

The RCT by Garland et al. (2007) extended to 12 weeks. A direct 12 week comparison with our trial would clearly have provided additional information. However, the E-PES trial data collection time points were set a priori, the protocol planned and research funding grants acquired prior to Garland et al.'s (2007) publication. To add another data collection point would have increased the burden on trial participants and was considered unwarranted.

It was determined that only one investigator, an experienced musculo-skeletal physiotherapist, would have contact with participants for the duration of the trial.

This was to eliminate any bias that may have been introduced by different clinical and/or communication approaches with participants.

Finally, the manner of application (neoprene wraps and size and placement of electrodes) was chosen to replicate the previous studies.

7.6 Results of the E-PES trial

Results of the E-PES trial showed that, in the sample studied, PES over 26 weeks was no better than placebo in improving pain, function, PGA, QoL and physical activity (Chapter 6). These results were clearly different to the previous RCTs of shorter duration (Zizic et al. 1995; Garland et al. 2007).

7.6.1 Comparison with other trials

The sample characteristics reported by Garland et al. (2007) and Zizic et al. (1995) were compared with those in our trial. While the comparison is limited by the different outcome measures used and characteristics reported, both Garland et al. (2007) and Zizic et al. (1995) reported higher scores in function at baseline meaning that OAK was impacting on the health status of their participants to a greater extent than it was on participants in our trial. Additionally, while the pain VAS scores reported by Garland et al. (2007) were similar to ours, the WOMAC pain scores were higher. As WOMAC pain scores are related to functional tasks, this is consistent with OAK having a greater impact on their participants than on ours.

It was not possible to compare the radiographic scores in Zizic et al. (1995) with those in the E-PES trial because a different measurement (Lequesne's) was used and baseline data were not presented. However, all participants in the Garland et al. (2007) trial had Kellgren-Lawrence radiographic scores of 3 or 4, signifying moderate to severe radiographic disease, whereas 69% of the participants in the E-PES trial had these scores. Where reported, age and years since diagnosis were similar, while Garland et al.'s (2007) participants had higher BMI scores and a higher proportion of females (66%) than we did (47%). It is unlikely though that these differences alone account for such contrasting results.

Table 7.1 Pain VAS comparisons between E-PES trial and Garland et al. (2007)

	Pain VAS		
	Baseline*	Follow up*†	Change*
Treatment devices			
E-PES trial	51.5 (17.2)	39.5 (23.6)	12.0 (22.6)
Garland et al	50.9 (17.9)	36.2 (26.1)	14.7 (23.1)
Placebo devices			
E-PES trial	52.3 (18.2)	37.8 (23.8)	14.4 (27.4)
Garland et al	48.1 (16.8)	45.7 (21.8)	2.3 (22.0)

* Mean (SD); † E-PES follow up 16/52, Garland et al. (2007) follow up 12/52

Abbreviations: VAS – visual analogue scale, E-PES – effectiveness of pulsed electrical stimulation.

All other PES studies have used the Bionicare® BIO-1000™ device. Of concern for this thesis was that the results of the E-PES trial might have been different to previous ones purely because of the slightly different current parameters used. In order to address this concern, comparisons were made between the E-PES trial 16 weeks mean change data and those reported at 12 weeks by Garland et al. (2007).

Strikingly similar 'PES treatment group' outcomes are apparent in the pain VAS scores in the two studies (Table 7.1). However, while our placebo device response was consistent with that expected in OA clinical trials (Zhang et al. 2008) it was very different to those reported by Garland et al. (2007) (Table 7.1).

There was variability in the results for PGA and function between the studies (Table 7.2). Baseline data for both PGA and function confirm the greater impact that OAK was having on participants in the Garland et al (2007) trial in comparison to ours. The larger mean changes noted in both these variables in the treatment group from Garland et al. (2007) may reflect the greater scope for improvement these participants had available. Of note, function in Garland et al.'s (2007) treatment group was, in fact, the only outcome variable to achieve a mean change greater than or equal to its MCII benchmark of 9.4 (Tubach et al. 2005).

Table 7.2 Patient global assessment and function comparisons between E-PES trial and Garland et al (2007)

	Patient Global Assessment			Function		
	Baseline*	Follow up*†	Change*	Baseline*	Follow up*†	Change*
Treatment devices						
E-PES	44.3(19.3)	36.8(21.2)	7.5(16.5)	35.2(17.6)	31.2(18.7)	3.9(13.8)
Garland	51.3(17.4)	39.3(26.1)	12.9(24.5)	51.9(16.0)	39.9(24.6)	12.0(19.2)
Placebo devices						
E-PES	46.6(24.4)	42.1(19.8)	4.4(26.2)	33.7(16.5)	24.6(15.6)	9.1(14.7)
Garland	41.4 (16.1)	45.1(21.4)	-3.7(23.43)	44.9(14.9)	46.6(18.3)	-1.7(13.5)

* Mean(SD); †E-PES follow up 16/52, Garland et al. (2007) follow up 12/52. Abbreviation: E-PES – effectiveness of pulsed electrical stimulation

By contrast, the PGA and function responses in the placebo group in Garland et al.'s trial (2007) were minimal. In fact, a slight mean change for the worse in both PGA and function variables was demonstrated (Table 7.2). This differs markedly from the responses demonstrated by those using the placebo devices in the E-PES trial. Positive mean changes for both PGA and function were achieved, with that for function approaching the MCII for that variable. Again our placebo responses are consistent with that expected in OA clinical trials (Zhang et al. 2008).

The concerns that BioniCare Medical Technologies Inc had verbally expressed about their placebo device are also important to note. Participants using it could turn up the intensity and receive a further three minutes of treatment. That is, the current flow cut out after three minutes but would automatically come back on if the intensity was readjusted. The placebo device developed for our trial did not allow this to happen. Consequently, if there were to be a difference between studies in placebo responses, it might have been expected that the Bionicare® response would have been the larger one given the potential for increased dosage of PES.

It appears that the differences between results reported in the E-PES trial and those in Garland et al (2007) are more likely due to differences in placebo responses and not due to differences in PES characteristics or equipment.

7.6.2 Placebo

Placebo responses in OA studies are sizeable (Zhang et al. 2008). Factors such as maintenance of blinding and treatment aims that include a reduction in pain contribute to a robust placebo response (Zhang et al. 2008). Additionally, it has been noted that placebo responses tend to increase in trials of longer duration (Walsh et al. 2002), in trials where there are larger active treatment effect sizes (Zhang et al. 2008) and where patients consider the intervention to be a new treatment (Doherty and Dieppe 2009). Further, placebo responses are also strongly affected by expectations of treatment effectiveness, desire for improvement in symptoms and the treatment environment (Koshi and Short 2007; Linde et al. 2007; Benedetti 2008; Price et al. 2008; Finniss et al. 2010).

The E-PES trial design had characteristics that could have demonstrably contributed to a large placebo effect. Blinding was apparent throughout, pain was the primary outcome, and the level of commitment required to participate was considerable and over an extended period of time. As the treatment is not in widespread use it was also perceived as being a new and modern intervention by the participants.

Participants were all volunteers and had been informed that previous trials of the modality had produced encouraging results. As a consequence, their expectations regarding improvement, the supportive environment of a clinical trial, and their willingness to contribute all may have contributed to the placebo group responses.

The possibility that the three minutes of placebo treatment per day could be therapeutic should be considered. However, as the placebo device used by Zizic et al (1995) and Garland et al (2007) also delivered three minutes of treatment and did not show a therapeutic effect, this is unlikely to be the case. Additionally, reported effective dosages used for related electrotherapeutic modalities such as TENS and interferential consistently exceed an average of three minutes per day (Adedoyin et al. 2002; Johnson 2008; Rutjes et al. 2009)

7.6.3 Sample characteristics

Men accounted for slightly greater than 50% of the sample whereas OA of the knee is more prevalent in women in the age group represented by this sample (van Saase et al. 1989; Felson 2006). The mild to moderate baseline pain scores, mild levels of

impairment and disability and higher than usual physical activity levels are also not typical suggesting the sample may not be representative of the wider OAK population.

Additionally, the SF-36 MCS shows that participants in the E-PES trial demonstrated a general sense of well-being that would be expected in the normal population and that the subscale scores of general health, vitality and social functioning were also above those usually found in the OA population (Table 4 in chapter 6). These results suggest a group of people with a positive outlook on life and good social support networks. These attributes are considered to have a mediating influence on a person's pain perception (Ferreira and Sherman 2007) and confirm this self-selecting sample of volunteers appeared to be managing their OAK better than usual OAK study populations.

It is unknown what influence these sample characteristics may have had on the trial outcome. However, they do suggest that some caution be exercised when generalising the trial results to a wider population of people with OAK.

7.6.4 Physical activity

The moderately active HAP scores in the E-PES trial are consistent with those described by Bennell et al. (2004) where people with OAK and people without OAK were able to be distinguished on the basis of their HAP AAS. Bennell et al. (2004) demonstrated that people with OAK, while still being classified as moderately active using the HAP, were less active than those without OAK (Bennell et al. 2004). That people with OA are generally less physically active than people without OA has also been reported in large epidemiological studies (Hootman et al. 2003; Shih et al. 2006).

The HAP questionnaire asks whether or not a person is currently still performing a task. A limitation of this tool is that frequency, duration and intensity of the task are not recorded. That is, a person may record that he or she is still bicycling for one kilometre. However, the frequency and intensity at which this task is completed is not measured. As a consequence, a person with OAK may be classified as moderately active using the HAP yet may not meet the recommended physical activity guidelines where intensity and duration are included (Haskell et al. 2007;

Brown et al. 2008). In the epidemiological studies (Houghton et al. 2003; Shih et al. 2006), the type, frequency, intensity, and duration of specific activities were recorded by interview thus providing more detail about the activity. Additionally, it is recognised that the ability of the HAP to respond to interventions is yet to be determined (Bennell et al. 2004).

Accelerometer data in the E-PES trial nevertheless reflected the HAP scores and demonstrated that this particular group of people with OAK were achieving more than the minimum of 30 minutes of moderate intensity activity recommended every day for the general adult population (Haskell et al. 2007). Accelerometer data also showed that this group were meeting the recommendations that people with OA of the hip and knee should accumulate 30 minutes of moderate intensity physical activity or exercise on at least three days per week (Minor et al. 2003). Once again though, limitations in the recording instrument are noted. The accelerometer data were recorded and reported cumulatively and, without conducting more detailed manual data extraction, it was not possible to determine the pattern of activity. That is, whether moderate physical activity was performed in blocks of at least 10 minutes as recommended by Haskell et al (2007). Additionally, no record of the specific nature of the activity was recorded. For example, it is unknown how much strengthening, endurance, coordination/balance and functional exercise was being undertaken to enhance health status.

While recognising limitations in the instruments used, that each measurement tool reflected the other is of note. Confirmation that both groups were, in general, at least moderately physically active at baseline reduced the likelihood of large increases of activity occurring. The very small changes detected in both HAP scores and accelerometer data over 16 weeks appeared to confirm this. Equally, the change in physical activity measures reflected those of all the other variables studied in the trial with no difference between the PES and placebo groups being noted.

7.6.5 Strengths of the E-PES trial

The trial was designed so that reporting of results would conform to the CONSORT statement (Begg et al. 1996; Moher et al. 2001). Consequently it included key elements such as clear participant eligibility criteria; a priori power and sample size calculations; pre-specified primary and secondary outcome measures; computer-

generated randomisation and device allocation conducted by someone independent of the study; and intention to treat data analysis using confidence intervals. It was registered prior to commencement, funding sources were acknowledged and the full protocol was published. Additionally, only valid and reliable outcome measures for the trial population were used.

The sub-sensory nature of PES and robust allocation concealment meant that blinding was successfully maintained until after data analysis was complete. Additionally, all participants were screened, assessed and managed over the duration of the trial by the one experienced musculo-skeletal physiotherapist (RF). Any bias that may have resulted from different styles of clinical supervision and attention were thereby eliminated.

Only two people formally withdrew (one from each group, before the 16 week data collection point) and another one person from the PES group failed to attend the final appointment at 26 weeks. The participant who withdrew from the PES group cited that using the device was uncomfortable while the other found the protocol too difficult for them. No reason for the failure to attend at 26 weeks was elicited. In the context of two very hot Western Australian summers during the time frame of the trial, maintaining 96% of the sample over 26 weeks was a very positive outcome.

Finally, the trial was undertaken independent of industry funding thus avoiding any real or perceived bias in results.

7.6.6 Limitations of the E-PES trial

Since the participants were highly motivated volunteers, there may have been higher than usual levels of compliance with what was a protocol that required considerable commitment over a lengthy time period. Additionally, highly motivated volunteers may have contributed to a sample with characteristics less representative of the OA population. Furthermore, their strong sense of commitment and desire to please may have enhanced the placebo response.

So as not to disadvantage those in the control group over such a lengthy period, participants continued with their usual OA management. It was assumed that with a robust randomisation process any variations in usual management would be reflected in both groups. However, other than medications, no other treatments that were being

used at the outset or any new ones that participants may have added of their own volition over the 26 weeks were recorded. While PES would most likely be used in conjunction with other treatments in clinical practice, whether other treatments confounded the results or not is unknown.

It is also well recognised that OA is a heterogeneous disease (Goldring and Goldring 2007; Brandt et al. 2009; Felson 2009) and that causes of pain and pain mechanisms in OA are multi-factorial (Kidd 2006; Gwilym et al. 2008; Hunter 2008). This trial took a broad approach to disease diagnosis. It may well be that PES is an effective modality in those patients in whom local pain mediators are the main cause of pain where externally applied electrical stimulation may mediate the actions of inflammatory cytokines (Seegers et al. 2001). It also may be more effective in those for whom abnormal pain sensitivity is a feature (Bhave and Gereau 2004; Felson and Schaible 2009) where electrical stimulation may affect firing of the voltage-gated channels of the sensory nerve endings. However, systems to accurately identify these sub groups are yet to be established. Additionally, the trial was not powered to undertake any analysis of sub groups, in particular gender and baseline pain severity.

Another potential limitation was the absence of another comparative group. That is, a third arm with 'usual treatment only', or even a fourth where an intervention recommended in treatment guidelines like exercise or TENS was given. Given the size of the placebo effect in OA trials, a head to head randomised placebo-controlled trial in the absence of more sensitive selection criteria and larger sample sizes may be of limited value. There are though other limitations associated with the inclusion of these other arms. Blinding could not be maintained with either and the lack of outcome expectation within a 'usual treatment only' arm cannot be discounted in influencing the results.

The intensity at which participants used their devices was not recorded. It is unknown whether there is a critical intensity at which sub-sensory treatment needs to be delivered to be effective. Additionally, device usage hours were recorded by participants on a self-report basis.

7.7 Implications of results and future directions

This research provides evidence that PES is not an effective treatment option in managing symptoms associated with mild to moderate OAK over 26 weeks. It adds to the body of evidence regarding transcutaneous electrostimulation. A recent Cochrane review (Rutjes et al. 2009), which included the PES RCTs by Zizic et al. (1995) and Garland et al. (2007), proved to be inconclusive with regards the effectiveness of these types of electrotherapy modalities in providing pain relief for people with OAK. Small studies of questionable quality were cited as a reason for the inability to draw conclusions. It is contended that the E-PES trial, while still relatively small, was well-designed with adequate power to provide convincing evidence to contribute to any later meta-analysis of transcutaneous electrostimulation.

Most importantly, this doctoral research provides information with low risk of bias regarding the effectiveness of this modality. With the wide variety of treatment options available, people with OA and their health care professionals need to be able to make informed choices about best available treatment options. This research provides useful evidence on which these decisions can be made.

The implications of continuing to use treatments that are not effective also need to be considered. Segal et al. (2004) presented data showing the cost-effectiveness of some commonly used treatments for OA and demonstrated that few of the most commonly used treatments had convincing evidence for cost-effectiveness. Currently, the commercially available PES device is being sold in the United States for $US1465 (Calloway 2010). Our data would bring into question the cost-effectiveness of buying and using this device. In addition to the financial costs, continuing to use ineffective treatments does little to decrease the personal health burden for individuals with the disease.

While the results presented here provide evidence against the use of PES for OAK, the limitations cited previously do suggest some direction for future research. Investigating the key characteristics of specific subgroups of OAK is of particular importance in that their identification may enable more appropriate targeting of treatment. Increased specificity in subject selection criteria may provide greater

opportunity to detect clinically meaningful differences when investigating the effectiveness of treatment modalities in managing OAK.

The question regarding the putative disease-modifying effects of PES in vivo also remains unanswered. While this is a tantalising prospect to explore, until there is clear evidence of symptomatic improvement with long term use, it is difficult to see further clinical research in this area developing.

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Appendix 1a: Participant information form – pilot study

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Information for Participants

Investigating the effectiveness of pulsed electrical stimulation in the management of osteoarthritis of the knee.

Principal Investigator:

Robyn Fary
Physiotherapist and Lecturer, School of Physiotherapy,
Curtin University of Technology, Western Australia.

Project Supervisor:

Associate Professor Kathy Briffa
Senior Lecturer, School of Physiotherapy,
Curtin University of Technology, Western Australia.
Phone: 9266 3666

Purpose of Study

Osteoarthritis of the knee is a very common condition that can be very painful and disabling. It affects the cartilage that covers the surfaces of the joints. Current treatment forms centre around medication, exercise and surgery and while these can be very effective they can also sometimes have unpleasant side effects for some people. In the main, they treat the symptoms of the condition rather than the condition itself.

A new form of treatment that uses pulsed electrical stimulation and claims to affect the condition itself by repairing the damaged cartilage has recently been introduced into Australia. It has been approved for use in America by the Food and Drugs Administration (FDA) and in Australia by the Therapeutic Goods Administration (TGA). It is now freely available on the market here. Being approved by these agencies means that it has met the strict requirements that it does no harm.

This new treatment is delivered via the Bionicare® BIO-1000™ device – a device specifically developed for treating osteoarthritis of the knee. It is a soft wrap, battery-operated device that encloses the knee with Velcro and may be worn under clothing during the day or at night during sleep. It has a detachable belt for use during the day. Two electrodes are incorporated inside the wrap and gel is used on the skin under the electrodes. A control unit may be attached to the belt. To use it, the control unit is turned on until a tingling sensation is felt. The intensity is then adjusted down to the point of disappearance of the sensation. This means that during its use you do not feel anything. You will be asked to wear this device for a minimum period of eight hours per day. Most people find wearing it at night in bed the most convenient way to use it.

Short-term studies where people have used the device for four weeks have been published. The purpose of this study is to examine the effectiveness of this treatment over a longer time period of 16 weeks. We will be measuring effectiveness in a number of ways. These will mainly be by asking you to complete questionnaires relating to any

pain you may have in your knee and your general functional ability. We will also ask you to use an accelerometer, a small device that measures your physical activity, for seven days at the beginning of the study and for seven days at the end of the study.

You have been specially chosen because you participated in a recent self-management program at the Arthritis Foundation of Western Australia. This is being done as, with your express permission, some of the final measurements taken at the end of that study will provide us with some baseline information for this study.

Procedures

If you agree to be involved in this study, you will, at most, be required to visit Curtin University of Technology, School of Physiotherapy in Bentley on four occasions over the sixteen week period. You will be able to continue your usual osteoarthritis management, including taking any medication that you usually do, for the duration of the study. You will be asked to maintain a medications diary so that we can keep a track on what you are taking.

Visit 1 – Baseline data collection and instructions on the use of the accelerometer and the medications diary

Upon arrival, you will be allocated an identification number to be used for all data collection. You will be asked to complete several questionnaires that relate to your osteoarthritis, have your height, weight and leg measurements taken, have a test completed for sensation acuity and shown how to maintain the medication diary. You will then receive instructions on how to use the accelerometer. This visit should take no longer than one hour.

Visit 2 – Seven days after the first visit for return of the accelerometer and instructions about the use of the Bionicare® BIO-1000™

At this visit, the accelerometer will be returned so that the data recorded within it may be collected. You will then be given a demonstration as well as verbal and written instructions about the use of the Bionicare® BIO-1000™. You may use this opportunity to ask further questions about the use and maintenance of the medications diary.

Four weeks after the start of using the Bionicare® BIO-1000™

At this time you will be asked to complete the same questionnaires that you did on your first visit again. The questionnaires will be sent to you by mail with a reply paid envelope enclosed in which to return the completed forms.

Visit 3 – Sixteen weeks after the start of using the Bionicare® BIO-1000™

At this visit you will be asked to once again complete the same questionnaires as on your first visit. You will also be asked to return the Bionicare® BIO-1000™ and the completed medications diary. Once again you will be given an accelerometer and asked to use it for the next seven days

Visit 4 – One week after visit 3.

This visit is for the return of the accelerometer only.

Risks, Discomforts and Benefits:

As the aim of the study is to look at the effectiveness of pulsed electrical stimulation you will be asked to use the equipment for a minimum of eight hours every day. After the initial mild tingling sensation that you will feel when turning the unit on, there should be no further sensation for the duration of its use on a daily basis. You may find it more convenient to wear the device in the evening and overnight in bed. However, you may also wear it under clothes during the day with the operating unit attached to the belt.

You should feel ***no pain*** at all from the Bionicare® BIO-1000™. If you do feel pain, discontinue use immediately. Skin burns are possible is there is a device malfunction or if it is not applied correctly.

One side effect that has been occasionally noted is skin irritation from the use of the electrode gel. Should you experience this you are advised to discontinue use of the equipment and to contact Robyn Fary on 0437 524 387 or 9266 3675 who will arrange for you to try a different gel.

If you decide to take part in this study you will have the opportunity of trialing a treatment that may have a positive affect on your osteoarthritis.

Confidentiality:

You will be allocated an identification number that will remain confidential to the investigators and the project supervisor. All recorded data will be entered in an excel program, on a Curtin School of Physiotherapy computer using your identification number only, no names will be used. Access to the stored data will be restricted by a password known only by the investigator and the project supervisor. All data collected and consent forms will be stored safely in a locked cupboard at the Curtin School of Physiotherapy.

The results of the study will be reported, although it will not be possible to identify individual subjects as no identification numbers or names will be included in report material. On completion of the study, all data will be stored in a secure and confidential location with the project supervisor for five years. After this time, all data will be destroyed. This is a Curtin University of Technology requirement.

Request for Further Information:

You are encouraged to discuss and/or express any concerns or questions regarding this study with the investigator and/or supervisor at any time. You should feel confident and secure about your involvement in the study.

Refusal or Withdrawal:

You may refuse to participate in the study and if you do consent to participate then you will be free to withdraw from the study at any time without fear or prejudice.

If you do decide to withdraw from the study at any time please contact the investigators at the earliest possible convenience. All data will be destroyed if you do decide to withdraw.

Approval

This study has been approved by the Curtin University Human Research Ethics Committee (approval number PT0029). If needed, verification of approval can be obtained by either writing to the Curtin University Human Research Ethics Committee, c/- Office for Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning (08) 9266 2784.

Appendix 1b: Participant information form – equipment testing study

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CRICOS Provider Code 00301J

Information for Participants

The assessment of comfort and skin reaction with the use of a modified transcutaneous electrical nerve stimulation (TENS) device.

Principal Investigator:
Robyn Fary
PhD Candidate
Physiotherapist and Lecturer,
School of Physiotherapy,
Curtin University of Technology, Western Australia.
Phone: 9266 3667 / 0437 524 387

Project Supervisor:
Dr Kathy Briffa
Associate Professor,
School of Physiotherapy,
Curtin University of Technology, Western Australia.
Phone: 9266 3666

Introduction

This participant information form describes this study and its purpose; outlines the procedures and time commitments required; explains the risks and benefits involved with being a part of the study; and informs you of your rights to confidentiality, to ask questions and to refuse or withdraw as you choose. If any part of it is unclear please feel free to ask questions of the principal investigator.

Purpose of Study

Osteoarthritis of the knee is a very common condition that can be very painful and disabling. It affects the cartilage that covers the surfaces of the joints. Current treatment options focus on medication, exercise and surgery and while these can be very effective they can also sometimes have unpleasant side effects for some people. In the main, they treat the symptoms of the condition rather than the condition itself.

A new form of treatment that uses pulsed electrical stimulation and claims to affect the condition itself by repairing the damaged cartilage has recently been introduced into Australia. The use of pulsed electrical stimulation to manage symptoms of osteoarthritis of the knee has been approved in America by the Food and Drugs Administration (FDA) and in Australia by the Therapeutic Goods Administration (TGA). Being approved by these agencies means that it has met the strict requirements that it does no harm.

The device that we are currently testing is a modification of a commercially available (without prescription) transcutaneous electrical nerve stimulation (TENS) device. The modifications have been done to ensure constant delivery of specific parameters to match those approved by the FDA and TGA. We are testing it on healthy individuals to ensure that its comfort and any skin reactions noted are in line with those previously reported with this form of treatment.

Procedure

Prior to screening, a test to determine your skin's ability to discriminate between sharp dull stimuli will be conducted by Robyn Fary. If this is achieved the modified TENS device will be applied.

To use this device, two electrode pads placed over moist material pads will be placed on the skin – one above the thigh and one over the knee-cap. A control unit adjusts intensity. To use it, the control unit is turned on until a tingling/prickling sensation is felt. The intensity is then adjusted down to the point of disappearance of the sensation. This means that during its use you do *not* feel anything. You will be asked to wear this device for a period of 10 to 15 minutes.

During the 10-15 minute period, you will be asked questions about the comfort and sensation (if any) felt. After removal of the electrodes and pads, your skin will be inspected for any sign of redness or irritation, a response which can be expected in some cases.

Your responses will be recorded on a spreadsheet developed for this study, as will be the intensity at which you first felt the electrical stimulation and the intensity the device was set on for the remainder of the testing time.

Risks, Discomforts and Benefits:

After the initial mild tingling sensation that you will feel when turning the unit on, there should be no further sensation for the duration of its use.

You should feel absolutely ***no pain*** at all from the device. If you do feel pain, alert the tester to this situation and the testing will be discontinued immediately. Skin burns are possible if there is a device malfunction or if it is not applied correctly so all care will be taken to avoid this and should you feel any discomfort alert the tester immediately.

One side effect that has been occasionally noted in previous studies with this form of electrical stimulation is skin irritation. Should you feel any sensation of irritation under the electrodes during the testing period, alert the tester to this situation and the testing will be discontinued immediately. The skin will immediately be inspected for any signs of irritation.

If you decide to take part in this study you will be taking the opportunity to assist with formative work that will ultimately lead to a study where the effects of this type of treatment on osteoarthritis of the knee will be examined.

Confidentiality:

You will be allocated an identification number that will remain confidential to the investigators and the project supervisor. All recorded data will be entered into an *Xcel* spreadsheet. Access to the stored data will be restricted by a password known only by the principal investigator and the project supervisor. All data collected and consent forms will be stored safely in a locked cupboard at the Curtin School of Physiotherapy.

On completion of the study, all data will be stored in a secure and confidential location with the project supervisor for five years. After this time, all data will be destroyed. This is a Curtin University of Technology requirement.

The results of the study will be reported, but it will not be possible to identify individual subjects as no identification numbers or names will be included in report material.

Request for Further Information:

You are encouraged to discuss and/or express any concerns or questions regarding this study with the investigator and/or research supervisor at any time. You should feel confident and secure about your involvement in the study.

Refusal or Withdrawal:

You may refuse to participate in the study and if you do consent to participate then you will be free to withdraw from the study at any time without fear or prejudice.

If you do decide to withdraw from the study at any time please contact the investigators at the earliest possible convenience. All data will be destroyed if you do decide to withdraw.

Approval

This study has been approved by the Curtin University Human Research Ethics Committee (Approval number:PT0090). If needed, verification of approval can be obtained by either writing to the Curtin University Human Research Ethics Committee, c/- Office for Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning (08) 9266 2784.

Appendix 1c: Participant information form – E-PES trial

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CRICOS Provider Code 00301J

Information for participants

The effectiveness of pulsed electrical stimulation (E-PES) in the management of osteoarthritis of the knee: a randomised controlled trial.

Principal Investigator:

Robyn Fary
PhD Candidate
Physiotherapist and Lecturer,
School of Physiotherapy,
Curtin University of Technology, Western Australia.
Phone: 9266 3667 / 0437 524 387

Project Supervisor:

Dr Kathy Briffa
Associate Professor,
School of Physiotherapy,
Curtin University of Technology, Western Australia.
Phone: 9266 3666

Introduction

This participant information form describes this study and its purpose; outlines the procedures and time commitments required; explains the risks and benefits involved with being a part of the study; and informs you of your rights to confidentiality, to ask questions and to refuse or withdraw as you choose. If any part of it is unclear please feel free to ask questions of the principal investigator.

Purpose of Study

Osteoarthritis of the knee is a very common condition that can be very painful and disabling. It affects the cartilage that covers the surfaces of the joints. Current treatment options focus on medication, exercise and surgery and while these can be very effective they can also sometimes have unpleasant side effects for some people. In the main, they treat the symptoms of the condition rather than the condition itself.

A new form of treatment that uses pulsed electrical stimulation and claims to affect the condition itself by repairing the damaged cartilage has recently been introduced into Australia. The use of pulsed electrical stimulation to manage symptoms of osteoarthritis of the knee has been approved in America by the Food and Drugs Administration (FDA) and in Australia by the Therapeutic Goods Administration (TGA). Being approved by these agencies means that it has met the strict requirements that it does no harm.

This new treatment is delivered via a soft wrap, battery-operated device that encloses the knee with Velcro and is most conveniently worn at night during sleep. Two electrode pads are incorporated inside the wrap and gel is used on the skin under the electrodes. A control unit adjusts intensity. To use it, the control unit is turned on until a tingling sensation is felt. The intensity is then adjusted down to the point of disappearance of the sensation. This means that during its use you do *not* feel anything. You will be asked to wear this device for a minimum period of seven hours per day. Most people find wearing it at night in bed the most convenient way to use it.

Short-term studies where people have used a similar device for four weeks have been published. The purpose of this study is to examine the effectiveness of this treatment over a longer time period of 26 weeks. To do this, half of the participants will be given an active device and half an inactive (placebo) device to wear. The placebo device is identical in appearance and operation to the active one. Neither the participants nor *any* of the investigators will know which one you have been given. It is important that we have a control (placebo) group like this (that is, those who wear the inactive device) so that we may truly measure the effects of the treatment itself.

We will be measuring effectiveness of the device in a number of ways. These will mainly be by asking you to complete questionnaires relating to any pain you may have in your knee and your general well-being and functional ability. We will also ask you to use an accelerometer, which is a small device that measures your physical activity, for seven days at the beginning of the study and for seven days at the 16 week time point of the study.

Procedures

If you agree to be involved in this study, you will be required to visit Curtin University of Technology, School of Physiotherapy in Bentley on four to five occasions over a period of 26 weeks. You will also be asked to complete questionnaires at home and return them to the university by mail once during this time. We shall provide stamped, self-addressed envelopes for you to do this.

If you do not have a recent X-ray of your affected knee (that is, one taken within the previous two years) you will be asked to undergo a plain knee X-ray at a radiology facility. An X-ray request form will be given to you for this purpose. The cost of this X-ray will be covered by the study. You will *not* be excluded from the study if you meet all criteria but do not wish to have an X-ray.

You will be able to continue your usual management, including taking any medication that you usually do, for the duration of the study. You will be asked to maintain a medications diary so that we can keep a track on what you are taking. If you agree, we shall write a letter to your managing doctor explaining your involvement in this study. Included with the medications diary will be a record of PES for you to complete as well. This will give an indication of how long you are using the PES for.

Visit 1 – Final screening for inclusion into the study and collection of baseline data

Upon arrival, you will be met by the principal investigator who will complete screening procedures. This will include an examination of your knee and an assessment of your knee pain. Once accepted into the study, you will be asked to complete several questionnaires that relate to your osteoarthritis. This visit will take approximately three-quarters of an hour. If you do not have a current X-ray and have consented to having one, you will be given a request form for one to be taken during the following week. You will be fitted with an accelerometer for use during the week.

Visit 2 – One week after your first visit to be fitted with the pulsed electrical stimulation (PES) device, be advised on the use of a medication diary and PES use record and be given the opportunity to ask any further questions about study.

At this visit, you will return the accelerometer, be fitted with the PES, advised how to use it and be given written instructions on its use and care. Additionally, you will be taught how to maintain a medications diary for the duration of the study as well as to keep a record of your use of the PES device. This visit will take approximately half an hour.

One week after the start of using the PES device

You will be contacted by phone at this time to ensure that you are managing to use the device without difficulty and to allow you the opportunity to ask any further questions.

Four weeks after the start of using the PES device

At this time you will be asked to complete most of the questionnaires that you did on your first visit again. The questionnaires will be sent to you by mail with a reply paid envelope enclosed in which to return the completed forms.

Visit 3 - Sixteen weeks after the start of using the PES device

At this visit you will be asked to complete all previously completed questionnaires with the addition of one extra assessment form. You will be asked to bring in your medication diary and record of PES use to this visit where the number of hours it has been used for will be recorded. It is at this stage that the accelerometer will be used again for a period of seven days. This visit will take no longer than half an hour.

Visit 4 – Seventeen weeks after the start of using the PES device

This visit will be for return of the accelerometer. We will endeavour to arrange for the return of the accelerometer without you having to make this visit.

Visit 5 – Twenty-six weeks after the start of using the PES device - Final data collection

At this visit you will be asked to complete the questionnaires again and return both the pulsed electrical stimulation device and the completed medications diary and PES use record.

Risks, Discomforts and Benefits:

As the aim of the study is to look at the effectiveness of PES you will be asked to use the equipment for a minimum of seven hours every day. It is important that you try to maintain this level of use for the duration of the study. After the initial mild tingling sensation that you will feel when turning the unit on, there should be no further sensation for the duration of its use on a daily basis. The best time to wear the device is in the evening and overnight in bed.

You should feel absolutely ***no pain*** at all from the PES device. If you do feel pain, discontinue use immediately. Skin burns are possible if there is a device malfunction or if it is not applied correctly.

One side effect that has been occasionally noted is skin irritation from the use of the electrode gel. Should you experience this you are advised to discontinue use of the equipment and to contact Robyn Fary on 9266 3667 or 0437 524 387 who will arrange for you to try a different gel.

There is minimal risk associated with the use of plain X-rays of the knee. The amount of radiation from a knee X-ray such as the one requested in this study falls well below the maximum dose recommended by the National Health and Medical Research Council (NHMRC). Please inform the principal investigator if you have had other radiological examinations (for example, other X-rays and CT scans) in the previous 12 months. If you do not have a recent X-ray (within the past two years) it may be of benefit to your clinical management to have an up to date X-ray taken.

If you decide to take part in this study you will have the opportunity of trialing a treatment that may have a positive effect on your osteoarthritis.

Confidentiality:

You will be allocated an identification number that will remain confidential to the investigators and the project supervisor. All recorded data will be entered into an *Access* computer program. Access to the stored data will be restricted by a password known only by the principal investigator and the project supervisor. All data collected and consent forms will be stored safely in a locked cupboard at the Curtin School of Physiotherapy.

On completion of the study, all data will be stored in a secure and confidential location with the project supervisor for five years. After this time, all data will be destroyed. This is a Curtin University of Technology requirement.

The results of the study will be reported, but it will not be possible to identify individual subjects as no identification numbers or names will be included in report material.

Request for Further Information:

You are encouraged to discuss and/or express any concerns or questions regarding this study with the investigator and/or research supervisor at any time. You should feel confident and secure about your involvement in the study.

Refusal or Withdrawal:

You may refuse to participate in the study and if you do consent to participate then you will be free to withdraw from the study at any time without fear or prejudice.

If you do decide to withdraw from the study at any time please contact the investigators at the earliest possible convenience. All data will be destroyed if you do decide to withdraw.

Approval

This study has been approved by the Curtin University Human Research Ethics Committee (Approval number: HR 122/2006). If needed, verification of approval can be obtained by either writing to the Curtin University Human Research Ethics Committee, c/- Office for Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning (08) 9266 2784.

Appendix 2a: Participant informed consent form – pilot study

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Participant Consent Form

Investigating the effectiveness of pulsed electrical stimulation in the management of osteoarthritis of the knee.

Principal Investigator:

Robyn Fary
PhD candidate
Physiotherapist and Lecturer, School of Physiotherapy,
Curtin University of Technology, Western Australia.

Project Supervisor:

Dr Kathy Briffa
Associate Professor, School of Physiotherapy,
Curtin University of Technology, Western Australia.
Phone: 9266 3666

You are of your own accord making a decision whether or not to participate in this research study. Your signature verifies that you have decided to participate in the study, having read and understood all the information accessible. Your signature also officially states that you have had adequate opportunity to discuss this study with the investigators and all your questions have been answered to your satisfaction. You will be given a copy of this consent document to keep.

I, (the undersigned)

_____

Please PRINT

of _____

Postcode _____ *Phone* _____

consent to involvement in this study and give my authorisation for any results from this study to be used in any research paper, on the understanding that confidentiality will be maintained. I understand that participation in this study will cause me to feel a mild tingling sensation at the front of the affected knee and thigh at the beginning of each use of the device only. I also understand that I may withdraw from the study at any time without discrimination. If so, I undertake to contact Robyn Fary (Tel. 0437 524 387) at the earliest opportunity.

Signature _____ *Date* _____

Participant

I have explained to the participant the procedures of the study to which the subject has consented their involvement and have answered all questions. In my appraisal, the participant has voluntarily and intentionally given informed consent and possesses the legal capacity to give informed consent to participate in this research study.

Principal Investigator: _____ *Date:* _____

Appendix 2b: Participant informed consent form – equipment testing study

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Participant Consent Form

The assessment of comfort and skin reaction with the use of a modified transcutaneous electrical nerve stimulation (TENS) device.

Principal Investigator:
Ms Robyn Fary
PhD Candidate
Physiotherapist and Lecturer, School of Physiotherapy,
Curtin University of Technology, Western Australia.
Phone: 9266 3667

Project Supervisor:
Dr Kathy Briffa
Associate Professor, School of Physiotherapy,
Curtin University of Technology, Western Australia.
Phone: 9266 3666

You are of your own accord making a decision whether or not to participate in this research project. Your signature verifies that you have decided to participate in the study, having read and understood all the information accessible. Your signature also officially states that you have had adequate opportunity to discuss this study with the investigators and all your questions have been answered to your satisfaction. You will be given a copy of this consent document to keep.

Please PRINT

I, (the undersigned)

_____

of _____

Postcode _____ *Phone* _____

consent to involvement in this study and give my authorisation for any results from this study to be used in any research paper, on the understanding that confidentiality will be maintained. I understand that participation in this study will cause me to feel a mild tingling sensation at the front of the knee and thigh at the beginning of use of each device only and that a mild skin rash may result from its use. I also understand that I may withdraw from the study at any time without discrimination. If so, I undertake to contact Robyn Fary (Tel.9266 3667 or 0437 524 387) at the earliest opportunity.

Signature _____ *Date* _____

Participant

Participant consent form – PES equipment testing

I have explained to the participant the procedures of the study to which the subject has consented their involvement and have answered all questions. In my appraisal, the participant has voluntarily and intentionally given informed consent and possesses the legal capacity to give informed consent to participate in this research study.

Principal Investigator: _____ Date: _____

Appendix 2c: Participant informed consent form – E-PES trial

Curtin
University of Technology

School of Physiotherapy

GPO Box U1987
Perth Western Australia 6845

Telephone +61 8 9266 4644
Facsimile +61 8 9266 3699
Email reception@physio.curtin.edu.au
Web physiotherapy.curtin.edu.au

CRICOS Provider Code 00301J

Participant Consent Form

Title of Project:

The effectiveness of pulsed electrical stimulation (E-PES) in the management of osteoarthritis of the knee: a randomised controlled trial.

Principal Investigator:

Ms Robyn Fary
PhD Candidate
Physiotherapist and Lecturer, School of Physiotherapy,
Curtin University of Technology, Western Australia.
Phone: 9266 3667

Project Supervisor:

Dr Kathy Briffa
Associate Professor, School of Physiotherapy,
Curtin University of Technology, Western Australia.
Phone: 9266 3666

You are of your own accord making a decision whether or not to participate in this research project.

Your signature verifies that you have decided to participate in the study, having read and understood all the information accessible. For those participants who have agreed to have a plain X-ray taken of their knee, it also verifies that you have had the risks and benefits of such a procedure explained to you and have agreed to undergo an X-ray with the associated cost being covered by the project.

Your signature also officially states that you have had adequate opportunity to discuss this study with the investigators and all your questions have been answered to your satisfaction. You will be given a copy of this consent document to keep.

Please PRINT

I, (the undersigned)

_____

of _____

Postcode _____ *Phone* _____

consent to involvement in this study and give my authorisation for any results from this study to be used in any research paper, on the understanding that confidentiality will be maintained. I understand that participation in this study will cause me to feel a mild tingling sensation at the front of the affected knee and thigh at the beginning of each use of the device only. I also understand that I may withdraw from the study at any time without discrimination. If so, I undertake to contact Robyn Fary (Tel.9266 3667 or 0437 524 387) at the earliest opportunity.

Signature _____ *Date* _____

Participant

I have explained to the participant the procedures of the study to which the subject has consented their involvement and have answered all questions. In my appraisal, the participant has voluntarily and intentionally given informed consent and possesses the legal capacity to give informed consent to participate in this research study.

Principal Investigator: _____ Date: _____

Appendix 3: E-PES trial administrative checklist

Planning and administration checklist

Timing	Tasks	Outcome of contacts
After positive phone screening Make first appointment	Send out: ▪ letter of confirmation ▪ parking permit ▪ parking map ▪ participant info sheet	
Visit 1	Final screening and subject details Informed consent Baseline data collection Accelerometer Confirm 2nd visit Parking permit	Randomisation and allocation of device
Visit 2	Return of accelerometer Teach use of PES Instruction booklet Medication diary and hours of use record	Download accelerometer data Enter data
After 3/52 of use	Send out 4/52 follow up questionnaires ▪ letter with instructions ▪ 4/52 questionnaires ▪ self-addressed, reply paid return envelope	
After 5/52 of use	Ensure all 4/52 data collected and returned	Enter data
After 14/52 of use	Phone contact re week 16 appointment Send out: ▪ letter of confirmation (ask them to bring in med diary) ▪ parking permit	
Visit 3 After 16/52 of use	Complete questionnaires Distribute accelerometer Parking permit for return of devices Confirm date of return	
Visit 4 After 17/52 of use	Return of accelerometer	Download accelerometer data Enter data
After 24/52	Phone contact re week 26 appointment Send out: ▪ letter of confirmation ▪ parking permit	
Visit 5 After 26/52 of use	Return of equipment and medication diary Exit study	Enter data Clean and check equipment

Appendix 4: E-PES trial telephone screening form

Curtin University of Technology
School of Physiotherapy
E-PES Study Screening Questionnaire

Thank you for taking the time to answer the following questions. They are designed to aid in research into a new form of treatment for osteoarthritis of the knee. The questions will also determine whether you fit the criteria set out for involvement in the study. All the information given will be held with strictest confidence.

Date: _____ Title: _____

Family Name: _____

First Name: _____

Telephone Number: _____ (Home)

_____ (Mobile)

_____ (Work)

Email Address: _____

Date of Birth: _____ Age: _____

X-rays

Has your doctor given you a diagnosis of osteoarthritis in the knee?	Yes/No
Have you had an X-ray of your knee within the last two years?	Yes/No
If yes, do you have access to your X-ray films?	Yes/No
If no, do you think that it would be possible to obtain them?	Yes/No
If no, would you mind having an X-ray taken (at our cost) for the study?	Yes/No

Osteoarthritis

Do you suffer from pain in your knee?	Yes/No
If yes, has it been stable during the past three months?	Yes/No

Subject ID:

Medical History

Do you have any of the following conditions/or had any of the following procedures?

Diabetes	Yes/No
Pacemaker	Yes/No
Cancer/Malignancy in the past five years	Yes/No
Rheumatoid Arthritis	Yes/No
Any other form of arthritis	Yes/No
Stroke	Yes/No
Multiple Sclerosis	Yes/No
Any other neurological disease diagnosed by your doctor	Yes/No
Skin conditions near the knee and thigh	Yes/No
Knee joint replacement or metal in or around the knee	Yes/No
Are you pregnant or are you planning a pregnancy in the next six months? (Think before asking)	Yes/No

Other Questions

Are you a confident reader of English?	Yes/No
Are you scheduled to have a knee replacement in the next six months?	Yes/No

Accepted for second screening /Not accepted for second screening

Reasons:

_____

_____

_____

Appendix 5a: Pain and patient global assessment visual analogue scales

Pain and Patient Global Assessments

Study Number _____

Week Number _____

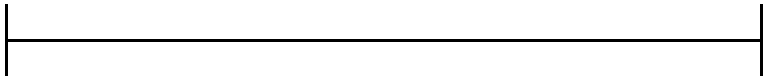
Visual Analogue Scale of Pain

Consider the amount of pain that you have experienced due to arthritis in your *treated* KNEE over the past 48 hours. Please make a vertical mark crossing the line below at a point that you consider indicates how severe your pain has been.

No Pain Extreme Pain

Patient Global Assessment

Consider all the ways in which your arthritis affects you at this time. Please make a vertical mark on the line below to show how you feel you are doing.



Very Well Very Poorly

Appendix 5b: Medical Outcomes Study Short-Form 36 survey

Your Health and Well-Being

This questionnaire asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

(IQOLA SF-36v2 Standard, Australia (English))

3 The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a kilometre	☐ 1	☐ 2	☐ 3
h Walking several hundred metres	☐ 1	☐ 2	☐ 3
i Walking one hundred metres	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

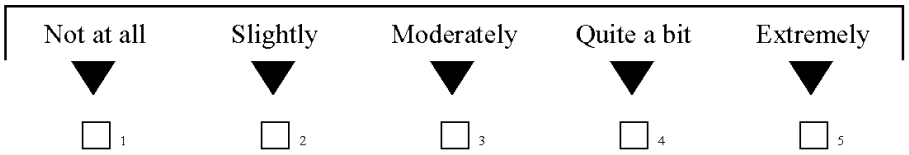
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

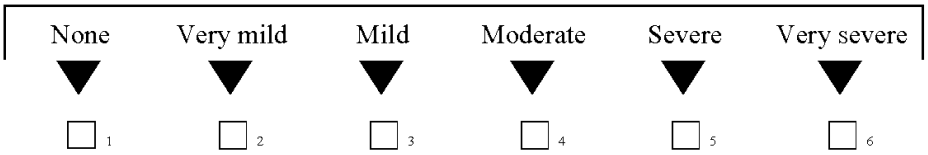
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

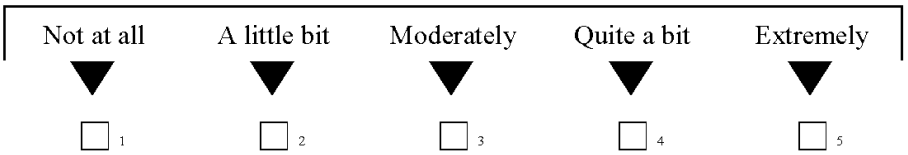
6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?**



7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**



8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**



(IQOLA SF-36v2 Standard, Australia (English))

9. **These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. **During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

(IQOLA SF-36v2 Standard, Australia (English))

Global Perceived Effect Scale

Study Number _____

Week Number _____

Compared with when you first started using the E-PES device, how would you describe your treated knee **these days**?

Choose one of the numbered boxes below that you feel reflects your description.

-5	-4	-3	-2	-1	0	1	2	3	4	5

vastly worse — unchanged — completely recovered

HUMAN ACTIVITY PROFILE

Instructions

Please check each activity according to these directions:

Check Column 1 ("Still Doing This Activity") if:

you completed the activity unassisted the last time you had the need or opportunity to do so.

Check Column 2 ("Have Stopped Doing This Activity") if:

you have engaged in the activity in the past, but you probably would not perform the activity today even if the opportunity should arise.

Check Column 3 ("Never Did This Activity") if:

you have never engaged in the specific activity.

Human Activity Profile Test

By David M. Daughton and A. James Fix, Ph.D.

Study Number: _____

Week Number: _____

	Still doing this activity	Have stopped doing this activity	Never did this activity
1. Getting in and out of chairs or bed (without assistance)			
2. Listening to the radio			
3. Reading books, magazines or newspapers			
4. Writing (letters, notes)			
5. Working at a desk or table			
6. Standing (for more than one minute)			
7. Standing (for more than five minutes)			
8. Dressing or undressing (without assistance)			
9. Getting clothes from drawers or closets			
10. Getting in or out of a car (without assistance)			
11. Dining at a restaurant			
12. Playing cards/table games			
13. Taking a bath (no assistance needed)			
14. Putting on shoes, stockings or socks (no assistance needed)			
15. Attending a movie, play, church event or sports activity			
16. Walking 25 metres			
17. Walking 25 metres (non-stop)			

Human Activity Profile Test (cont.)

	Still doing this activity	Have stopped doing this activity	Never did this activity
18. Dressing/undressing (no rest or break needed)			
19.Using public transportation or driving a car (150 kilometres or less)			
20. Using public transportation or driving a car (150 kilometres or more)			
21. Cooking your own meals			
22. Washing or drying dishes			
23. Putting groceries on shelves			
24. Ironing or folding clothes			
25. Dusting/polishing furniture or polishing cars			
26. Showering			
27. Climbing six steps			
28. Climbing six steps (non-stop)			
29. Climbing nine steps			
30. Climbing 12 steps			
31. Walking halfway around the block on level ground			
32. Walking halfway around the block on level ground (non-stop)			
33. Making a bed (not changing sheets)			
34. Cleaning windows			
35. Kneeling, squatting to do light work			
36. Carrying a light load of groceries			
37. Climbing nine steps (non-stop)			

Human Activity Profile Test (cont.)

	Still doing this activity	Have stopped doing this activity	Never did this activity
38. Climbing 12 steps (non-stop)			
39. Walking half a block uphill			
40. Walking half a block uphill (non-stop)			
41. Shopping (by yourself)			
42. Washing clothes (by yourself)			
43. Walking one block on level ground			
44. Walking two blocks on level ground			
45. Walking one block on level ground (non-stop)			
46. Walking two blocks on level ground (non-stop)			
47. Scrubbing (floors, walls or cars)			
48. Making beds (changing sheets)			
49. Sweeping			
50. Sweeping (five minutes non-stop)			
51. Carrying a large suitcase or bowling (one line)			
52. Vacuuming carpets			
53. Vacuuming carpets (five minutes non-stop)			
54. Painting (interior/exterior)			
55. Walking around six blocks on level ground			
56. Walking around six blocks on level ground (non-stop)			
57. Carrying out the garbage			

Human Activity Profile Test (cont.)

	Still doing this activity	Have stopped doing this activity	Never did this activity
58. Carrying a heavy load of groceries/shopping			
59. Climbing 24 steps			
60. Climbing 36 steps			
61. Climbing 24 steps (non-stop)			
62. Climbing 36 steps (non-stop)			
63. Walking one and a half kilometres			
64. Walking one and a half kilometres (non-stop)			
65. Running 100 metres or playing softball/baseball			
66. Dancing (social)			
67. Doing calisthenics or aerobic dancing (5 minutes non-stop)			
68. Mowing the lawn (power mower, but not a riding mower)			
69. Walking three kilometres			
70. Walking three kilometres (non-stop)			
71. Climbing 50 steps			
72. Shoveling, digging or spading			
73. Shoveling, digging or spading (five minutes non-stop)			
74. Climbing 50 steps (non-stop)			
75. Walking five kilometres or playing 18 holes of golf without a riding cart			
76. Walking five kilometres (non-stop)			
77. Swimming 25 metres			

Human Activity Profile Test (cont.)

	Still doing this activity	Have stopped doing this activity	Never did this activity
78. Swimming 25 metres (non-stop)			
79. Bicycling one and a half kilometres			
80. Bicycling three kilometres			
81. Bicycling one and a half kilometres (non-stop)			
82. Bicycling three kilometres (non-stop)			
83. Running or jogging half a kilometre			
84. Running or jogging one kilometre			
85. Playing tennis or racquetball			
86. Playing basketball (game play)			
87. Running or jogging half a kilometre (non-stop)			
88. Running or jogging one kilometre (non-stop)			
89. Running or jogging one and a half kilometres			
90. Running or jogging three kilometres			
91. Running or jogging five kilometres			
92. Running or jogging one and a half kilometres in 12 minutes or less			
93. Running or jogging three kilometres in 20 minutes or less			
94. Running or jogging five kilometres in 30 minutes or less			

Appendix 5e: Western Ontario and McMaster Universities Osteoarthritis Index information

WOMAC® OSTEOARTHRITIS INDEX

The WOMAC® Index is a proprietary disease-specific, tri-dimensional self-administered questionnaire, for assessing health status and health outcomes in osteoarthritis of the knee and/or hip. The questionnaire contains 24 questions, targeting areas of pain, stiffness and physical function, and can be completed in less than 5 minutes. Usually patient self-administered, the Index is amenable to electronic data capture (EDC) formats using mouse-driven curser, touch screen, and to interview administration by telephone. Available in over 80 alternative language forms, there are several different forms of the WOMAC® Index suitable for different clinical practical and clinical research applications. The most recent version of the Index is WOMAC® 3.1, which is a joint targeted version of the Index, and for most purposes has superseded earlier versions of the Index.

Questionnaire Content

Pain Subscale:

1. Walking on flat surface
2. Going up/down stairs
3. At night
4. Sitting/lying
5. Standing upright

Stiffness Subscale:

6. After first awakening
7. After periods of inactivity

Physical Function Subscale:

8. Descending stairs
9. Ascending stairs
10. Getting out of chair
11. Remaining in standing position
12. Bending
13. Walking on flat surface
14. In/out of car
15. Shopping
16. Socks/stockings on
17. Getting out of bed
18. Socks/stockings off
19. Lying in bed
20. In/out bath
21. Sitting
22. Toileting
23. Heavy domestic duties

24. Light domestic duties

Alternate language translations:

ARGENTINA
AUSTRALIA
AUSTRIA (GERMAN)
BELGIUM (FRENCH, FLEMISH)
BRAZIL
BRAZIL (JAPANESE)
BULGARIA
CANADA (ENGLISH, FRENCH)
CHILE
CHINA (MANDARIN)
COLUMBIA
COSTA RICA
CROATIA
CZECH REPUBLIC
DENMARK
ECUADOR
EGYPT (ARABIC)
ESTONIA
FINLAND
FRANCE
GERMANY
GREECE
GUATEMALA
HONG KONG (CANTONESE, CHINESE)
HUNGARY
ICELAND
INDIA (BENGALI, GUJARATI, HINDI, KANNADA, MALAYALAM, MARATHI, TAMIL, TELEGU, URDU)
ISRAEL
ITALY
JAPAN
KOREA
LATVIA (LATVIAN, RUSSIAN)
LEBANON
LITHUANIA
MALAYASIA (CANTONESE, ENGLISH, MALAY, TAMIL)
MEXICO
NETHERLANDS
NEW ZEALAND
NORWAY
PERU
PERU (JAPANESE)
PHILIPPINES (ENGLISH, TAGALOG, CEBUANO)
POLAND
PORTUGAL
PUERTO RICO
ROMANIA
RUSSIA
SERBIA
SINGAPORE (MANDARIN, ENGLISH)
SLOVAKIA
SLOVENIA
SOUTH AFRICA (ENGLISH, AFRIKAANS)
SPAIN
SWEDEN
SWITZERLAND (GERMAN, FRENCH, ITALIAN)
TAIWAN (MANDARIN)
THAILAND
TURKEY
UKRAINE (UKRAINIAN, RUSSIAN)
UNITED KINGDOM
USA (ENGLISH, SPANISH, FLORIDA)
VENEZUELA

The WOMAC® Index has been subject to a multiple validation studies, and is reliable, valid and responsive. The VA (100 mm) form of the Index may be slightly more responsive than the LK (5-point) form of the Index, but both have proven very responsive in various research environments. The Index may be presented with or without access to prior scores, our preference being for the latter. The time-frame may be varied from last 24 hours to last one month, depending on the trial design and research question. The object of measurement may be tailored to individual patients using the signal version of the instrument, although overall we have favoured using the entire instrument. The WOMAC® Index is relevant to both clinical research and clinical practice applications.

Use of the WOMAC® Index is supported by a User Guide. Information about the WOMAC® Osteoarthritis Index and the User Guide can be obtained direct from the constructor (Professor Nicholas Bellamy) at www.womac.org.

WOMAC® is the registered trademark of Professor Nicholas Bellamy [CDN No. TMA 545,986)] [EU No. 004885235] [USA No. 3520667]

Instructions for use of the pulsed electrical stimulation (PES) device

Arthritis AUSTRALIA

Physiotherapy Research Foundation

Contents

Introduction

You have been selected to participate in this new research study investigating pulsed electrical stimulation (PES), which is a non-drug and non-invasive treatment for osteoarthritis of the knee. It is important that you understand how to use and care for your treatment device. Please read the following instructions carefully.

Study Requirements

For the study to achieve its desired outcome of determining whether or not this treatment is effective, it is essential that the PES device be used as directed.

The critical electrical stimulation parameters being investigated have been specifically developed for, and installed into, this device and as such, should not be altered in any way. The only change that is to be made to any of the device settings is via the intensity control.

It is asked that you wear the device for at least seven hours every day over a period of 26 weeks. The best time for this to happen is overnight. All instructions assume that you will be using the device overnight.

Warnings

- This device is for use by the person to whom it has been loaned and should not be used by anyone else. This is because it may interfere with other equipment (for example, a cardiac pacemaker or a metal implant) or other conditions (for example, in someone who is pregnant or has a neurological condition) and as such should not be considered safe for use by others who have not been specifically assessed by the physiotherapist.

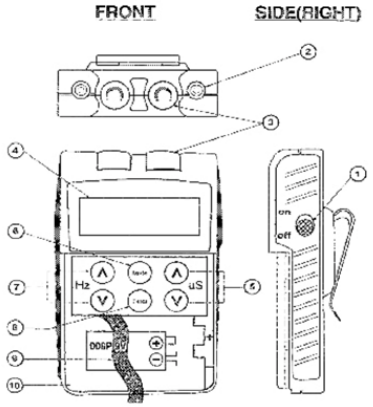
- The device should only be used as instructed on the nominated knee.

- If you feel pain or burning, or note any skin irritation with use of the device, stop use immediately and contact Robyn Fary on 9266 3667 or 0437 524 387.

Equipment Provided

- One pulsed electrical stimulation (PES) device
- Two pairs of electrode leads joined at one end for single connection to the control unit and separate at the other end.
  - One separate end with red connector
  - One separate end with black connector
- Two rubber electrodes
- Four electrode pockets
  - Two with red backing and red Velcro
  - Two with black backing and black Velcro
- One knee wrap
- Two 9V rechargeable batteries
  - This will allow one battery to be used while the other is being recharged.
- One battery recharger
- Six containers of gel
- Instruction booklet
- Carry case

PES Device Construction



(1) POWER ON/OFF SWITCH
(2) LEAD CONNECTOR
(3) INTENSITY CONTROL
(4) LCD
(5) PULSE WIDTH CONTROL
(6) MODE CONTROL
(7) PULSE RATE CONTROL
(8) TIMER CONTROL
(9) BATTERY STRIP
(10) BATTERY CASE

Adapted from Everyway Digi-10s Instruction Manual

Prior to use

- Ensure that the batteries are fully charged by placing them in the charger and waiting for confirmation of full charge.
- Ensure that your skin is clean, dry and devoid of any moisturisers or powders.

Steps for using the PES device

- Ensure the unit is switched to the off position. Switch is on the side of the unit. The off position is when the switch is pushed downward.
- Insert one fully charged 9V battery into the PES device. The battery casing is accessed by sliding the front cover off the unit in a downward direction.
- Thread the separated electrode lead ends through small holes in knee wrap. The red lead needs to go through the top hole (closest to the red Velcro) and the black one through the lower hole (closest to the black Velcro).
- Connect each electrode lead to an electrode.
    - It doesn't matter which electrode lead goes into which electrode.
    - Use care when you plug and unplug the wires. Jerking the wire instead of holding the insulated connector body may cause wire breakage.

Continued next page… … … .

- Connect the combined end of the electrode leads into the PES device itself. The lead connector jack socket is found on the top of the unit. Use the one on the left hand side when you are looking at the digital screen.
- Insert the electrode with the red electrode lead into the electrode pocket with red backing and red Velcro. Make sure that the flat side of the electrode is facing the cream calico side of the pocket. This is the side that will be next to your skin so it is important that it is a smooth surface.
- Insert the electrode with the black electrode lead into the electrode pocket with black backing and black Velcro. Again make sure that the flat side of the electrode is facing the cream calico side of the pocket.
- Attach each pocket to the inside of the knee wrap matching the coloured Velcro tags. (That is, red to red and black to black).
- Spread about one fifty cent sized amount of gel across the black electrode pocket and two fifty cent sized amounts across the red electrode pocket. Make sure to spread it out well across the whole electrode pocket area.
- Place the knee wrap across the front of the knee with the lower black electrode directly in front of the knee (knee cap area) itself. The red electrode should then be positioned on the front of the thigh.

Continued over the page … … … ..

- Secure the wrap starting with the middle strap followed by the other two straps to firmly secure the electrodes in place.
- Turn on the PES device using the on/off switch on the side of the unit. Pushing the switch upward turns the power on.
- The LCD screen on your unit should appear as below. You will need to contact Robyn Fary if the screen is different. She will talk you through how to change the settings so that they are correct.

Continued next page……..

- Turn the intensity up by turning the left intensity control knob at the top of the unit in a clockwise direction until you feel a tingling sensation under one or both of the electrodes.
- **Now turn the PES device down until the sensation disappears.**
- **Remember that you SHOULD NOT FEEL ANYTHING throughout the treatment time.**
- Secure the settings by pressing the red lock button on the side of the unit and sleep well!
- At the end of the treatment time, turn off the PES device using the on/off switch at the side of the unit and remove the wrap and electrodes. Check your skin for any signs of redness or irritation.
- **In general circumstances there will be no need to change any settings once the treatment has commenced. However, if a lead is inadvertently disconnected, or for any other reason you need to adjust the intensity, it is important that the device is switched off completely before any corrections are made. Once the corrections are made repeat the previous seven steps again.**

Care of PES device and wrap

- Alternate the batteries each day. We are using high capacity batteries with a quick charging time. Depending on your intensity settings and individual skin resistance the battery charge will be depleted at different rates. Use one battery in the device and charge the other one to maintain maximum charge and prolong the batteries' life. Do not use any battery if it is showing signs of corrosion, damage or leakage.
- The PES device may be wiped down with a damp cloth when it is turned off. However, but it must not be immersed in water under any circumstances.
- Hand wash the knee wrap in warm water using a mild detergent.
- Hand wash the electrode pockets in warm water using a mild detergent.

Parts Replacement

If at any time during the study you need new electrodes or electrode pockets, more gel, or should any part of the equipment appear to be malfunctioning, please contact Robyn Fary as soon as possible so that it may be sorted out for you.

Contact details

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Appendix 7a: Medication diary – pilot study

Medication Diary For: _____

Please keep a record of medications that you have taken during each week.

	Medication Name	Dosage of Medication	How many per day?
Accelerometer Week			
Week 1			
Week 2			
Week 3			
Week 4			

Medications Diary – Bionicare Pilot Study

Page 1 ONLY of 3 pages.

Appendix 7b: Medication diary – E-PES trial

Instructions for use. Please fill in this diary on a weekly basis while making special note of any CHANGES in medication use. In particular, please ensure that you record any changes in anti-inflammatory or pain killing medications. Also please record weekly how many hours you use the PES for.

Week 1	Medication Name		Dosage of Medication		Average how many per day during the week	
	PLEASE RECORD HOURS OF PES USE HERE					
	Mon	Tues	Wed	Thurs	Fri	Sat	Sun
						Total Hours Used	

Week 2	Medication Name		Dosage of Medication		Average how many per day during the week	
	PLEASE RECORD HOURS OF PES USE HERE					
	Mon	Tues	Wed	Thurs	Fri	Sat	Sun
						Total Hours Used	

Page 1 ONLY of 13 pages.