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Transcutaneous electrical nerve stimulation in management of knee osteoarthritic pain: A Placebo?

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Abstract
Background: Osteoarthritis is a late onset degenerative disorder particularly of the knee and hip. It is the most common joint disease of adults globally. Optimal management of osteoarthritis requires a combination of non-pharmacological and pharmacological modalities. Non-pharmacological management of osteoarthritis of the knee includes physiotherapy, transcutaneous electrical nerve stimulation (TENS), acupuncture and thermotherapy. Although there is widespread use of TENS for acute and chronic pain management, its effectiveness has been challenged by some authors and recommendations for its use in clinical settings appear inconsistent.
Materials and Methods: A narrative review of recently published randomized clinical trials, meta-analysis and systematic reviews on transcutaneous electrical nerve stimulation in the management of knee osteoarthritic pain has been performed
Results: Evidence from literature has shown that TENS is safe and it is associated with minimal side effects. Its mechanism of action is also well established. Reports from randomized controlled trials and systematic reviews explored in this essay show an equally divided opinion on the superiority of TENS over placebo in the management of knee osteoarthritis pain. Some of the studies concluded that pain control in osteoarthritis management with TENS was more effective than with placebo, while others showed that TENS provided comparable pain relief with placebo and exercise
Conclusion: Due to poor evidence from available literature, it is difficult to conclude whether the clinical effects experienced when TENS has been used in the management of knee osteoarthritic pain is as good as or superior to placebo.

Keywords: knee osteoarthritis pain management, transcutaneous electrical nerve stimulation

Introduction

With improvement in healthcare and social services in most developed and developing countries, there has been an increase in life expectancy. The latest report by the office for national statistics in Great Britain shows that life expectancy in England and Wales is 78.5 years for males and 83.6 years for females [1]. This represents an increase of 1.0 and 1.3 years in females and males respectively between 2006-2008 and 2010-2012. However, this improved longevity is also associated with increased incidence of age related degenerative disorders such as osteoarthritis [2].

Osteoarthritis is a late onset degenerative joint disorder particularly of the knees and hip. It is the most common joint disease of adults globally. The osteoarthritis of the knee has a prevalence of 50% in persons aged 75 years and above, it is less common in men (risk ratio 0.63) [3]. The articular cartilage and sub-chondral bone are affected. As the cartilage degenerates, the surfaces of the bones contact each other, create friction and manifest with pain on movement, reduced mobility and reduced quality of life.

The goal of therapy in osteoarthritis is to alleviate clinical manifestations, slow disease progression and to improve quality of life [2]. The Osteoarthritis Research Society International (OARSI) recommend that ''optimal management of osteoarthritis requires combination of non-pharmacological and pharmacological modalities'' [4]. Pharmacological options such as opioids, non-steroidal anti-inflammatory drugs and simple analgesics have been used in the management of osteoarthritic pain. Non-pharmacological management includes physiotherapy, transcutaneous electrical nerve stimulation (TENS), acupuncture and thermotherapy. There can be much deterioration of this condition such that joint replacement becomes inevitable.

Although strong analgesics such as opioids may be effective in osteoarthritis pain management, the aged population, are prone to co-morbidities like cardiac and respiratory diseases with possible renal impairments which may hinder their effective utilization. As defined by the American physical therapy association, TENS is ''the application of electrical stimulation to the skin for pain control'' [5]. It is non-invasive, safe, cost effective and easy to use. Although there is widespread use of TENS for acute and chronic pain management, its effectiveness has been challenged by some authors and recommendations for its use in clinical settings appear inconsistent [6].

This essay will review the clinical research evidence to support the use of TENS in the management of knee osteoarthritic pain and try to determine whether it is better than placebo.

Literature Review and Critical Analysis

TENS is a self-administered non-invasive analgesic technique which delivers pulsed electrical current through the intact skin surface to activate a peripheral nerve [7, 8]. Evidence from studies suggest that ''TENS -induced afferent activity inhibits onward transmission of nociceptive information in the CNS and this generates hypoalgesia in healthy humans exposed to non-injurious experimentally induced pain and pain relief in pain patients'' [9]. This follows the gate control theory as expounded by Melzack and Wall. During TENS, electrical current of high frequency (50-100 Hz), low intensity and small pulse width (50-200μs) is applied. This stimulates the large diameter non-noxious (Aβ) afferents. Activation of these low threshold afferents result in transmission of impulses via the dorsal horn of the spinal cord, through the spino-thalamic tract to the brain. With the

active engagement of these second order neurons, nociceptive stimuli from Aδ and C afferents within the same dermatomal levels are prevented from passing through same pathway to the higher centres. This causes segmental analgesia.

Related techniques such as acupuncture-like transcutaneous electrical nerve stimulation (AL-TENS) employ high intensity and low frequency (2-4Hz) electric current with a longer pulse width (100-400μs). It mobilizes the descending inhibitory pain pathway via stimulation of the GIII and Aβ afferents which relays impulses through the dorsal horn of the spinal cord to the higher centres. It produces muscle twitches and extra-segmental analgesia. It may be used when a patient is unresponsive to conventional TENS. Meanwhile, the intense TENS technique utilizes high intensity and high frequency currents over nerves arising from the site of injury (Aδ fibres) to ''produce maximum tolerable (painful) TENS paraesthesia'' [10]. This results in peripheral nerve block and extra-segmental analgesia. It is useful for wound dressing and removal of stitches.

Intensity of conventional TENS should be strong but not painful, creating a tingling sensation which occurs in a zone between sensory and painful thresholds. TENS pattern may be continuous, burst or amplitude modulated. However, continuous pattern is commonly applied with adjustments until patient is most comfortable. Similarly, high pulse frequency (50-100Hz) which is initially deployed is adjusted until patient is most comfortable. TENS has a rapid onset and offset. Maximum analgesia is obtained while the machine is switched on. Dual channel TENS devices utilizing four electrodes are reserved for large or multiple pains [10]. Although TENS is associated with few side effects and drug interactions with no toxicity or overdose, it requires laborious patient education. It is unsuitable for the cognitively impaired. Also, the TENS machine can malfunction.

A Cochrane review in 2000 analyzed seven randomized placebo controlled trials which utilized conventional TENS and AL-TENS in the management of osteoarthritis of the knee [11]. Seven randomized clinical trials (RCTs) with a total of 294 patients (148 active TENS and 146 placebo) were involved in these studies that were reviewed. The outcome measures were pain relief, functional status, patient global assessment and change in joint imaging. In all the trials (6 TENS, 1 AL-TENS), pain control was more effective than placebo [risk ratio 2.4 (95% Cl: 1.58 to 3.69)].This implies that, participants who received active TENS were more than twice likely to experience pain relief than those who got placebo. Also significant improvement in joint stiffness was noticed in the active TENS group. These results were achieved despite the use of different patterns of TENS settings. Generally, the study design and outcome measures in the trials analyzed were heterogeneous.

In 2002, a randomized placebo controlled clinical trial evaluated the cumulative effect of repeated TENS in knee osteoarthritic pain management over four weeks [12]. Sixty-two patients were stratified according to age, gender and body mass index before randomized allocation to four groups. They received either 60 minutes of TENS, 60 minutes of sham TENS (placebo), isometric exercise training or TENS and exercise, five days weekly over four weeks. Knee pain intensity was the primary outcome, measured by the visual analogue scale (VAS).There was significant cumulative reduction in visual analogue scores across the four treatment options. However, ''the four treatment protocols did not show significant between-group difference over the study period'' [12]. This shows that TENS provided comparable pain relief with placebo and exercise in this study. The reduction in VAS scores following exercise training could have occurred because exercise training improves muscle strength and leads to reduction in pain due to osteoarthritis of the knee [13]. However this study is flawed by a lack of statistical power calculation. The small sample size (average of 15 patients per group) increased the risk of type 2 error in the analysis.

Previous research has demonstrated that TENS analgesia involved activation of endogenous opioids [14]. The release of these endogenous opioids from the body takes time and pain relief derivable lasts a period before they diminish. With this background, a randomized placebo controlled clinical trial examined the analgesic effects of different durations of application of TENS in knee osteoarthritic pain treatment [15]. The aim of this study was to determine the optimal treatment duration of TENS and the duration of post simulation analgesia. Thirty eight patients, divided into four groups had either 20 minutes (TEN_{20}), 40 minutes ($TENS_{40}$), 60 minutes ($TENS_{60}$) or 60 minutes of placebo TENS ($TENS_{pl}$) for five days per week over two weeks. The outcome measure was pain relief assessed by VAS before and every 20 minutes after TENS application for a duration of 1 hour. Subsequent VAS assessments were self-administered by the patients every 2 hours at home for the remaining period of the study each day. After the first session of TENS, a significant differential reduction in pain relief was noticed between the three active TENS group and the placebo group. ($p-0.003$). After 10 days of treatment, they reported significantly greater cumulative pain relief in $TENS_{40}$ (83.46%) and $TENS_{60}$ (68.37%) groups than $TENS_{20}$ (54.59%) and $TENS_{PL}$ (6.14%) groups ($p-0.000$). While the significant difference in pain relief between the TEN_{40} and TEN_{PL} groups is appreciable based on percentage difference (83.40% vs 6.14%), the reported significance of same between $TENS_{60}$ and $TENS_{20}$ groups (68.37% vs 54.59%) is controversial. The longest duration of analgesia was noticed with the $TENS_{40}$ group while the $TENS_{PL}$ group recorded the least duration of analgesia. They concluded that 40 minutes was the optimal treatment duration of TENS in the management of knee osteoarthritic pain. However, majority of the data was obtained from patients self-administered and self-reported pain assessment at home, thereby diminishing the credibility of the results from the study. The clinical acceptability of the findings of this study is questionable because it is grossly underpowered.

Also, a double-blinded, randomized, placebo controlled clinical trial investigated the efficacy and safety of pulsed electric stimulator (HF TENS) in patients with knee osteoarthritic pain [16]. Fifty eight patients with moderate to severe osteoarthritis had either an active or placebo TENS for 6 to 14 hours daily at home for 3 months. The primary outcome was global evaluation of osteoarthritis symptoms measured by Western Ontario and McMaster Universities (WOMAC) questionnaire. Another outcome measure was pain relief, assessed by percentage change from baseline visual analogue scores. They recorded a 50.6% greater improvement of global osteoarthritis symptoms from the use of active TENS than placebo (p-0.003). The percentage of

patients with pain relief greater than 50% from baseline was also significantly higher in the active TENS group (43.6%) compared to placebo (15, 8%), p-value-0.004. However, the uneven distribution of participants, evidenced by a2:1 randomization (active vs placebo TENS), makes a fair comparison of the effects of the two interventions difficult. Patients were maintained on their ''stable doses of analgesics and NSAIDs'' from one month prior to and throughout the duration of the study. This hinders objective assessment of the clinical effects of the interventions. Patients should have been properly advised to maintain the TENS current at a point of comfort instead of the instruction to ''turn down the current until no tingling sensation was felt''. This reduces the chance of obtaining maximum benefit from the TENS device [10]. The questionnaires were self-administered by patients at home at the end of every 24 hours following the use of TENS, ''usually at night''. Such assessments made when the device was switched off, may have been unreliable because analgesia from TENS is most effective while it is switched on. Reliance on patients' report on self-administered treatments may be misleading due to bias or improper application of protocol. This further diminishes the credibility of this study.

In 2010, there was a review of the previous Cochrane report of 2000 on TENS for osteoarthritis of the knee pain management [17]. This was based on analysis of 18 randomized controlled trials utilizing different forms of TENS on 813 patients. Eleven of these studies used conventional TENS involving 275 and 190 patients who received active TENS and placebo/no intervention respectively. It was reported that both active TENS and placebo TENS provided an improvement in pain relief of 2 out of a scale of 10 after 4 weeks of treatment. The review failed to confirm that TENS was effective in osteoarthritis of the knee management. Lack of conclusion was attributed to ''inclusion of only small trials of questionable quality''.

Another randomized double blind placebo controlled clinical trial was also conducted in 2012 on 75 patients on treatment for knee osteoarthritic pain [18]. The study assessed the effects of high frequency TENS (HF TENS), low frequency TENS (LF TENS) and sham TENS (placebo) on pain at rest, movement evoked pain and pain sensitivity. The primary outcome was cutaneous mechanical pain threshold which was measured by a set of 20 'von Frey filaments'. Other outcome measures were pressure pain threshold(PPT), heat temporal summation threshold, timed up and go test (TUG), pain intensity at rest and during TUG was also measured using 'verbal rating scale' (VRS). While pressure pain threshold was not significantly affected by sham TENS, it was increased by HF TENS and LF TENS. Cutaneous mechanical pain threshold was not affected by TENS. Subjective pain scores at rest and during movement were similarly reduced by active and sham TENS. They therefore suggested a ''strong placebo component of the effect of TENS''. This study may be adjudged unspecific and poorly sensitive because of the numerous outcome measures it assessed. The primary outcome measure was stated as cutaneous mechanical pain threshold whereas sample size estimation was calculated with a power of 0.80 to measure pressure pain threshold (expected PPT difference; 100kPa); this diminishes the reliability of the study. Inclusion criteria allowed ''VRS>3/10'' without a mention of the maximum value allowable, this implied possible arbitrary recruitment of mild, moderate and severe knee arthritic pain patients which might have confounded the study. Although it was stated that change in VAS greater than 10mm following intervention will be considered 'significant' they had earlier mentioned that ''a pain rating of less than 3 of 10 was needed to derive a clinically meaningful change attributable to intervention''. This contradiction creates a confusion as to what pain assessment tool (VAS vs NRS vs VRS) was utilized in the study. The suggestion that TENS was as good as placebo in pain relief is also debatable because the study was not powered to assess such. Moreover there was no distinct change in the value of pain assessment (? <3/10) that enables such assertion. Finally, sham TENS delivered standard current for 30 seconds and suboptimal current for another 15 seconds, thereby increasing the likelihood of release of some endogenous opioids which activates the descending spinal inhibitory pain pathway (13). This could have nullified any intended placebo effect and possibly confounded the findings of this clinical trial.

A randomized sham-controlled clinical trial was conducted in 2014 [19]. The objective was to determine the additional effect of TENS for knee osteoarthritis management when combined with a group education and exercise programme. A total of 224 participants (mean age 61 years, 37% males) were randomized into 3 arms. All the participants entered an evidence–based 6 weeks group education and exercise programme. Primary outcome was Western Ontario and McMaster Universities osteoarthritis index (WOMAC), function subscale at six weeks. Secondary outcome included WOMAC pain, stiffness and total scores. All arms improved over time ($p<0.05$), but there was no difference between the trial arms (p.0.05).It was concluded that there was no additional benefit of TENS, failing to support its use as a treatment adjunct within this context.

Conclusion

Osteoarthritis is a disease associated with pain, disability, reduction in function and quality of life [2]. Effective intervention should be based on a bio-psychosocial approach which accommodates the multiple dimensions of this disease. It is therefore necessary to combine pharmacotherapy, physical therapy, psychotherapy, social welfare services and rehabilitation therapy in order to achieve a satisfactory outcome.

Evidence from literature shows that TENS is safe and associated with minimal side effects [5]. Mechanism of action of TENS is also well established [5, 8]. Proponents of this intervention in the management of knee osteoarthritis have based their arguments mainly on authority and case reports of its efficacy. Reports from randomized control trials explored in this essay show an equally divided opinion on the superiority of TENS over placebo in the management of knee osteoarthritic pain [11, 15-18]. Whereas the initial Cochrane systematic review involving 7 RCTs (294 patients) reported the superiority of TENS over placebo, a review of this position by the same organization 9 years later (involving 18 RCTs and 813 patients) was inconclusive due to insufficient evidence. All the studies reported 'clinical effects' following the use of placebo TENS and TENS in knee osteoarthritic pain management [9-12, 15-18].

However, research methodologies adopted in all the RCTs analyzed in this essay were controversial. Only one RCT was adequately powered [16]. Due to poor evidence from available literature, it is difficult to conclude whether the

clinical effects experienced following the use of TENS in the management of knee osteoarthritic pain is as good as placebo [11, 12, 15-18].

TENS is a novel therapeutic innovation with huge potentials. Unfortunately, most of the studies which have tested its potency so far have been flawed by poor statistical power and methodological shortcomings. The challenges of randomization, blinding, bias and cost in conducting clinical trials using TENS is understandable. However, more effort is required to overcome these obstacles in order to produce good clinical evidence that supports its use in the management of knee osteoarthritic pain.

Recommendations

With the dearth of gold standard clinical research on TENS and the understanding that clinical outcomes are critically affected by poor TENS technique, more randomized, placebo-controlled clinical trials that are adequately powered to assess the effects of TENS on the knee osteoarthritic pain using appropriate methodologies is recommended. Adequate sample population for such study can be derived from a previous study with good methodology. Alternatively, a well-designed pilot study may be conducted with the aim of producing results that will be used to calculate ideal sample size using a statistical power of 80% (β=0.20).

The challenges of blinding and bias may be reduced by conducting more hospital based studies using appropriate equipment and personnel throughout the periods of patient selection, assessment, collation and data analysis. This may also be improved by patient conditioning and sham TENS equipment which produces skin sensation for a very short period of time. To conduct trials that are representative of the potentials of TENS, effects of the interventions should be assessed during the period of use rather than afterwards. Also, standardized treatment protocols (electrode placement, treatment time and settings), outcome measures and assessment tools are required in such trials to achieve uniformity and fair comparison of clinical outcomes.

More political will needs to be attracted to the use of TENS by use of well publicized seminars, symposia and conferences so as to attract the interest of governmental agencies and research donor groups. Finally, to improve credibility and overcome the problems of small sample population, multicenter clinical trials on the use of TENS in knee osteoarthritic pain management is recommended.

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