Transcutaneous Spinal Electroanalgesia
Its effects in healthy volunteers, acute and chronic pain patients

Thesis submitted to the University of Leicester for the degree of Doctor of Medicine by

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Transcutaneous Spinal Electroanalgesia: Its effects in healthy volunteers, acute and chronic pain patients.

Dr Anne Margaret Heffernan.

Epidemiological studies have shown that chronic pain is a major public health problem, because of the huge suffering of patients and the enormous medical and social resources required to optimise patient care. Currently there is a lot of interest in non-pharmacological, non-invasive therapies for both acute and chronic pain conditions. Transcutaneous Electrical Nerve Stimulation (TENS), by stimulation of Aβ fibres peripherally, interrupts the ascending transmission of painful impulses. However, its effects are known to diminish with time. Furthermore, it is not possible to undertake randomised double-blind trials with TENS, as the patients will always feel the tingling sensation when the machine is switched on. For patients with severe chronic intractable pain, a small device may be implanted around the spinal cord, which also interferes with ascending pain transmission – spinal cord stimulation. However this is a costly, invasive procedure with potentially serious complications. The new non-invasive technique of Transcutaneous Spinal Electroanalgesia (TSE) is thought to simulate the effect of spinal cord stimulation. As patients feel no peripheral stimulation when the device is switched on, all trials were double blinded with sham electrodes.

Postoperatively, TSE did not reduce the incidence of request for postoperative analgesia or the time to first request for analgesia. However, a trend towards lower pain scores was demonstrated. In the three sub groups of chronic pain patients studied, TSE did not bring about a reduction in pain intensity. Furthermore, there were no significant differences in quality of life following active TSE apart from a difference in the social functioning component of the SF-36 questionnaire in patients with chronic lumbar radiculopathy. TSE treatment did not affect thermal sensation, pain or mood in healthy volunteers.

This thesis has failed to demonstrate any effect of TSE treatment in healthy volunteers, in patients postoperatively and patients in the chronic pain clinic.
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To my family, for their constant support, encouragement and belief in me.

To Dad, I know how much this would mean to you and so I dedicate it you.
List of abbreviations

ACC  anterior cingulated cortex
AKU  acupuncture-like
AMP  adenosine mono phosphate
AMPA  α-amino-3-hydroxy-5-methylisoxazole
APN  anterior pretectal nucleus
APS  acute pain service
ASA  American Society of Anaesthesiologists
ASIC  acid-sensing ion channel
ATP  adenosine triphosphate
BDNF  brain-derived neurotrophic factor
Ca²⁺  calcium ion
CCK  cholecystokinin
CGRP  calcitonin gene related peptide
CI  confidence intervals
cm  centimetre
CNS  central nervous system
COX  cyclo-oxygenase
δ  delta opioid receptor
DBS  deep brain stimulation
DOP  delta opioid receptor
DR  dorsal root
DRG  dorsal root ganglion
FBSS  failed back surgery syndrome
GABA  gamma-amino-butyric acid
GDNF  glial-derived neurotrophic factor
GP  general practitioner
H⁺  hydrogen ion
HF  high frequency
HIE  Health Insurance Experiment
5HT  5 hydroxy tryptamine
HT  high threshold
HWT  Heat Wave Therapy
Hz  hertz
IASP  International Association for the Study of Pain
IL  interleukin
IPG  intracorpeal pulse generator
IQR  inter quartile range
IUPHAR  International Union of Pharmacology
κ  kappa opioid receptor
K⁺  potassium ion
kg  kilogram
kHz  kilohertz
KOP  kappa opioid receptor
LF  low frequency
LREC  Leicestershire Research Ethics Committee
LT  low threshold
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<td>milliamps</td>
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<tr>
<td>MAOI</td>
<td>monoamine oxidase inhibitors</td>
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<tr>
<td>Mg&lt;sup&gt;2+&lt;/sup&gt;</td>
<td>magnesium ion</td>
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<tr>
<td>MOP</td>
<td>mu opioid receptor</td>
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<td>MOS</td>
<td>Medical Outcome Study</td>
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<td>mg</td>
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<td>mins</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>mRNA</td>
<td>messenger ribonucleic acid</td>
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<td>mV</td>
<td>millivolt</td>
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<td>Na&lt;sup&gt;+&lt;/sup&gt;</td>
<td>sodium ion</td>
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<td>NA</td>
<td>Negative Affect</td>
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<td>NGF</td>
<td>nerve growth factor</td>
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<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
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<td>NO</td>
<td>nitric oxide</td>
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<td>NS</td>
<td>nociceptor specific</td>
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<td>PAG</td>
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<td>PA</td>
<td>Positive Affect</td>
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<td>PPI</td>
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<td>PRN</td>
<td>pro re nata</td>
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<td>PX</td>
<td>purine receptor</td>
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<td>SD</td>
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<td>SIC</td>
<td>stretch inactivated channel</td>
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<td>SPSS</td>
<td>Statistical Package for Social Sciences</td>
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<td>SSRI</td>
<td>selective serotonin reuptake inhibitors</td>
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<td>TAES</td>
<td>transcutaneous acupoint electrical stimulation</td>
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<td>tricyclic antidepressants</td>
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<td>trk</td>
<td>Tyrosine kinase receptor</td>
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<td>TTX-R</td>
<td>Tetrodotoxin resistant</td>
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<td>TNF</td>
<td>Tumour necrosis factor</td>
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<td>μ</td>
<td>Mu-opioid receptor</td>
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<tr>
<td>μg</td>
<td>Microgram</td>
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<td>V</td>
<td>Volt</td>
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<td>VRL-1</td>
<td>Vanilloid receptor-like protein</td>
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<td>WDR</td>
<td>Wide dynamic range</td>
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Chapter 1

Introduction

1.1 Aims of this thesis

1.2 Definitions

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1.1 Aims of this thesis

The overall aim of this thesis is to evaluate thoroughly the new technique of Transcutaneous Spinal Electroanalgesia (TSE). This is a non-invasive, non-pharmacological form of pain relief, which transmits its analgesic effect by a high frequency current transmitted through surface electrodes placed over the spinous processes (Macdonald & Coates 1995). These devices are being used with increasing frequency throughout chronic pain clinics in the UK. As there is limited work on TSE available in the literature, it was thought that full evaluation of these devices was required. Unlike the technique of Transcutaneous Electrical Nerve Stimulation (TENS), which always induces tingling at the skin surface, no tingling is felt with activation of a TSE device. This means that it is possible to double blind trials by means of placebo electrodes.

The rest of this chapter is concerned with definitions of terms used in pain management. In Chapter 2, the physiology of pain, its transmission and the development of pathological pain states are reviewed. The next chapter (3) gives an overview of the management of both acute and chronic pain, in order to demonstrate the place of the electrical methods of pain relief in pain management. Chapter 4 reviews the electrical methods of pain relief that are currently available focusing on the two most commonly used methods (TENS and spinal cord stimulation (SCS)). In Chapter 5, the new technique of TSE is reviewed with the limited evidence available to support its analgesic effect. The general methodology of all six trials, including selection criteria, pain measurement devices and data analysis is outlined in Chapter 6. In Chapters 7 to 12 inclusive, TSE is evaluated in relation to its effects in acute pain (Chapter 7,8), in chronic pain (Chapters 9,10 and 11) and on healthy volunteers (12). The final chapter
interprets the findings of these trials, discusses any issues arising and outlines possible future work.

1.2 Definitions

Pain
As defined by the International Association for the Study of Pain (IASP), pain is described as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage” (Merskey & Bogduk 1994).

It is important to remember that pain is always subjective and is learned by every individual by experiences related to injury in early life. As most stimuli that cause pain also cause tissue damage, pain is an experience that we associate with tissue damage. However, many people report pain in the absence of tissue damage or any likely pathophysiological cause (Gamsa et al 1990). Usually this happens for psychological reasons. If they regard their experience as pain and report it in the same ways as pain caused by tissue damage, it should be accepted as pain. It is known from clinical pain states that the brain can generate the sensation of pain in the absence of input from the periphery or the spinal cord e.g. phantom limb pain and pain perceived by paraplegic patients below the level of a total spinal cord transection. Therefore, a “pattern generating mechanism” exists in the brain that has an image of the body on which sensory data are played (Melzack & Loeser 1978). Pain has sensory and emotional dimensions and they interact together to produce what is termed the “overall pain experience”. In other words, pain “is what the patient says it is” and this applies to both acute and chronic pain (Loeser & Melzack 1999).
There are four broad categories associated with pain, (i) nociception, (ii) pain perception, (iii) suffering and (iv) pain behaviours. Behind them are anatomical, physiological and psychological substrates (Loeser & Melzack 1999). The relationship between these is illustrated in Figure 1.

(i) **Nociception**

This is the detection of tissue damage by specialised transducers attached to Aδ and C fibres. These transducers may be influenced by inflammatory and neural changes in their environment. Non-steroidal anti-inflammatory drugs can change this “inflammatory soup” (discussed in Chapter 2, Section 2.2.1) and produce pain relief by the restoration of nociceptive sensitivity to its resting state.

(ii) **Perception of pain**

Pain is frequently triggered by a noxious stimulus, such as injury or disease. It can also be generated by lesions in the peripheral or central nervous system, eg diabetic neuropathy, spinal-cord injury or stroke. When acute pain occurs, it is initially associated with specific autonomic and somatic reflexes, which disappear in patients with chronic pain. Many physicians do not realise that pain can occur without nociception. Pain due to nerve injury may not respond to analgesics such as morphine as well as pain caused by tissue damage. Furthermore, the intensity of chronic pain often bears little or no relation to the extent of tissue injury.

(iii) **Suffering**

This is a negative response induced by pain and also by fear, anxiety, stress and other psychological states. Not all suffering is caused by pain but, in our culture, suffering is described in the language of pain.

(iv) **Pain behaviours**

These result from pain and suffering and are what a person does or does not do that can be ascribed to the presence of tissue damage. Examples of pain behaviours include saying ‘ouch’,
limping, lying down, recourse to health care, refusing to work. Such behaviour can be observed by others and can be quantified. All these behaviours are real and are also influenced by actual or expected environmental consequences.

[Chapter 1].[Figure 1]

The relationship between pain, suffering and behaviour.

**Types of pain**

*Transient (phasic) pain*

Short duration phasic pain reflects the immediate impact of the onset of injury. Traumatic injuries such as lacerations or burns provoke reflexive withdrawal, protective movements recognizable as pain to onlookers (Craig et al 1992). It is thought that the primary biological function of pain may be to trigger recuperative behaviour rather than to signal physical threat or danger. This was proposed by Wall who demonstrated that pain promotes actions directed at healing rather than defensive avoidance behaviour (Wall 1979). This theory is also supported
by Bolles & Fanselow who hypothesized that perception of traumatic threat, motivates physical fear and defensive self-preservative efforts (Bolles & Fanselow 1980). Anecdotal evidence is strong that people involved in activities that would be disrupted by pain sustain injuries without complaints e.g. soldiers on a battlefield or athletes.

**Acute pain**

A common definition of acute pain is “the normal, predicted physiological response to an adverse chemical, thermal or mechanical stimulus associated with surgery, trauma and acute illness” (Federation 1998). Acute pain begins sharply at a specific time, most often it is triggered by some defined pathology, injury or dysfunction (Forrest J 1998). It is provoked by tissue damage and comprises both phasic pain and a tonic state, which persists for a variable period of time until healing takes place. Therefore, it is a symptom that has a cause.

The intensity of acute pain is usually greatest at its beginning and, since its natural history is spontaneous resolution, the intensity reduces as healing occurs. Inadequate treatment of acute pain is common and may be a significant factor in the development of chronic pain behaviours that persist after physical healing has taken place (Carr & Goudas 1999). Acute pain is usually described in terms of its locus (e.g. cardiac pain, headache) or its cause (e.g. renal calculus, pancreatitis). When a patient presents with acute pain, a diagnosis is established first. Otherwise, removing the pain removes an important signal of the underlying pathology. Pain is the psychobehavioural and sensory experience that results from this activation of nociception. Therefore, establishing a diagnosis and relieving acute pain should be coincidental objectives.

In summary, the essential feature of acute pain is that it is self-limiting, ending with resolution of the underlying cause.
**Chronic pain**

Chronic pain has been recognized as pain that persists beyond the normal time of healing (Merskey & Bogduk 1994). This may be less than one month or, more often, more than six months. Generally with nonmalignant pain, three months is the most convenient point of division but, for research purposes, six months will often be preferred. However, there is a lot of debate as to the validity of these definitions as many syndromes are treated as examples of chronic pain, although normal healing has not occurred e.g. post herpetic neuralgia. Therefore, a simpler concept would be pain that persists for a given length of time and the length of time would be judged by common medical experience. It may be the time needed for inflammation to subside in the first instance. However, if waiting for peripheral nerves to grow back after trauma a longer period of time is required and chronic pain may be recognized when the process of repair is apparently ended. Sometimes repair is never complete. For example, neuromata in an amputation stump constitute a permanent failure to heal that may be a site of persistent pain.

Other syndromes are treated as examples of chronic pain although it is well recognized that normal healing has not occurred. These include rheumatoid arthritis and osteoarthritis. It appears to be best to allow for flexibility in the comparison of cases and to relate the issue to the diagnosis in particular situations (Merskey & Bogduk 1994).

Unlike acute pain, chronic pain has no useful physiological role i.e. it does not protect an injury from further damage until healing is complete. It has a huge impact on function and quality of life which is often disproportionately greater than may be explained by the underlying pathology (Doan & Wadden 1989). Chronic pain may be associated with mood changes,
depression, anxiety, anger or guilt (Sullivan et al 1992). Employment and social activity may also be impaired.

In understanding chronic pain, it is useful to break it down to the “overall pain experience” in terms of the pain and suffering that it causes (Figure 1). If pain is considered as nociception, it contributes to suffering as do other unpleasant physical and emotional states. A patient’s behaviour is the visible representation of suffering. Behaviour may be “appropriate” for the nociceptive stimulus or “inappropriate” (grimacing or wincing in the absence of a clear nociceptive cause of pain). The challenge to the chronic pain team is to determine the balance between the nociceptive and other components that lead to suffering and subsequent behaviour. This is best done by a multidisciplinary team which includes doctors, nurses, physiotherapists and psychologists (Katz WA 1996).

**Visceral Pain**

Pain from the viscera is usually vague, poorly localized and felt to arise from “inside” rather than near the body surface. Frequently, it is referred to structures distant from the source e.g. pain from myocardial ischaemia referred to the left arm.

The viscera are innervated mainly by C fibres (Chapter 2, Section 2.1.2) and they are activated by distension of hollow viscera, with increased activation in the presence of inflammation. The afferent neurones travel in autonomic nerves, mainly those of the sympathetic system. Furthermore, sympathetic denervation is often an effective means of intractable pain control for visceral pain, e.g. coeliac plexus block for pain from pancreatic carcinoma. There is also evidence that the parasympathetic system carries some afferent fibres e.g. the pelvic nerves carry fibres from the bladder (McMahon S 1994).
Neuropathic Pain

Neuropathic pain as defined by the IASP is pain initiated or caused by a primary lesion or dysfunction in the nervous system (Mersey & Bogduk 1994). It has been described in about 1% of the population (Nicholson B 2000) and can arise from peripheral or cranial nerve trauma (entrapment, trigeminal neuralgia, amputation); infection (post herpetic neuralgia, HIV-associated neuralgia); pressure due to growth (neoplasm); metabolic disturbances (diabetic neuropathy), infarct (stroke), or have an idiopathic cause. The symptoms of aching, squeezing, burning, shooting, uncomfortable paraesthesia, profound hypersensitivity and numbness may all coexist. In understanding the concept of neuropathic pain, it is useful to remember that pain may be any unpleasant sensation, not necessarily one evoked solely by nociceptor activation. Intense and persistent stimulation of Aβ neurons may produce “painful” paraesthesia (Chapter 2).

Referred pain

This is pain experienced at a site distant from the nociceptive stimulation. It occurs within the distribution of the spinal nerve innervating the source of the pain, whether the source is visceral or somatic (Cousins & Power 1999). Although many examples of referred pain exist (e.g. diaphragm irritation to the shoulder, cardiac pain to the left arm) it is important to remember that virtually any deep somatic or visceral pain may be referred. It is generally described as an ache and is not associated with any other sensory abnormality. Therefore, it may be differentiated easily from neuropathic pain.

Alldynia

This is pain due to a stimulus which does not normally provoke pain (Mersey & Bogduk 1994). Originally the stimulus was described as “non-noxious”. However, this has since changed as a
stimulus may be noxious at some times and not at others and also the boundaries of noxious stimulation may be hard to outline. Allodynia involves a change in the quality of a sensation, whether tactile, thermal or of any other sort. The original modality is normally non-painful but the response is non-painful.

**Hyperalgesia**

This is an increased response to a normally painful stimulus (Mersey & Bogduk 1994). The term reflects increased pain on suprathreshold stimulation. For pain evoked by stimuli that usually are not painful, the term allodynia is preferred, while hyperalgesia refers to an increased response at a normal threshold, or at an increased threshold e.g. patients with neuropathy. There are two types of hyperalgesia. Primary hyperalgesia refers to enhanced sensitivity occurring at the injury site, whereas secondary hyperalgesia refers to changes observed in non-traumatised regions surrounding the injury. Primary hyperalgesia becomes evident within minutes of the injury and is characterized by increased sensitivity to both heat and mechanical stimuli (LaMotte et al 1982). It correlates with a decrease in pain threshold and enhanced sensitivity of C-fibre and Aδ mechano-heat nociceptors after pressure or thermal injury. Secondary hyperalgesia has a delayed onset and different character in that sensitivity is increased only in response to mechanical stimuli (Ali et al 1996). These terms will be further discussed in Chapter 2, Sections 2.2.1 & 2.4.1.

**Hyperesthesia**

This is defined as increased sensitivity to stimulation, and does not include the special senses (Mersey & Bogduk 1994). It may refer to various modes of cutaneous sensibility including touch and thermal sensation without pain, as well as to pain. It indicates a diminished threshold to any stimulus and an increased response to stimuli that are normally recognized.
**Hyperpathia**

Hyperpathia is defined as a painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus. It may occur with allodynia, hyperesthesia, hyperalgesia or dysesthesia (an unpleasant abnormal sensation). Faulty identification and localization of the stimulus, delay, radiating sensation and after-sensation may be present and the pain is often explosive in character.

**Hypoalgesia**

This is defined as diminished pain in response to a normally painful stimulus.
Chapter 2

Pain Mechanisms and Pathophysiology

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This chapter deals with the physiology of pain, its transmission and the development of pathological pain states.

2.1 Pain Mechanisms

In recent years, there have been significant advances in the understanding of the physiological and biochemical processes that are involved in pain processing at the level of the spinal cord. This has meant a shift away from the conceptualization of pain as a simple "hard-wired" system with a "pure-stimulus" response relationship. Theories now take into account the changes that occur within the nervous system after any prolonged noxious stimulus and include processes such as "descending modulation" and local inhibitory mechanisms that are activated after a noxious stimulus. It is now known that long term changes can occur after noxious input and that this "plasticity" of the nervous system alters the body's response to further stimuli. It has now been proposed that pain should be divided into two entities "physiological" and "pathophysiological" (Woolf CJ 1989a). Physiological pain describes the situation in which a noxious stimulus activates peripheral nociceptors which transmit information to the brain where it is recognized as a potentially harmful stimulus. Pathophysiological processes that occur after tissue injury result in a stimulus-response pattern that is quite different and is therefore termed pathophysiological pain.

2.1.1 Nociceptors

Acute pain begins when a mechanical, chemical or thermal stimulus activates specific sensory nerve terminals, termed nociceptors, which are located throughout the body. They are thought to be the free naked nerve endings of the Aδ and C fibre nociceptive afferents. Providing the stimulus is of sufficient intensity, nociceptor activation occurs whether or not tissue damage
has occurred though generally the latter has occurred. Nociceptors require a high stimulus before they are activated. The initial stimulus for activation is probably mechanical distortion of the nerve terminal, followed by an increase in local concentration of potassium ion \( (K^+) \) and hydrogen ion \( (H^+) \). Tissue damage and inflammation lead to a reduction in the threshold for stimulation and, because this is at the site of tissue damage, it is termed “peripheral sensitization” (Siddall & Cousins 1997). An overview of the basic anatomy of the pain pathway is shown in Figure 1.

[Chapter 2].[Figure 1]

Basic anatomy of the pain pathway.
2.1.2 Primary afferent fibres

Two types of nerve fibres transmit impulses from the periphery to the spinal cord, A\(\delta\) and C fibres. A\(\delta\) fibres, which are stimulated by mechanical or thermal, high or low threshold stimuli, are myelinated and conduct impulses at a much faster speed than the smaller unmyelinated C fibres (Table 1). C fibres are stimulated by high-threshold chemical, mechanical and heat stimuli and are also termed C polymodal fibres. Both types of fibres do not only act as inert conductors of sensory information, as damage to a peripheral nerve results in number of physiological, morphological and biochemical changes that act as a focus of pain in themselves (Devor M 1989). These changes include abnormal nerve activity that arises from the peripheral ends of primary afferents or from the dorsal root ganglia (DRG).

| [Chapter 2]. [Table 1] Characteristics of primary afferent fibres | \(A\beta\) is included for comparison |
|---|---|---|
| C | A\(\delta\) | A\(\beta\) |
| Conduction velocity | \(< 2\text{m/s}\) | 10-40\text{m/s} | \(> 40\text{ m/s}\) |
| Myelination | No | Yes | Yes |
| Receptors | High threshold | High and low threshold | Low threshold |

Following a noxious stimulus, an immediate sharp pain is experienced which reduces in intensity after a few seconds and is replaced by a persistent burning pain. The first and second pain sensations follow activation of A\(\delta\) and C fibres, respectively. The first pain allows rapid reflex and behavioural mechanisms to remove the tissue from the source of pain, the second pain persists to prevent further injury and tissue damage when immediate danger has been averted. These fibres transmit impulses to the dorsal horn and synapse within the DRG. 40% of lumbar dorsal root cells (large diameter) are made up of A\(\beta\) and A\(\delta\) cells, which express trkB
and trkC. The latter are high-affinity tyrosine kinase receptors for brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) respectively (Michael et al 1997). Small diameter cells give rise to mainly unmyelinated axons (C fibres). One population of small cells synthesizes neuropeptides and responds to the high-affinity nerve growth factor (NGF), whereas the other expresses the lectin IB4 and responds to glial cell line-derived neurotrophic growth factor (GDNF) (Besson JM 1999). Both populations of small cells (C fibres nociceptors) express the vanilloid receptor (VR-1) (Kidd & Urban 2001). Under normal conditions, rapidly conducting Aβ fibres are mainly concerned with non-noxious input from specialized encapsulated receptors. Aδ and C fibres have free nerve endings which respond to noxious stimuli. Whilst most C fibres show polymodal responses, some are exclusively chemosensitive under normal conditions and do not respond to mechanical and thermal stimuli. These silent nociceptors were first described in joints but later found in other tissues (Schaible & Grubb 1993).

2.1.3 Ion channels

Within the nervous system, activation of inward (depolarizing) membrane currents, or inactivation of outward currents, will lead to increased excitability of the membrane, whereas the opposite changes will inhibit the cell from firing. The main channels responsible for inward membrane currents in nociceptive afferent neurons are the voltage gated activated sodium and calcium channels, while outward current is carried by potassium channels.

Sodium (Na⁺) channels

These open rapidly and transiently when the membrane is depolarized beyond about −60 to −40mV and are responsible for action potential generation and conduction. These are classified into those that are sensitive to the puffer fish tetrodotoxin (TTX-S) and those that are resistant
(TTX-R). Small diameter (C cells) nociceptor neurones express both TTX-S and TTX-R channels, whereas large diameter (A cells) neurones express only TTX-S sodium channels. SNS/PN3 and SNS2/NaN are two sensory neurone-specific TTX-R sodium channels which have been cloned (Akopian et al 1996). The amounts of SNS/PN3 protein are increased during chronic inflammation (Novakovic et al 1998). Prostaglandin E2(PGE2), adenosine and serotonin all enhance the SNS/PN3 channel sensitivity (England et al 1996). Local anaesthetics e.g. lidocaine and anticonvulsants e.g. carbamazepine block sodium channels but also sodium channels on other non nociceptor neurones within the CNS which causes side effects and limits their widespread application. Selective blockade of TTX-R channels could be a highly specific and therapeutic strategy for relieving both neuropathic and chronic inflammatory pain states.

**Calcium (Ca^{2+} channels)**

Several voltage-gated calcium channels (L, N, P/Q, T and R) have been shown to be involved in transmitter release and prolonged excitatory states of the neuronal membrane. Calcium entry through voltage-gated Ca^{2+} channels can affect many cellular processes, including activation of other membrane channels, release of transmitters and regulation of many enzymes (especially kinases and phosphatases) (Bevan S 1999). The inward current contributes directly to membrane depolarization and characteristic “hump” on the falling phase of the C-cell action potential is due to a Ca^{2+} current. Gabapentin has high affinity and specificity for the α2δ subunit of these channels (Gee et al 1996). Blocking calcium channels using ω-conotoxin, (a toxin derived from snails) produces analgesia. However, because it does not allow differentiation between various channels, it has a limited therapeutic window (Xiao et al 1994). Selective blockade of the pre-synaptic N-type channel could provide a potential useful target for broad-spectrum analgesics as it controls transmitter release at the dorsal horn (Kidd et Urban 2001).
Potassium K⁺ channels

The opening and closing of potassium channels is an important regulatory process for cell excitability and this is reflected in a great heterogeneity of K-channel subtypes. A variety of voltage-gated K⁺ channels are found in sensory neurones. Several delayed rectifier type K⁺ channels have been described in small as well as larger, diameter DRG neurones (Gold et al 1996). These channels open in response to depolarization and are largely responsible for the rapid depolarization of the membrane that terminates the action potential. A second type of K⁺ current activates more rapidly in response to depolarization but also inactivates if the membrane remains even slightly depolarized.

2.1.4 The spinal cord

The cell bodies of afferent fibres lie in the dorsal root ganglion and the fibres synapse with cells in the dorsal horn of the spinal cord (Figure 1). Dorsal horn neuronal output is dependent on input from afferent nerves but also on the activity of other neuronal systems on the synapse. Some afferent neurons divide before entering the cord and send branches caudad and cephalad in the longitudinal tract of Lissauer before synapsing with a dorsal horn neuron (Figure 2). Therefore, several dorsal horn neurones may be innervated by a single C-fibre afferent.
Cross section of the spinal cord showing the 10 anatomically and physiologically distinct layers termed Rexed laminae and the longitudinal tract of Lissauer.

**Neurotransmitters**

The cell bodies of afferent neurones produce excitatory neurotransmitters which are transported to the nerve terminal in the spinal cord. These include the neuropeptides substance P, neurokinins (NK1 & 2), calcitonin gene-related peptide (CGRP), cholecystokinin (CCK), vasoactive intestinal peptide (VIP), and somatostatin, gamma-aminobutyric acid (GABA) and serotonin (Kidd & Urban 2001). Excitatory amino acids released include glutamate, N-methyl D-aspartate (NMDA) and α-amino-3-hydroxy-5-methylisoxazole (AMPA). Receptors for the above neurotransmitters are located presynaptically and postsynaptically. Glutamate acting on AMPA receptors mediates spinal responses to non-tissue damaging noxious stimuli (Dickenson & Sullivan 1987). NMDA receptors are also sensitive to glutamate and respond to stimuli...
associated with tissue damage (Dickenson & Sullivan 1987). Activation of this receptor leads to a sequence of events leading to increased excitability of dorsal horn neurones. The NMDA receptor channel is “blocked” by a magnesium (Mg$^{2+}$) “plug”. Depolarisation of the neuron displaces the magnesium plug from the NMDA receptor and subsequent calcium reflux into the cell (Woolf & Costigan 1999). Greater stimulus intensity is associated with the release of neuropeptides, including substance P from central terminals of C fibres. Acting via neurokinin receptors located on dorsal horn neurones, substance P generates a greater post-synaptic response and enhances the activity of NMDA receptors. By the activation of protein C, which phosphorylates the NMDA receptor, it increases its responsiveness to subsequent stimuli (Thompson et al 1994).

**Newly described ion-channel-linked receptors**

Recently a series of ion-channel linked receptors has been described, related to the sensory transduction of noxious stimuli. These include heat-activated vanilloid receptors and others, sensitive to protons and products of purine metabolism. Vanilliod receptors (VR-1) can be characterized by their sensitivity to capsaicin, the active ingredient in spicy ‘hot’ foods. This receptor has been isolated in sensory neurones and is known to be a ligand-gated, non-selective cation channel (Caterina et al 1997) which belongs to a family of receptors that also includes the vanilloid receptor-like protein (VRL-1) and the stretch-inactivated channel (SIC). As well as being sensitive to capsaicin, VR-1 responds to moderate stimuli (approximately 43°), suggesting a heat-transduction role for this receptor. VRL-1 is insensitive to capsaicin but is activated by higher temperatures with a threshold of approximately 52°C (Caterina et al 1999). VR-1 also responds to protons, suggesting that its activity may be enhanced within the acidic environment of inflamed tissues (Nagy et al 1999). Another ligand is thought to be the cannabinoid ligand anandamide (Zygmunt et al 1999).
There are also receptors occurring widely throughout the nervous system which respond to a low pH with the acid-sensing ion-channel (ASIC) receptor subtype being most closely associated with the dorsal root ganglion (Waldmann R et al 1997). P2X purinoreceptors are inotropic ligand-gated ion channels mediating fast synaptic transmission by extracellular adenosine triphosphate (ATP) (Burnstock G 1996). This receptor is expressed selectively in small diameter neurones that label with lectin IB4 (see above), suggesting that it plays a role in nociception.

**Rexed laminae**

In 1952, Rexed proposed the anatomical division of the spinal cord grey matter into 10 regions, or laminae, based on Nissl-stained preparations of the cat spinal cord (Rexed B 1952). The laminae are organized as columns and extend throughout the entire length of the spinal cord. Laminae 1 to 6 and lamina 10 are the sites at which sensory afferents synapse with dorsal horn cells. Laminae 7-9 represent the motor horn. Aδ and C fibres terminate in several layers, including the outer marginal layer (lamina 1) and the substantia gelatinosa (lamina 2).

**Dorsal horn neurones**

In 1966, Mendell proposed a descriptive system of nomenclature (Mendell 1966) for dorsal horn neurones. Some dorsal horn neurones in layers 3,4 and 5 are able to respond to a wide range of inputs including light touch and pain and so are termed “wide dynamic range neurones” (WDR). Their characteristic feature is the phenomenon of “wind-up”, in which the output increases in the presence of a continuous, low-frequency C fibre input and possibly even when the input has stopped (see Section 2.3.1). Another important feature is the convergence of neurones from both the somatic and visceral structures on the same WDR cell. This accounts for the phenomenon of referred pain, in which pain from a visceral source is experienced in a
part of the body innervated by cells that converge on the same dorsal horn neurone. Dorsal horn neurones driven only by nonnoxious stimuli are classified as “low-threshold” (LT) neurones and those driven only by noxious stimuli are classified as “nociceptive specific” (NS) or “high-threshold” (HT) neurones.

**Ascending pain pathways**

Most dorsal horn neurones project to higher centers in the brain by ascending several segments in the spinal cord before crossing over to the opposite ventral side. They then join one of three major spinal systems i.e.

- Spinothalamic tract
- Spinoreticular tract
- Spinomesencephalic tract

Collectively, these are termed the “spinal lemniscus” or the anterolateral fasciculus. These pathways are organized predominantly in the anterolateral white matter of the spinal cord and their involvement in pain transmission has been demonstrated by Willis and colleague (Willis & Coggeshall 1978).

**Spinothalamic tract**

Neurones projecting to the lateral thalamus are concentrated mainly in laminae V and VI, and those projecting to the medial thalamus are concentrated primarily in laminae I and VI to VI (Craig AD et al 1989). These axons project directly to the ventroposterolateral (VPL) thalamus and the medial part of the posterior (VPM) thalamus, where they synapse onto fibres that in turn project to the somatosensory cortex. They also have collaterals that project to the midbrain, pontine and medullary reticular formations, the periaqueductal grey matter, and the hypothalamus where they synapse with neurones that, in turn, project to forebrain limbic
structures. It is a contralaterally organised ascending pathway. The majority of axons composing the spinothalamic tract cross in the ventral white commissure within several segments of their cell bodies of origin (Willis 1986). Two distinct components of the spinal cord are recognized, a dorsolateral and a ventral spinothalamic tract (Apkarian & Hodge 1989). The dorsolateral spinothalamic tract comprises about 25% of the total spinothalamic input and is made up of axons predominantly in lamina I. In contrast, the ventral spinothalamic tract is composed of axons originating in spinal cord laminae IV, V and VII to X (Jones et al 1987). Spinothalamic tract neurones are activated by low-threshold, multireceptive and high-threshold inputs. They can have either excitatory or inhibitory receptive fields. The fields that project to the ventroposterolateral thalamus are small; these neurones may be involved in sensory discriminative aspects of nociceptive processing. In contrast, neurones that project predominantly to the medial thalamus tend to have large whole-body receptive fields; these may be involved in emotional aspects of pain (Willis & Coggeshall 1978).

Spinoreticular tract

This tract is thought to play a role in the alerting and arousal behaviours associated with the pain reaction. It has both ipsilateral and contralateral components. It ascends the spinal cord in the anterolateral quadrant medial to the spinothalamic and spinomesencephalic tracts and projects to many nuclei in the pontine and medullary nuclei (Willis & Coggeshall 1978). Their neurons have been shown to respond to a variety of nociceptive and non-nociceptive peripheral cutaneous and visceral stimuli including non-noxious and noxious mechanical cutaneous stimuli, noxious radiant heat and light tactile stimuli (Fields et al 1977).
Spinomesencephalic tract

Spinomesencephalic neurones have been identified mainly in lamina I and V (Zhang D et al 1990). It is predominantly a contralateral ascending pathway. Those neurones originating in lamina I have been reported to ascend in the contralateral dorsolateral funiculi and axons of spinomesencephalic neurones originating in lamina V ascend in the ventrolateral funiculi (Hylden JLK et al 1986). They terminate in the mesencephalic reticular formation and periaqueductal grey matter. These neurones respond almost exclusively to nociceptive stimuli and probably are involved in behavioural responses to pain.

Descending pathways

It is often noted that injuries sustained during sporting events, or even on the battlefield, are reported as being relatively painless, at least until the event is over. Attention on survival or winning exerts a powerful effect on pain intensity. This is thought to be as a result of activation of descending inhibitory pathways from the brain to the spinal cord. Such pathways arise from discrete centres in the brain and stimulation of these centres produces analgesia. The two most important areas in the brain associated with descending inhibitory pathways are the periaqueductal grey (PAG) in the midbrain and the rostral ventromedial medulla (RVM). The hypothalamus and locus ceruleus are also involved. These have inputs from many areas of the brain in addition to each other (Willis WD 1982). All these contain endogenous opioids and opioid receptors and activation of these receptors increases activity in descending monoamine pathways (serotonin and norepinephrine) that project to the dorsal horn. Many of the strategies available in pain management, such as the use of opioids (systemic and spinal), act via these inhibitory mechanisms. Techniques such as spinal cord stimulation, transcutaneous electrical nerve stimulation and transcutaneous spinal electroanalgesia may work through activation of both ascending and descending inhibitory mechanisms. The Gate Control Theory of Pain
(Melzack & Wall 1965) describes descending inhibitory control “which closes the gate”. This will be described in Chapter 4, Section 1.

2.2 Pathophysiology of Acute Pain

Tissue damage, whether from trauma or surgery, initiates changes in the pain pathway that maintain and even increase the pain experienced by the individual. These changes, which involve a reduction in the threshold for stimulation, occur at the site of tissue damage (peripheral sensitization) and at the dorsal horn of the spinal cord (central sensitization). The nervous system displays the important property of plasticity, i.e. the ability to change, that is responsible for the generation of clinical pain states (Coderre et al 1993).

2.2.1 Peripheral sensitization

Minor injury produces the familiar ‘triple response’ of redness (capillary dilatation), wheal (oedema) and flare (arteriolar dilatation). Histamine is one of the first few substances to be released into the surrounding tissue and is responsible for the wheal. Antidromic conduction in the C neuron releases substance P from nerve endings in the skin. Substance P is believed to act primarily on post capillary venules to produce plasma extravasation, whereas CGRP acts on arterioles to produce vasodilatation (Kidd & Urban 2001).

Depending on the magnitude of the injury, additional inflammatory mediators are released, including ions ($K^+$, $H^+$), bradykinin, histamine, 5-hydroxytryptamine (5-HT), ATP and nitric oxide (NO). There is activation of the arachidonic acid pathway leading to the production of prostaglandins and leukotrienes. Immune cells release further mediators including cytokines
and growth factors. All of these mediators make up what is often referred to as the "inflammatory soup" (Figure 3). These are discussed below.

[Chapter 2].Figure 3

The inflammatory mediators involved in peripheral sensitization. SP, substance P.

Bradykinin

Bradykinin, formed from the precursor kallidin, produces pain, inflammation and hyperalgesia when given experimentally to human subjects (Meller et al 1992). Bradykinin and kallidin,
together with their degradation products des-Arg$^9$ bradykinin and des-Arg$^9$ kallidin, have complex effects on primary afferent neurones, including both activation and sensitization by direct and indirect pathways. Substance P is released following sensitization of nociceptors by bradykinin. Bradykinin B2 receptors, which bind bradykinin and kallidin, are found on both neuronal and non-neuronal cells. The selective B2 receptor antagonist Bradyzide has been shown to block inflammatory hyperalgesia in animal models (Burgess et al 2000). B1 receptor agonists have been shown to produce pain only during inflammation (Burgess et al 2000).

**Cytokines**

In addition to their effects on immune and inflammatory cells, cytokines exert considerable influence over sensory neurones (Kidd & Urban 2001). They act directly on nociceptors or, more commonly, indirectly stimulating the release of prostaglandins. Acutely, they induce sensitization via receptor-associated kinases and phosphorylation of ion channels (Opree & Kress 2000). Injections of pro-inflammatory cytokines including tumour necrosis factor alpha (TNFα), Interleukin –1(IL-1) and IL-6 produces mechanical and thermal hyperalgesia (Kidd & Urban 2001). Anti TNF therapies in rheumatoid arthritis are accompanied by reductions in pain scores (Mani et al 1998).

**Prostaglandins**

Prostaglandins are also important mediators of inflammation, fever and pain. They are synthesized by the enzymes cyclo-oxygenase-1 (COX-1) and COX-2, which are induced in peripheral tissues by cytokines, growth factors and other inflammatory stimuli. The precursor of prostaglandins, arachidonic acid is itself produced following activation of phospholipase A$_2$ by bradykinin. Although they have a direct action on nociceptors, they are generally considered to be sensitizing agents. They increase levels of cyclic-adenosine-monophosphate AMP and
may enhance nociceptor sensitization by reducing the activation threshold for TTX-R sodium channels via a protein kinase A pathway (England et al 1996).

**Growth factors**

Neurotrophic growth factors, including NGF, make significant changes to neurone sensitivity observed during inflammation. A large number of inflammatory mediators act to increase NGF production, particularly IL-1β and TNFα (Woolf et al 1997). Increased levels of NGF have been reported in humans with arthritis, cystitis and asthma (McMahon & Bennett 1999). NGF produces hyperalgesia at its injection site in humans and deep pain which persists for several days. It is thought these effects are mediated directly on nociceptors and indirectly via mediators released by NGF-activated mast cells and other inflammatory cells. It is also known that NGF also regulates the expression of neuropeptides, substance P and CGRP as well as receptors including VR-1 and bradykinin B2. (Levine & Reichling 1999).

**Neurogenic factors**

The nervous system acts in association with the immune and endocrine systems to constitute an interactive, communicative network. Substance P and CGRP are believed to act synergistically. They have a broad spectrum of effects within peripheral tissues and make a significant contribution to the “triple response”. It is also thought that these neuropeptides make indirect contributions to nociceptors during inflammation. Substance P degranulates mast cells to produce histamine release, induces release of the prostaglandin PGE2 and may stimulate the release of cytokines from macrophages (Leib et al 1996).

Some of these mediators activate peripheral nociceptors directly and lead to spontaneous pain, whereas others act indirectly via inflammatory cells to stimulate the release of additional pain-
inducing (algogenic) agents. The effect on the C-afferent terminal of this "inflammatory soup" is one of sensitization and its threshold for stimulation is reduced. After sensitization, low intensity stimuli that normally would not cause pain are perceived as painful. This occurs within the area of the injury (primary hyperalgesia) and in the surrounding uninjured tissue (secondary hyperalgesia) (Raja et al 1988). This change in sensitivity is thought to occur when an inflammatory mediator binds to a receptor on an afferent terminal resulting in an alteration in the afferent's sensitivity by the phosphorylation of a membrane-bound receptor (Rang & Ritchie 1988). Tissue damage and inflammation also result in the expression of opioid receptors in peripheral sites; these receptors may be activated by local release of endogenous opioids (Stein et al 1989). Not only are nociceptors sensitized following injury but the number of nociceptors is increased. This may be because one-third to one-half of the population of nociceptors are in a "dormant" state and are not stimulated unless tissue damage occurs (McMahon & Koltzenburg 1990).

2.2.2 Central sensitization

These changes are too small to account for all the injury-induced alterations in either behaviour or sensibility (Raja et al 1984). Therefore, a central process acting in conjunction with central sensitization can produce the full picture of clinical pain (Woolf CJ 1983). The synapse between the C-afferent neurone and the dorsal horn cell does not simply relay information from one cell to the other. It allows modulation of the afferent input, so that activity in the dorsal horn may be increased or decreased depending on the activity of other systems acting on the synapse. Information via high-threshold afferents overwhelms tonic inhibitory mechanisms and triggers long lasting changes in dorsal horn receptive fields. This phenomena is termed "central sensitization" and is characterized by facilitated activation of nociceptor specific spinothalamic
neurones by non-noxious sensory inputs conveyed via low-threshold afferent fibres. There is an exaggerated response of the dorsal horn cell, not only to C-fibre input, but also to Aβ input. Clinical manifestations of pain associated with central sensitization and secondary hyperalgesia include increased pain intensity, allodynia, prolonged facilitation of ipsilateral and contralateral flexion reflexes and alterations in regional sympathetic tone (Woolf CJ 1989a). The pain is therefore perceived at many dermatomes above and below the site of trauma and this is worsened by ambulation or movement of the injured region. "Wind-up" occurs, that is increasing output from the wide dynamic range neurons in the presence of a continuous, low-frequency C fibre input (Mendell LM 1984). Neurotransmitters involved in producing the long-lasting changes in spinal excitability are glutamate, substance P and brain-derived neurotrophic factor (BDNF) (King et al 1988). Increased release of peptide transmitters from primary afferent fibres activates second messenger systems and results in increased influx of Ca^2+ ions and phosphorylation of proteins (Woolf & Costigan 1999). The net result is that the responsiveness of the dorsal horn cells is increased, leading to exaggerated responses to normal stimuli, expansion of receptive field size and reduction in the threshold for activation by new inputs (e.g. Aβ fibres). Central sensitisation appears to be caused by NMDA receptor activation and experimentally induced wind-up can be prevented by NMDA antagonists such as ketamine (Kidd & Urban 2001). Prostaglandins and nitric oxide facilitate spinal excitability, α-2 adrenergic and opioid receptor agonists produce analgesia by presynaptic inhibition of C fibre neurotransmitter release (Besson JM 1999). It also appears that Aβ sensitization is mediated via inhibition of pathways that use GABA. GABA is an inhibitory neurotransmitter and a reduction in the inhibitory pathways produces an indirect increase of activity in excitatory pathways.
2.2.3 Neuroendocrine responses

After extensive tissue injury, there is also what is known as the “stress response to injury.” This is characterized by an increased secretion of catabolic hormones (cortisol, glucagon, growth hormone and catecholamines) and inhibition of anabolic mediators, insulin and testosterone (Chernow B 1987). This leads to hyperglycaemia, protein breakdown and increased lipid turnover. However, when prolonged, these catabolic effects may have an adverse outcome leading to muscle wasting and impaired immunocompetence and decreased resistance to infection. Hume and Egdahl were among the first to propose that nociceptive impulses (travelling up the spinal cord via the midbrain reticular formation), were capable of activating hypothalamic centres and initiating the neuroendocrine stress response (Hume & Egdahl 1959). Plasma endorphin concentrations are also known to increase threefold after surgical incision and remain elevated well into the postoperative period (Levy et al 1986).

2.2.4 Sympathoadrenal responses

Responses mediated by the sympathetic nervous system constitute the classic “fight or flight” reaction, which protects the organism from a variety of adverse conditions (Cousins MJ 1989). After an injury, nociceptive impulses stimulate sympathetic preganglionic neurones in the anterior lateral horn. These cells initiate a variety of stimulatory effects including increased cardiac inotropic and chronotropic activity, a pronounced increase in peripheral vascular resistance and a redistribution of blood flow away from viscera to heart and brain. Although such adaptive responses act to maintain blood pressure and cardiac output, a prolonged duration of heightened sympathetic activity may initiate many pathophysiological changes, including altered regional perfusion, altered function of vital organs, activation of the rennin angiotensin
system, increased platelet activation and reflex efferent hyperactivity which, if they persist, will have a deleterious effect on the patient (Ellis et al 1991).

2.3 Pathophysiology of Chronic Pain

As with acute pain, pain perception in chronic pain begins with activation of peripheral nociceptors and conduction through myelinated Aδ and unmyelinated C fibres to the dorsal root ganglion. From here, signals travel via the spinothalamic tract to the thalamus and the somatosensory cortex. Modulation of the sensory input (i.e. pain) can occur at many levels. Peripheral sensitization i.e. a reduction in the threshold for stimulation at the periphery may play a role in chronic pain, particularly after nerve injury.

2.3.1 Wind-up

Expansion of the receptive field that occurs with central sensitization and the development of "wind-up" is one of the features that leads to the development of chronic pain. Within a narrow frequency range of C fibre input, the wide dynamic range neurones do not respond with a fixed frequency output but rather by producing an output whose frequency progressively increases (Figure 4). Sensitization in the dorsal horn results in an exaggerated response, not only to C fibre input, but also to Aβ input. A few days after the original injury, conditioning in afferent C fibres can induce prolonged stability in a now expanded receptive field. This can lead to ongoing alterations in the nociceptor-specific stimulation of certain neurones to include non-nociceptive stimuli, causing allodynia and sympathetic-maintained states (Section 4.2). This process may be the basis of chronic pain development and highlights the importance of early institution of anti-nociceptive therapy.
After peripheral nerve injury, it has been demonstrated that the terminals of myelinated afferents sprout in neighbouring regions of the dorsal horn. If contact is made between these terminals that normally transmit non-noxious information and neurones that normally receive nociceptive input, this may provide a framework for the pain and hypersensitivity to light touch that is seen after nerve injury (Woolf et al 1992).

Factors such as arousal, attention and emotional stress can alter the response to pain by involving CNS mechanisms. A network linking the hypothalamus with the brain stem has been described which is sensitive to opioids, influences dorsal horn neurones and triggers

![Diagram showing frequency in the WDR neurone](image)

Each tick represents a separate impulse arriving at the dorsal horn in a C-afferent neurone

[Chapter 2],[Figure 4]

Phenomenon of wind-up. WDR neurones respond by producing an output whose frequency progressively increases.
their ascending nociceptive transmissions (Hagbarth & Kerr 1954, Carpenter et al 1965). Stimulation of specific brain areas inhibits incoming noxious nociceptive afferents and results in analgesia. Impulses from the frontal cortex synapse with cells in the periaqueductal grey matter can modulate ascending painful transmission, similarly impulses from the ventromedial medulla (Reichling & Baushaun 1990).

Specific genes in the nucleus of the neurone code neuropeptides. Genes transcribe messenger RNA (mRNA) and translates to protein precursors of active neuropeptides. C-fos and C-jun are proto-oncogenes (Morgan & Curran 1989). These proteins are transcriptional factors that regulate the expression of a host of other genes. Fos protein may serve as a “third messenger” by signaling short-term neurological events into long-term potentiation (e.g. acute to chronic pain). It is known that stimulation of certain areas of the medulla significantly reduces noxious-stimulus-evoked fos-protein expression (Jones & Light 1990). NMDA antagonists are known to block wind-up and c-fos expression, it is possible that these are two areas of nociception modulation at the level of the spinal cord (Bashbaum et al 1992). The mechanism of central sensitization can be studied by monitoring fos-protein expression in dorsal horn neurons.

Chronic compression of dorsal roots or peripheral nerves (carpel tunnel syndrome or herniated intervertebral discs) causes pain by a marked increase in their mechanosensitivity (Markenson JA 1996). Chronic compression of a nerve root causes repetitive firing of that root which is caused by low threshold mechanical pressure (Nordin et al 1984, Howe et al 1977). Phantom limb pain, causalgia and some peripheral nerve injuries are thought to be caused by loss of inhibitory control (Markenson JA 1996). The brain stem reticular formation is thought to exert tonic inhibitory influences on transmission at all synaptic levels. However, this depends on
normal sensory input. Loss of normal sensory input that occurs after amputation, peripheral nerve lesions and emotional stress impairs this mechanism and leads to increased pain.

Psychological behaviour (personality, mood, attitude) and social factors (family, work, culture) contribute to the perception of chronic pain. A higher level of hypochondria has been found in patients with musculoskeletal disorders with chronic pain, compared with those without (Sternback RA 1981). Characteristics reported in patients with chronic pain include sleep disturbance, appetite changes, increased irritability and reduced pain tolerance (Sternbach & Timmermans 1975). It is thought that these characteristics may involve depletion of serotonin and endorphins. Data and clinical experience indicate that the longer the duration of chronic pain, the greater the psychological, emotional and behavioural changes (Gamsa A 1990).

2.4 Pathophysiology of Neuropathic Pain

As defined in Section 1.2, Chapter 1, neuropathic pain is pain initiated or caused by a primary lesion or dysfunction in the nervous system and has been described in about 1% of the population. Some patients investigated in this thesis suffered from neuropathic pain (Chapter 10). Neuropathic pain can have a number of causes i.e. metabolic (e.g. diabetes mellitus), traumatic (e.g. nerve injury, amputation), infection (e.g. postherpetic neuralgia, HIV-associated neuralgia), infarct (e.g. stroke) or idiopathic.

2.4.1 Symptoms of neuropathic pain

The symptoms of neuropathic pain can be extremely debilitating. Many patients exhibit persistent continuous or paroxysmal pain that is independent of a stimulus. This stimulus independent pain can be shooting, lancinating or burning and may depend on activity in the
sympathetic nervous system. Spontaneous activity in nociceptor fibres is thought to be responsible for persistent burning pain and the sensitization of dorsal horn neurones. Similarly, spontaneous activity in large myelinated A fibres (which normally signal innocuous sensations) is thought to be related to stimulus-independent parasthesias and, after central sensitization, to dysaesthesias and pain (Woolf & Mannion 1999). The common component of peripheral nerve injury damage is stimulus-evoked pain and has two key features: hyperalgesia and allodynia. Stimulus-evoked hyperalgesias are commonly classified into subgroups on the basis of modality i.e. mechanical, thermal or chemical. Mechanical hyperalgesias are further classified as brush-evoked (dynamic), pressure evoked (static) and punctate hyperalgesias.

Both central and peripheral pain-related phenomena have been associated with peripheral nerve injury. It appears that any one of these (or more likely a combination) may contribute to the symptomatology in individual patients suffering from neuropathic pain. Because of this, it is thought that the management of neuropathic pain is more suited towards a mechanistic as opposed to a disease based approach (Woolf & Mannion 1999).

2.4.2 Peripheral mechanisms

In pathological states, A\(\beta\) fibres play a significant role in the transmission of painful stimuli and maintenance of allodynia. This happens by the process of peripheral sensitisation (as described in Section 2.3.1) and is associated with the release of inflammatory mediators. The end result is chemical sensitization of high-threshold nociceptors and the transmission of low-intensity painful stimuli. It is characterized by an increased responsiveness to thermal and mechanical stimuli at the site of injury or the zone of “primary hyperalgesia”. Demyelination may occur, leading to the production of ectopic impulses that discharge along the nerve fibre
length (Siddall & Cousins 1997). Ectopic signals provide sustained afferent input from the damaged nerve to the spinal cord. These can persist long after the triggering stimulus has subsided and are believed to play a role in the initiation and maintenance of neuropathic pain (Bridges et al 2001). Ectopic discharges may also arise from a neuroma (swelling at the proximal end of the injured nerve). A small number of A-fibres are known to exhibit membrane oscillations in their resting state (Liu et al 1999). Following nerve injury, an increase in oscillations of both A and C fibres has also been seen (Amir et al 1999). This increase in oscillatory behaviour leads to an increase in ectopic firing as the oscillations reach threshold and there is “cross-excitation” of other neurones. This is called ephaptic conduction or “cross talk” of other neurones and also contributes to an increase in ectopic firing (Bridges D et al 2001). It is now known that two populations of afferent nerve fibres develop ectopic activity following nerve injury, the injured sensory neurone and its uninjured neighbour (Gold MS 2000).

An abnormally high number of sodium channels are found in the area around neuroma formation. There are two main types (see Section 2.1.3) i.e. TTX-sensitive and TTX-resistant. TTX-sensitive sodium channels are expressed throughout the CNS and predominantly in A-fibres within the DRG. TTX resistant sodium channels are only found in C fibres in the dorsal root ganglion. Following nerve injury, there is a reorganization of the nature and levels of expression of the various channels, which consists of an upregulation of Type III TTX-sensitive channel and a down regulation of TTX-resistant channels (Waxmann et al 1994). This leads to sodium channel-induced hyperexcitibility and is likely to manifest itself as an increase in ectopic firing.
Calcium channels have also been shown to influence the generation of hyperalgesia and allodynia (Bridges et al 2001). Calcium channel antagonists have been shown to reduce heat hyperalgesia and mechanical allodynia when administered directly to the site of nerve injury (Xiao et Bennett 1995). There is a loss of high-voltage activated N-type Ca^{2+} channels, which increases the excitability of the neurones. The anticonvulsant gabapentin has been found to inhibit monoamine neurotransmitter release, possibly through its interaction with Ca^{2+} channels (Taylor et al 1998).

Sprouting of collateral fibres from sensory axons into skin in denervated areas has been described following nerve injuries (Devor et al 1979). This effect appears to be blocked by nerve growth factor.

Changes in the sympathetic nervous system may also occur as a result of peripheral nerve injury and it is this which is thought to contribute to sympathetically-maintained pain. Abnormal contact develops between the sympathetic nervous system and the sensory nervous system in a number of ways. There is direct chemical coupling at the periphery between the noradrenergic and sensory neurone terminals. Indirect coupling via a peripheral sensitising mechanism, involving the release of inflammatory mediators from sympathetic terminals and the sensitisation of primary sensory neurone axons also occurs. Finally, there is sprouting of noradrenergic neurons into the dorsal root ganglion forming basket like structures around sensory neurones (McLachlan et al 1993). It is thought that nerve growth factor has a role to play in the mechanism of sprouting (Isaacson et al 1992).
An increase in bradykinin has also been demonstrated following nerve injury in animal studies, associated with the symptom of hyperalgesia (Petersen et al 1998). This may suggest that bradykinin antagonists may have role to play in the treatment of neuropathic pain.

2.4.3 Central mechanisms

Spinal cord-anatomical re-organisation

A considerable degree of re-organisation of the spinal cord occurs in response to peripheral nerve injury. As mentioned earlier, Aβ fibres sprout into the more superficial laminae I and II of the spinal cord. The consequence of this is that second order neurones within the spinal cord begin to receive inputs from low-threshold mechanoreceptors. Low threshold information may be interpreted as nociceptive, providing another explanation for the emergence of allodynia after peripheral nerve injury.

Spinal cord-hyperexcitability

The dorsal horn neurones develop into a state of sustained hyperexcitability, a process called "central sensitization". This has been described earlier and is characterized by the appearance of "wind-up" (Bridges et al 2001). Neurotransmitters such as substance P, glutamate, CGRP, GABA and neurokinin appear to play a role in central sensitization. Removal of the Mg²⁺ dependent ion channel block and receptor phosphorylation are important steps in "activating" the NMDA receptor so that glutamate is able to exert its effects. There is evidence to suggest that NMDA antagonists may have a role in attenuating neuropathic pain (Rabben et al 1999). The flux of Ca²⁺ ions in the cell is important to the maintenance of central sensitisation. Acting as second messengers, they lead to the activation of protein kinase C, phospholipase C, NO
synthetase and induction of early gene expression (McFarlane et al 1997). The GABA pathway forms a major inhibitory neurotransmitter system in the CNS. Suppression of this pathway by the GABA_A receptor antagonist bicuculline is associated with dose-dependent allodynia (Yaksh TL 1989) and GABA levels in the spinal cord are decreased within 2 weeks of sciatic nerve axotomy. A separate inhibitory pathway in the CNS is that of the purinergic system, specifically adenosine. Adenosine exhibits both pre- and post-synaptic actions (Bridges et al 2001). A significant decrease in blood and CSF adenosine concentrations has been demonstrated in neuropathic pain patients (Guieu et al 1996). Therefore the role of adenosine in modulating the development of neuropathic pain is a possibility.

In summary, there is evidence that a combination of increased activity in the excitatory and decreased in inhibitory systems within the spinal cord both contribute to the phenomenon of central sensitisation after peripheral nerve injury and the development of neuropathic pain.

2.5 Summary

There has now been a shift away from the conceptualization of pain as a simple "hard-wired" system with a "pure stimulus" response relationship. It has been shown that pain and its perception is a complex system starting from the peripheral nociceptor with the impulse passing through the spinal cord to the brain. The signal is subject to significant modulation at different sites along this pathway and also from descending inhibitory control. Long-term changes occur after noxious input and this "plasticity" of the nervous system alters the body's response to further peripheral stimuli. The different mechanisms of modulation have been described. Furthermore the different pathophysiological processes that occur after tissue damage result in a stimulus-response pattern that is quite different from that seen after
physiological pain. These pathophysiological processes have been reviewed in relation to acute, chronic and neuropathic pain.
# Chapter 3

## Management of Acute and Chronic Pain

### 3.1 Management of Acute Pain

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It is beyond the scope of this chapter to review both the management of acute and chronic pain in any great detail. I have included it because it is necessary in order to put the use of electrical methods of pain relief in context. It is well known that they are not a mainstream method of relieving both acute and chronic pain, yet they are used. In this chapter, I will therefore outline the main methods in the relief of both acute and chronic pain and also include where electrical therapies fit with these techniques.

3.1 Management of Acute Pain

3.1.1 Background and approach to the management of acute pain

The basic principle in the treatment of acute pain is to alleviate distress, provide comfort for the patient to expedite their recovery. Studies have shown that acute pain may rapidly evolve into chronic pain if it is not treated promptly (Carr & Goudas 1999). For example, meticulous perioperative analgesia for radical prostatectomy has been shown to lower the analgesic requirement and improves functional status for months afterwards (Carr DB 1998). These observations and others indicate that the biological and psychological foundation for long-term persistent pain is in place within hours of injury (Niv & Devor 1998). New ways to control pain include novel or rediscovered molecules, delivery schedules superior to as-needed administration, and drug delivery targeted to peripheral sites of injury or central nociceptive pathways, chiefly the spinal cord (Ballantyne et al 1998). Combinations of drugs are increasingly used to control pain.

Acute pain should therefore be viewed as the initiation phase of an extensive, persistent nociceptive and behavioural cascade triggered by tissue injury (Carr & Cousins 1998). This
cascade has the potential to span orders of magnitude of space and time but generally subsides within weeks. An individual’s response for months after transient injury may be determined by processes that occur within the first day. Therefore, small differences in the initial state of the patient and the intensity, quality and meaning of the nociceptive stimulus can produce major differences in the manner in which it unfolds (Carr & Goudas 1999). Other methods besides pharmacological have been shown to be successful in the management of acute pain. Kehlet has shown a dramatically shortened length of hospital stay after surgery through the use of a multidisciplinary approach which includes perioperative rehabilitation, preoperative explanation, minimization of intraoperative stress, aggressive mobilization and early feeding (Kehlet H 1997). Untreated acute pain can lead to significant complications that can prolong a patient’s hospital stay. These include decreased respiratory movement and the inability to cough, thereby promoting atelectasis and infection. Decreased mobility due to pain increases the risk of thromboembolic complications. Increased levels of catecholamines in the postoperative period leads to an increase in systemic vascular resistance, increased cardiac work and oxygen consumption, particularly harmful to the patient with ischaemic heart disease.

Two other techniques are also used in the management of acute pain, that is preemptive analgesia and a balanced anaesthetic approach (Kehlet & Dahl 1993). Preemptive analgesia is administered prior to a painful stimulus, to prevent or reduce pain afterwards. However, studies looking at the effectiveness of preemptive analgesia with opioids, local anaesthetics and nonsteroidal anti-inflammatory drugs (NSAIDs) have been inconclusive in humans (Aida et al 1999, Yashpal et al 1996). For major surgery, an effective approach of balanced anaesthesia is one that utilizes both an opioid and a local anesthetic agent in epidural analgesia. This technique is widely used. Most patients should also receive an NSAID as part of a balanced
analgesia technique but preoperative administration of NSAIDs should be used with caution since they can increase bleeding time and delay coagulation (Pogliani et al 1992).

In discussing an approach to acute pain management, I will start by discussing the pharmacology of the drugs initially and then modes of delivery.

### 3.1.2 Opioids

These analgesics are the mainstay of the pharmacological management of moderate to severe postoperative pain. They act on injured tissue to reduce inflammation, in the dorsal horn to impede transmission of nociception and supraspinally to activate inhibitory pathways that descend to the spinal segment (Carr & Goudas 1999). They produce their effect by acting on specific opioid receptors i.e. μ, δ and κ receptors (the latest guidelines from the International Union of Pharmacology (IUPHAR) recommend that opioid receptors initially are referred to as MOP, DOP and KOP and thereafter by their Greek terminology (Cox et al 2001)). Based on their effects on opioid receptors, opioid drugs may be agonists, antagonists, partial agonists or agonist-antagonists.

Morphine is the agent most commonly but not exclusively used in acute postoperative pain. Intravenous patient controlled analgesia systems (PCAS) are available in most hospitals for postoperative pain. Some hospitals offer patient-controlled epidural analgesia. A recent review of the efficacy and safety of patient-control opioid analgesia for acute pain demonstrated improved analgesia, decreased risk of pulmonary complications and higher patient preference compared with conventional opioids (intramuscular, intravenously and subcutaneously), (Walder et al 2001). It is an effective way to deliver analgesia in patients with moderate to severe acute pain who cannot take oral medication. However, the success of these methods
depends on adequate staff training and careful monitoring by an acute pain team (Section 3.1.10).

Opioids can be given by numerous other routes also including intranasal, transbuccal, subcutaneous, intramuscular and rectally (Lambert DG 1998). Intraoperative infusions of short-acting opioids such as alfentanil and remifentanyl have demonstrated good analgesic profile (Burkle et al 1996, Schuttler et al 1996) and may be continued at reduced rates for postoperative analgesia. This should only be done however, in the presence of adequate staffing and patient monitoring. In practice, patients are more commonly switched to less resource demanding modes of postoperative analgesia, namely (PCAS). All opioid infusions need to be titrated carefully and even so can produce side-effects such as nausea or respiratory depression. Intrathecal and epidural routes are widely used to provide sustained postoperative analgesia, often in combination with local anaesthetics (Lowry et al 2001, Dahl et al 1999). Combinations of systemic opioids and NSAIDs are widely used and effective (McQuay & Moore 1998, Smith et al 2000). Partial agonists at the \( \mu \) receptor (tramadol, buprenorphine) do not provide better analgesia than morphine but may produce fewer respiratory, gastrointestinal or urinary difficulties. Cloning of \( \mu, \delta, \kappa \) receptors has stimulated clinical trials of receptor-selective opioids which show less dependence that \( \mu \) agonists but also less analgesic effect (Lambert DG 1998). Intra-articular dosing after knee arthroscopy is often used since it is known that opioids also have a peripheral effect (Carr & Goudas 1999). A recent review of intrarticular administered morphine demonstrated a definite but mild analgesic effect which appears to be dose dependent (Gupta et al 2001). The problems of tolerance, dependence and addiction are associated with prolonged opioid use and generally do not become an issue when treating patients in the acute situation.
3.1.3 Local anaesthetic agents

These agents (lidocaine, bupivacaine, laevo-bupivicaine and ropivacaine most commonly) are used widely in the management of acute pain. Topical application of lidocaine alone or with prilocaine produces cutaneous anaesthesia (Sinclair et al 1988). Their use in simple techniques such as field infiltration, digital nerve block, trigger point injection is common where they have been shown to be both pain reducing and opioid sparing (Tverskoy et al 1990, Moss et al 1986). They can also be used in more complex blocks, e.g. intercostal, ankle, and brachial plexus blocks, which should be performed by a suitably trained individual. Their relatively short duration of action limits their analgesic effect unless infusions are used. Similarly spinal administration of local anaesthetics is effective for control of pain after surgery or trauma, but requires expertise and infrastructure to administer and monitor properly postoperatively (Kathirvel et al 2000). Local anaesthetics can be used intrathecally or epidurally in association with opioids, adrenergic agents and NMDA receptor antagonists. However, there must always be adequate provision made for monitoring of these patients postoperatively. The amide local anaesthetics also appear to have a long-lasting anti-inflammatory effect, thereby blocking the postoperative inflammatory process on the surgical site (Lisander B 1996). Single enantiomer local anaesthetics such as ropivacaine or laevobupivicaine, are now currently available and appear to be associated with decreased cardiotoxic potential.

3.1.4 Nonsteroidal Anti-Inflammatory Drugs

NSAIDs act by inhibiting cyclooxygenase in the spinal cord and periphery (thereby decreasing the amount of prostaglandin and leukotriene production) thus diminishing postinjury hyperalgesia (McCormack K 1994). They are suitable for mild to moderate pain, after day case surgery and as an adjunctive agent with opioid use following major surgery (McQuay & Moore
1998) where they have been shown to have opioid sparing effects (Dahl & Reader 2000). They can be administered orally, rectally, topically and intra muscularly. Intravenous dosage options are limited, mainly ketorolac and tenoxicam. However the use of NSAIDs is limited by contraindications and potentially severe side effects. Gastric bleeding is a well known complication of NSAIDs (Elliott DP1990). Renal impairment is another risk particularly in hypovolaemic patients and patients with known kidney failure and congestive heart failure. 8-20% of patients with asthma will experience bronchospasm after using NSAIDs (Sturtevant J 1999).

It is now known that the cyclo-oxygenase enzyme exists as at least two different isoenzymes, the COX-1 and COX-2 enzyme (Hawkey CJ 1999). It is thought that the therapeutic activity of NSAIDs is primarily due to the inhibition of COX-2, whereas toxicity results from the inhibition of COX-1 (Hawkey CJ 1999). Selective COX-2 specific agents are now currently available and there is evidence to show that these agents lack the side effects of gastric ulceration and inhibition of platelet function (Warner et al 1999, Reuben & Connelly 2000). Both rofecoxib and celcoxib demonstrate morphine sparing effects and the analgesic effect appears to be longer lasting with rofecoxib (Reuben & Connolly 2000). NSAIDs, despite their side effects, are very useful in the management of postoperative pain particularly following gynaecological and orthopaedic surgery. They are generally well tolerated as long as the drug is used in appropriate doses and contraindications are respected. (Dahl & Raeder 2000).

3.1.5 Paracetamol

Paracetamol is a well-established drug for use in the postoperative period, and it is widely used. Given as a single dose of 1000mg, it has a number needed to treat (NNT) of 3.6 against placebo
in postoperative pain, which is better than tramadol 100mg or the combination of acetylsalicylic acid 650mg and codeine 60mg (Moore et al 1997). It probably has less analgesic potency compared to NSAIDs but seems to have an additional analgesic effect when given in combination (Dahl & Raeder 2000, Montgomery et al 1996). It is also morphine sparing (Montgomery et al 1996, Cobby et al 1999). When compared with oral paracetamol, rectal paracetamol has a somewhat slower onset of action with a maximum serum concentration at 2-2.5 hrs as compared with 0.6 hr for tablets. This should be taken into account when suppositories are used for postoperative pain treatment and the dosage should exceed the oral dose by 50%. Recently an intravenous precursor has been developed, propacetamol. One gram of the precursor converts to 0.5 g paracetamol. From a practical point of view, it is important to remember that the therapeutic window of paracetamol is very low and even slight amounts of paracetamol overdosage can result in significant liver damage.

3.1.6 Adrenergic agents

The use of adrenergic agents as analgesics were initially investigated about 15 yrs ago as a result of a growing interest in spinal analgesia (Carr & Goudas 1999). These drugs have sedative, anxiolytic, analgesic and haemodynamic properties. Alpha-2 receptors are located on primary afferent nerve terminals (centrally and in the periphery), the superficial laminae of the spinal cord and within several brainstem nuclei involved in analgesia (Johansson P 1984). Clonidine is an α2 agonist that at high doses has α1 receptor stimulation effects. The more selective α2 agonist dexmedetomidine produces analgesia and sedation when given systemically or intrathecally.

There have been extensive reports in clinical trials of analgesia after systemic, epidural, or intrathecal administration of clonidine (Goudas LC 1995). Epidural administration of clonidine
has been shown to produce 50% reduction in opioid requirement (Dahl & Raeder 2000). Clonidine will enhance and prolong the effect of local anaesthesia intrathecally (Racle et al 1987). However, its analgesia is shortlived after single doses and may be accompanied by side-effects of sedation, bradycardia and hypotension. The use of larger doses of clonidine as an analgesic is limited by its sedative / anaesthetic properties. Perioperative, as well as postoperative administration of clonidine may decrease oxygen consumption and episodes of shivering during recovery from anaesthesia (Quintin et al 1991).

3.1.7 Psychological methods
Optimum control of pain lessens psychological injury after an operation or trauma. Also psychological resilience and good preoperative preparation make it easier to control pain (Carr & Goudas 1999). High levels of stress, anxiety or pessimism in preoperative patients predict poor outcomes in measures that range from speed of wound healing to duration of hospital stay (Gibson HB 1994). A number of studies indicate that pre-emptive cognitive and behavioural interventions in unselected groups of patients decrease anxiety before and after surgery, reduce postoperative pain intensity and intake of analgesic drugs, improve treatment compliance, cardiovascular and respiratory indices and accelerate recovery (Kiecolt-Glaser et al 1998). Despite the evidence to show that cognitive-behavioural methods to help patients cope with acute pain and anxiety are cost-effective, the pressure of short-term cost savings has eroded the resources to support this approach.

3.1.8 Non-pharmacological therapies for acute pain
The following techniques will not suffice as the only analgesic therapy in the postoperative setting. Furthermore, they each require a period of assessment of anticipated efficacy and training, which is not always feasible in the acute postoperative or postinjury setting. The
techniques include Transcutaneous Electrical Nerve Stimulation (TENS) (Hamza et al 1999b), Acupuncture (Kotani et al 2001), Relaxation and Hypnosis (Good et al 2001) and Physiotherapy (Ostelo et al 2000). TENS (reviewed in Chapter 4, Section 4.2) has been shown to have only limited efficacy postoperatively (McQuay et al 1997). Acupuncture has been shown to have been beneficial not only on analgesia but on the reduction of postoperative nausea and vomiting (Kotani et al 2001).

3.1.9 Potential agents of the future

The next few drugs outlined are either used less frequently because of adverse effects or are possible agents of the future. These include NMDA receptor antagonists, neostigmine and cannabinoids.

NMDA receptor antagonists

Several sites on the NMDA receptor complex, activated by the excitatory amino acid glutamate, are analgesic targets (Woolf et al 1998). It is known that ketamine blocks the open calcium channel within this complex. This has prompted renewed interest in the use of this substance perioperatively and also for neuropathic pain (Woolf et al 1998). It is thought that after surgery, the response characteristics of neurones in the dorsal horn are altered and may influence the perception of postoperative pain (Woolf & King 1990). However, the adverse effects of these agents (undesirable psychic emergence effects and cardiovascular stimulating properties) may limit their use. A recent review suggests that low-dose ketamine may play an important role in postoperative pain management when used in conjunction with local anaesthetics, opioids, or other analgesic agents (Schmid et al 1999). Further research is needed for dose-finding studies with the use of ketamine as an adjunct to opioids and local anaesthetics, it's efficacy, optimal route of administration, spinal toxicity and its effects on
cognitive and memory functioning after surgery (Schmid et al 1999). Other compounds are known to target the same site as ketamine e.g. dextromethorphan and are thought to have better specificity and affinity for the NMDA receptor (Dahl & Raeder 2000).

Neostigmine

Neostigmine has been administered intrathecally in animals and been shown to produce analgesia (Naguib & Yaksh 1994). This analgesic effect can be reversed by a muscarinic antagonist. However, it has troublesome postoperative side effects namely nausea and vomiting. Lauretti and colleagues have also demonstrated a dose-independent analgesic effect of intrathecal neostigmine at doses of 1-4 μg/kg without any side effects after minor orthopaedic procedures (Lauretti et al 2000). However, it must be remembered that the use of neostigmine intrathecally as an analgesic is only experimental and only further studies will reveal its usefulness.

Cannabinoids

Cannabis has been used for thousands of years and is popular in recreational use for its psychoactive properties. It has also been used as a therapeutic agent against emesis, pain and loss of appetite. Two cannabinoid receptors have been identified (CB1- in the brain and CB2 in peripheral tissues including peripheral nerve terminals and spleen), (Hirst et al 1998). There is growing evidence for a potential therapeutic use of synthetic cannabinoid receptor agonists postoperatively and a number are under investigation (Hart et al 2001).

3.1.10 Acute pain teams

It is now becoming increasingly clear that if postoperative analgesia is to be improved on surgical wards, techniques such as PCAS, epidural analgesia and regional blocks have to be used on a regular basis. They provide superior analgesia to intramuscular opioids but have their
own risks and therefore require special monitoring. With these techniques, it is relatively easier to provide better analgesia, but there has to be a balance between acceptable risk, perceived benefit and cost-effectiveness. National interdisciplinary expert committee reports from the UK and the IASP have recommended the establishment of acute pain services (APS) based on a team approach (anaesthetists, surgeons, nurses) to improve pain management (RCS, RCA 1990, IASP1992) An acute pain nurse (APN) provides an effective link between the three disciplines. Another critical element to improving pain management is the development of protocols and training of ward nurses.

3.2 Management of Chronic Pain

3.2.1 Epidemiology

Epidemiological studies have shown that chronic pain is a major public health problem (Crombie et al 1998). In addition to the suffering of patients, enormous medical and social resources are spent on these patients (Latham & Davis 1994). This has led to increasing demands for effectiveness of therapy during the past decades and multidisciplinary treatment principles for chronic non-malignant pain have received increasing attention.

Relevant data to the UK was published recently (Elliot et al 1999). A random sample of 5000 patients in the Grampian region was investigated. The equivalent of 50.4% of the population reported chronic pain (defined as “pain or discomfort that persisted continuously or intermittently for longer than 3 months”). The pain in 15.8% of these patients was graded as “high disability, severely limiting”. In a measure of demand for, and uptake of, health-service resources, it was reported that 28% of those with chronic pain expressed a high degree of need (defined as seeking treatment and taking pain killers recently and often). Many of these patients
received some benefit from accepted pain management strategies such as drugs, physiotherapy, psychotherapy and invasive procedures. However, many found no relief and experience a very low quality of life.

As mentioned earlier, pain interpretation by a patient is individualized. As physicians, we have to believe it is what the patient says. The treatment of pain should be customised for each individual patient. To enable management to be best matched for the individual patient, a few general principles should be first applied. Because pain is subjective, there are no reliable means to assess it accurately. However, a thorough history, comprehensive physical examination and use of pain assessment devices will add to the objectivity. In the final analysis however, patients still render subjective assessments of pain and physicians subjectively assess these judgments in order to treat as appropriately as possible.

3.2.2 Principles of chronic pain management

History

The patient history is crucial. Certain diseases such as rheumatoid arthritis will demonstrate a good correlation between the amount of pain and that expressed through body language. However for some other patients there will be greater disparity.

There are several important aspects to the history which must be elucidated, including primarily full details about the nature of the pain i.e. any precipitating causes, location, radiation, duration, severity, constant or intermittent and character of the pain (dull, sharp, burning, shooting). Associated symptoms should also be looked for, e.g. if a patient complains of burning shooting leg pain, they should also be questioned for the presence or absence of numbness and parasthesia. The impact of the pain on the patients daily activities will give an
insight into the severity of the pain for that particular patient, i.e. sleep disturbance, not able to do housework or work because of pain. Persistence of the pain can also have a profoundly debilitating effect, it may dramatically impair the individual’s social, vocational and psychological well-being (IASP 1986). There may be deprivation from customary roles at work, in the family or in social and leisure settings. This may also be accompanied by a feeling of hopelessness and despair as various interventions by healthcare professionals have not been effective, not to mention the financial worries because of loss of income. Some patients may become angry and manipulative, and have been shown to report higher levels of frustration more than any other negative emotion (Wade et al 1990). Numerous studies have tried to investigate the relationship between chronic pain and depression (Doan & Wadden 1989, Gamsa A 1990). There are no definitive answers but results appear to suggest that emotional disturbance in pain patients is a consequence and not a cause of chronic pain (Gamsa A 1990) and that depression may be an important predictor of the degree to which pain patients’ activities are impaired (Dworkin et al 1986).

Finally, it is also important to ascertain what investigations have been performed to date and their results. Furthermore, what treatments and medications the patients is already on or has tried in the past and any benefits from these. Not to be overlooked is the presence of any concurrent pathology i.e. ischaemic heart disease, chronic obstructive airways disease, as the presence or absence of these may influence choice of further therapy.

**Physical Examination**

This may or may not confirm the source of pain. Proper pain assessment will require good trained diagnostic skills. This is important to out rule any sinister pathology that may require prompt definitive treatment initially. All patients need a full physical examination which may
indicate where the pathology lies. For example, if a patient has been complaining of chronic back pain associated with left leg pain, they need a full examination of their back, assessing particularly areas of tenderness, movement and muscle strength. However, a full neurological examination is also required including, straight leg raising to determine the presence or absence of sciatica and location of the level where any nerve compression may have occurred. If a patient complains of chronic neck pain associated with headaches, not only do they need a full examination of their neck and neurological examination of upper limbs but also cranial nerve examination. A good thorough history will provide clues as to where the appropriate clinical signs may be found. Environment, culture and psychological background of the patient must be considered as part of the overall assessment. In certain difficult cases, a psychiatric evaluation may be required. Although it is frustrating to the physician, patients who exhibit no objective signs to their pain, should not be told their symptoms are “in their head”. Certain anatomically based pain syndromes have no physical counterpart, at least at the time of the examination (Katz WA 1996).

Investigations

Abnormal laboratory findings and imaging studies may add validity to the symptoms experienced by the patient. Conversely, findings on physical examination or from ancillary studies may be more remarkable than the symptoms and thus may be misleading. For example, low back pain is one of the most common pain symptoms yet 30% of an asymptomatic population will exhibit some abnormality on magnetic resonance imaging of the spine (Wiesel et al 1984).
Pain Assessment Devices

Visual Analogue Scales (VAS) discussed in Chapter 6, Section 5 are used to determine pain intensity. They are useful but provide only a semi-objective means to assess the subjective estimate of pain by the patient. They are often used to monitor a patient’s response to treatment on each clinic visit. There are other scales also for assessing pain, e.g. the McGill Questionnaire both short and long form, also discussed in Chapter 6, Section 7. Another questionnaire not only assesses pain but also patient’s quality of life and has been shown to be effective. It’s use has been validated both in the USA and the UK. This is the Short Form-36 quality of life questionnaire and is discussed in more detail in Chapter 6, Section 9.

Respecting the pain

This further emphasizes the issue that pain is always an important symptom and is usually a sign of a significant underlying disorder. Patients with pain, even thought they may have been seen by many physicians, should be deemed credible until proven otherwise. Patients with disabling symptoms need priority.

Treating the underlying disorder

Chronic pain is best approached by treating the underlying disorder. For example, corticosteroids are very effective in polymyalgia rheumatica, often analgesics are not required. Furthermore, a sophisticated treatment programme may fail to control pain in the patient with severe osteoarthritis of the hip who requires a joint replacement to pain free and mobile. However, it is often not possible to effectively treat and eliminate the pain of the underlying disorder e.g. osteoarthritis of the lumbar spine.
Prompt treatment of pain

Moderate to severe pain should be relieved as soon as possible for humanitarian reasons. As reviewed in Chapter 2, unrelieved pain may cause a permanent change in nociceptor input to the spinal cord leading to a chronic pain syndrome (Wall & Woolf 1986). Persistent pain can also be a significant source of stress to the patient and family and also affect a patient's quality of life, which will already have been ascertained from the history. With all these factors affecting the patient, it is difficult to ascertain a true evaluation of response to therapy. This may be lessened somewhat by prompt pain management.

Psychological components

Notwithstanding all of the above, almost all pain has a psychological component (Clark WC et al 2001). This is quite understandable from a pathophysiological viewpoint when it is known that pain pathways extend into the cerebral cortex. The cognitive effects of pain are greatly influenced by a variety of factors, such as pain intensity and duration. Other influencing factors include personality and environment (Katz WA 1996).

3.2.3 Multidisciplinary pain management

Successful outcomes in chronic pain are believed to be dependent on a comprehensive, multidisciplinary approach that may include patient education, pharmacological intervention, physical medicine, non-invasive procedures, surgery, and psychological counseling (Katz WA 1996). These will all be discussed in the following sections.

Discussion with patient

Concerns of a patient with chronic pain, while they may be somewhat different than that of a patient with acute pain, will still include anxiety, worry about the future, dependents and
income. Therefore, it is important that they receive a thorough explanation of the nature of the disease, progression and intended treatment. This should also involve family. They will then have realistic expectations of pain relief and a good patient-physician relationship should develop (Katz WA 1982).

3.2.4 Analgesics

Rather than relying solely on analgesics, pain relief is maximized when used in conjunction with multidisciplinary management. They are known to vary in efficacy and some will have adverse effects, which may or may not be tolerable. Furthermore, tolerance and addiction may now become an issue particularly with opioid use in chronic pain. These issues should be presented to the patient before they commence therapy so they are fully informed on the aims and likely problems that may occur with their pain management.

NSAIDs

These act by inhibiting the mediators of inflammation that play a role in the induction of the pain experience. They reduce pain by inhibition of the cyclo-oxygenase enzyme (discussed earlier Section 3.1.4) for most inflammatory conditions but also for some seemingly non-inflammatory conditions such as osteoarthritis. There are a wide variety of NSAIDs available for use in chronic pain, the vast majority of which are not selective for COX-2 and thus cause the adverse reactions so commonly seen during NSAID treatment. These may be minimised by the new the newer COX 2 specific agents (Warner et al 1999).

There is little doubt that the NSAIDs are extremely beneficial in the management of pain in inflammatory forms of arthritis. However, they are used significantly in patients with ostearthritis and soft tissue rheumatic disorders. However, there is also some evidence to
suggest that paracetamol may be just as efficacious as NSAIDs in the treatment of osteoarthritis of the knee (Brooks P 1998, March et al 1994).

The main problem associated with their use is the occurrence of adverse effects. It is clear that these increase significantly with age (Johnson et al 1991). These have been alluded to in the section on acute pain but become more of a problem with chronic use. The major concern appears to be the gastrointestinal side-effects. Endoscopic studies have shown that 20% of patients on long-term NSAIDs will have peptic ulcer disease (Roth SH 1988). Drug interactions are also a common occurrence in patients taking NSAIDs because of the existence of co-morbidities. Care should then be taken when prescribing NSAIDs, particularly in elderly patients and all co-prescriptions should be noted. Several recent reviews have noted the advantages of the selective COX-2 inhibitors (Bell & Schnitzer 2001, Goodman SB 2000). They have recommended their use for older patients at risk of NSAID-related gastrointestinal toxicity. Two of these agents are now currently available, rofecoxib and celecoxib.

Paracetamol

In 1995, the American College of Rheumatology recommended paracetamol as first-line therapy for osteoarthritis of the hip or knee (Hochberg et al 1995). This recommendation was made on the basis of evidence from a double-blind randomised trial demonstrating that paracetamol at a dose of 4,000 mg daily was more effective than placebo and as effective as commonly used NSAIDs for relief of joint pain and improvement of function in patients with osteoarthritis (Bradley et al 1992). Paracetamol is an effective analgesic with antipyretic but not anti-inflammatory activity (Williams et al 1993). It is thought to be centrally active, producing analgesia by elevation of the pain threshold and antipyresis by inhibiting prostaglandin synthetase in the hypothalamus (Flower & Vane 1972).
The proper use of paracetamol is crucial to optimizing its effectiveness and achieving relief of chronic pain. Patients may conclude that paracetamol is ineffective after taking only 1 or 2 tablets a day for short periods of time and then stopping treatment. Chronic pain may require up to 4 g/day (1 g 4 times daily) for at least a week, before any benefit is noticed (Schitzer TJ 1998). Overdosage even with greater than 8 g daily can precipitate hepatotoxicity.

**Opioids**

These agents include the opioid agonists (e.g. morphine, oxycodone, fentanyl) and the use of these agents in chronic non-cancer pain is quite contentious. In a randomised double blind placebo-controlled trial, controlled release codeine has been shown to be effective in reducing pain and pain-related disability in patients with chronic non-malignant pain (Arkinstall et al 1995). In a class of its own is tramadol, a centrally acting analgesic with at least two mechanisms of action, 1) low-affinity binding to the μ-opioid receptors and 2) inhibition of adrenergic and serotonergic reuptake by nerve cells (Raffa et al 1992). Of course, all of these agents are not void of adverse effects, which included dizziness, somnolence, nausea, constipation, sweating and pruritis (Eggars & Power 1995). These effects are less with tramadol but it is associated with a decreased analgesic effect.

There is evidence to support the efficacy and safety of long-term opioid analgesics in carefully selected patients with chronic non-malignant pain (Portenoy & Foley 1986, Collett BJ 2001). There is concern about the use of opioids in chronic non-cancer pain, that they may be ineffective in the long-term and may lead to a deterioration in the patients pain. However it does appear that there is a subset of patients with chronic non-malignant pain that would function better if treated with opioids (Jamieson RN 1996, Portenoy RK 1996). There are guidelines produced as to which patients would benefit from the use of opioids for their chronic
pain (Portenoy 1996). This includes patients who have chronic pain in whom all other reasonable attempts at effective analgesia have failed. A definite treatment plan with regular review and careful documentation is recommended for this group of patients (Collett BJ 2001).

3.2.5 Adjuvant medications

This group of drugs include the antidepressants, anticonvulsants and topical agents that are used in the treatment of chronic pain.

Antidepressants

There is evidence that the tricyclic antidepressants (TCAD) and monoamine oxidase inhibitors (MAOI) can relieve chronic pain (Walsh TD 1983, Getto et al 1987, Feinmann C 1985). The dose required to raise the pain threshold is usually lower than that required to treat primary depression (Monks et al 1999). Amitriptyline is probably the most widely used. It is not known whether its analgesic effects are linked to its mood-altering activity or attributable to a discrete pharmacological action (or a combination of both) (Bryson & Wilde 1996). Three possible mechanisms have been put forward as a possible mechanism of action. Firstly, that it may alleviate depressive symptoms associated with chronic suffering (Feinmann C 1985). Secondly, that there may be a common biochemical mechanism underlying both depression and pain. It has been suggested that low brain serotonin may lead to hypersensitivity to pain and depression (Sterbach R 1976). Giving serotonin precursors such as L-tryptophan reduces pain perception and potentiates endogenous opiates (Taub1973). Finally, there may be an interaction between TCADs and opioid receptors in the brain (Beiggn & Samuel 1980). The newer selective serotonin reuptake inhibitors (SSRIs) have not been thoroughly studied in the treatment of chronic pain. As these have only serotonin-receptor-mediated side effects, it is plausible that they may be less effective than TCAD’s in treating chronic pain. (Barkin & Fawcett 2000).
The relationship between chronic pain and depression has been extensively investigated and it is thought as stated above that emotional disturbance in pain patients is more likely to be a consequence rather than a cause of chronic pain (Doan & Wadden 1989, Gamsa A 1990). A meta analysis of 39 placebo-controlled studies in chronic non-malignant pain has found the existence of an antidepressant-induced analgesic effect (Onghena & Houdenhove 1992). While it is thought that the antidepressant-induced analgesic effect might be understood as a secondary response to a psychological effect (antidepressant or sedating), the meta-analysis shows that the intrinsic analgesic properties appear to off the most plausible and economical explanation (Onghena & Houdenhove 1992). A few recommendations for the use of antidepressants in chronic pain have been made, namely that the antidepressants with both serotinergic and noradrenergic effects are more efficacious in the relief of chronic pain, and to start with lower dosages in non-depressed patients (as the TCADs may cause distressing anticholinerigc side effects in higher doses). These adverse effects (primarily dry mouth and sedation) are commonly reported, even at the low dosages used in the control of pain (Bryson & Wilde 1996). For this reason, patients are generally advised to take them before bed.

Anticonvulsants
The two main agents prescribed before the newer agent gabapentin became available were carbamezepine and phenytoin. They have been shown to be of benefit predominantly in neuropathic pain, especially trigeminal neuralgia and post herpetic neuralgia (McQuay et al 1995). This review also suggested that there was a need for high quality studies of the relative effectiveness of different anticonvulsants in treating chronic pain conditions and also for trials comparing the efficacies of different anticonvulsants. Their precise mechanism of action remains uncertain. There appears to be two standard hypotheses: enhanced inhibition of GABA
and a stabilizing effect on neuronal cell membranes (Monks R 1999). Their use is not without risk. Serious side effects include haematological reactions, but the commonest are impaired motor and mental function (Rall & Scliefer 1992).

Gabapentin is the most recently available anticonvulsant for use in neuropathic pain. Although it is a structural analog of GABA, it does not bind to GABA receptors (Nicholson B 2000). It does however increase the rate of synthesis of GABA in the brain (Petroff et al 1996). Because GABA receptors have been shown to mediate pre-and postsynaptic inhibition in sensory afferent fibres and GABA agonists have potent antiallodynic activity in animal models, it follows that gabapentin may be effective in antagonising some painful sensations. It also interacts with the recognition site of a neuronal transport system similar to system L (Thurlow et al 1993). Gabapentin may modulate certain types of calcium current (Taylor et al 1998). The partial N-terminal sequence of a gabapentin binding protein has been shown to be identical for the αδ subunit of the L-type voltage-dependent Ca^{2+} channel from skeletal muscle (Hamilton et al 1989). Gabapentin has high affinity and specificity for these channels.

Treatment with gabapentin has been shown to be efficacious for the treatment of pain associated with painful diabetic neuropathy and postherpetic neuralgia (Backonja et al 1998, Rowbotham et al 1998). In both these studies, gabapentin was found to significantly decrease pain intensity and improve sleep. It also demonstrated other significant benefits, namely positive effects on mood and improvement in quality of life. Its main side effects which can limit its use are that of sedation and dizziness.

Capsaicin
Capsaicin is the irritant in red-hot chilli peppers and belongs to the family of vanilloids. It has a direct and selective stimulatory action on most C fibres and Aδ fibres because it initially causes the release of substance P (Holzer 1991). After this initial excitation, capsaicin results in the depletion of substance P, thereby decreasing the nociceptive signal transmission. This is followed by a long lasting state of desensitization. Initially when it is applied topically, patients will notice burning and hyperalgesia due to the release of substance P. After prolonged administration, depletion of substance P then occurs and it produces its antinociceptive effect (Snijdelaar et al 2000). It is marketed in two forms of cream, 0.025% and 0.075%. It is important that the initial irritant effect of capsaicin is explained to patients so that they can understand how intrinsic it is to capsaicin’s mechanism of action and more importantly that they will have to endure it for approximately three weeks before they notice a beneficial effect.

**NK1 receptor antagonists**

NK1 receptor antagonists have been recently trialed but due to neurotoxic side effects they are not widely available (Bonnet et al 1996). They are being developed with the aim of treating pain by also antagonising the effects of Substance P (Snijdelaar et al 2000).

In using analgesics in clinical practice for chronic pain, it is important that a logical well-planned sequential approach is used. The therapy should be individualized for each patient and commenced with a simple single entity agent. Patients should be warned of potential adverse effects before administration of analgesics. Special care should be advised when using centrally acting analgesics to minimize adverse effects. Once the effective dose is titrated, it is better to administer the drug on a regular basis rather than as needed. Combination therapy may also be effective and patients should be monitored closely and reviewed regularly (Katz WA 1996a).
3.2.6 *Non pharmacological therapies for chronic pain*

**Physiotherapy**

This consists of physiotherapy alone or including the application of other physical modalities such as deep heat, electrotherapy, hydrotherapy, splints and braces. Properly used these modalities may decrease the need for analgesics. Poorly motivated patients often reject these therapies but once involved in a programme, they exhibit a sense of accomplishment and well-being (Katz WA 1996a). Minor and colleagues reviewed physical interventions for the management of chronic pain (Minor et al 1993). They found that superficial heat or cold combined with aerobic and strengthening exercises decreased pain and disability and improved function for patients with both rheumatoid and osteoarthritis. It was striking that physical therapies alone had little or no clinical meaningful effect on pain. Best results were found when they were combined with analgesic agents and regular exercise.

**Acupuncture**

Though it is widely used and has minimal side effects there is little in the literature to support a clinical significant improvement with acupuncture (White et al 1999, van Tulder et al 1999).

**Transcutaneous electrical nerve stimulation**

TENS and its mechanism of action will be discussed in detail in Chapter 4, Section 2. A recent review of 19 randomised controlled trials stated that the published trials to date to not provide information on the stimulation parameters likely to provide optimal pain relief (Carroll et al 2001). Nevertheless, it appears that more properly constructed randomised controlled trials are needed.

**Anaesthetic techniques**
Peripheral, epidural, intrathecal, sympathetic and plexus nerve blocks are usually reserved for nerve pain and may be used in conjunction with other forms of therapy or alone. They can be very effective in relieving pain and restoring function but unless a permanent procedure is performed as in an ablative procedure for chronic pain, their effects are only shortlived (Katz WA 1996a).

**Spinal cord stimulation**

This will also be discussed in more detail in the Chapter 4, Section 3. It is an invasive technique used for the treatment of chronic intractable pain syndromes (e.g. Failed Back Surgery Syndrome and diabetic neuropathy) for which evidence is now emerging of some benefit (Turner et al 1995, North et al 1995).

**Psychological / behavioural techniques**

**Psychosocial aspects of pain**

Anxiety, fear, depression, demoralization, frustration and other feelings may intensify the pain response. Psychosocial techniques for patients with acute and chronic pain may be valuable adjunctive treatments when used in combination with analgesics (Allegrante JP 1996). A good patient physician relationship is invaluable (Katz WA 1982b). Effective listening, communication and reassurance have also been shown to be useful (Rene et al 1992).

**Behaviour modification**

Numerous studies have highlighted the effect of behaviour modification therapies (Fordyce et al 1985). These include teaching the patient empowerment and coping mechanisms, stress management, relaxation techniques, and possibly job modification.
Psychotherapy

For some patients this can be as simple as reassurance by their physician. But in severe cases, the factors influenced and being influenced by pain are so complex that expert time-consuming psychosocial interventions is required. (Allegrante JP 1996).

3.3 Summary

This purpose of this chapter has been to briefly review the management of acute and chronic pain. It is important that acute pain is treated promptly and effectively as this will prevent the development of a chronic pain state. Numerous agents are available for the treatment of acute pain but it is probably most effectively treated as part of balanced multimodal analgesic technique. The most common agents used in the treatment of acute pain include opioids, local anaesthetic agents and NSAIDs, which can be administered by a variety of routes. Non-pharmacological methods can also be used but only as adjunctive therapies.

Effective chronic pain management is best achieved in a multidisciplinary setting by experts in a dedicated pain management centre. The pain management team should involve professionals from a wide variety of fields, medical, nursing, physical therapy, occupational therapy, psychology, social work and health education. Even with the support of a comprehensive pain management team, the effective treatment of patients with chronic pain provides the physician with hugh challenges and still is not treated to the patients satisfaction. Finally, management of a patient's pain should be individually tailored for each individual patient and will generally involve several different modalities. The electrical methods of pain relief, while not the sole method of pain relief in acute or chronic pain management, have a role to play, which will be reviewed in the next chapter (4).
Chapter 4

Electrical Methods of Pain Relief

4.1 Gate Control Theory of Pain

4.2 Transcutaneous Electrical Nerve Stimulation
   4.2.1 Mechanism of action
   4.2.2 Technical / practical aspects
   4.2.3 Limitations
   4.2.4 Methodology in research trials
   4.2.5 Efficacy of TENS

4.3 Spinal Cord Stimulation
   4.3.1 Mechanism of action
   4.3.2 Insertion
   4.3.3 Efficacy of SCS

4.4 Deep Brain Stimulation

4.5 Peripheral Nerve Stimulation

4.6 Percutaneous Electrical Nerve Stimulation

4.7 Electroanalgesia

4.8 Transcutaneous Acupoint Electrical Stimulation

4.9 H-Wave Therapy

4.10 Peizo-Electric Current Therapy

4.11 Summary
This chapter focuses on the electrical methods of pain relief that are currently available. The most popular methods currently in use are transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation (SCS). However, a few other less common forms are also discussed.

The introduction of the gate control theory of pain has facilitated a proliferation of different afferent stimulation techniques for pain alleviation (Melzack & Wall 1965). The quality of the scientific documentation of TENS as a pain-relieving measure does not however correspond to its widespread application in a multitude of painful conditions by different healthcare providers (McQuay et al 1997).

4.1 Gate Control Theory of Pain

Before the 1960's, pain was considered to arise from peripheral nerves and reach the cortex via a direct route with no modulation. It was clear, however, that this did not explain many clinical conditions such as phantom limb pain, hyperalgesia, alldynia and the effect of past experience. The gate control theory of pain, proposed in 1965 by Melzack & Wall was a huge shift in thinking about pain mechanisms and forms the basis of our current understanding (Melzack & Wall 1965).

The theory centres around the principle that inputs to the spinal cord (Aβ and C fibres) may be modulated by systems in the substantia gelatinosa of the spinal cord and also by descending systems from the brain (central control) (Figure 1). The gate refers to the interaction of different systems on the dorsal horn cell and it is opened by C-fibre activity. The gate is closed
by Aβ activity, which reduces C-fibre input by stimulating an inhibitory interneuron in the substantia gelatinosa. This explains why vigorous rubbing of a painful part of the body or the use of TENS helps alleviate the pain. The thalamus is thought to have a role in the supraspinal descending control (Oluasson et al 1994). The afferent patterns in the dorsal columns act, as a central control trigger, which activates selective brain processes that influence the modulating properties of the gate control system.

[Chapter 4].[Figure 1]
Gate Control Theory of Pain. SG; substantia gelatinosa, DHN; dorsal horn neurone
The detailed antinociceptor mechanisms of action of TENS are still largely unknown. A number of studies support the notion that afferent activity set up by TENS blocks nociceptive transmission in the spinal cord (Chung et al 1984, Garrison & Foreman 1996). Pre, as well as postsynaptic inhibitory mechanisms have been implicated. Thalamic regions are also involved (Oluasson et al 1994). It is not just pain sensations that appear to be altered by TENS. Pain associated with temperature is also affected. Woolf showed that high frequency TENS significantly altered the heat pain threshold and the tolerance to heat (Woolf CJ 1979). It appears that the most effective block of neurones of the cord is achieved by activation not only of large myelinated fibres (Aα, Aβ) but also of Aδ and C fibres (Chung et al 1984, Lee et al 1985). This implies that painful TENS would be more effective for pain alleviation but this is obviously not of practical use. More recently, TENS was shown to significantly reduce subjects' ratings of painful and near-painful heat stimuli and increased the heat pain threshold (Marchand et al 1991). The perception threshold to cold pain, as well as tolerance to ice pain, was demonstrated to be significantly increased by a variety of stimulation patterns using TENS (Johnson et al 1991). The conclusion that may be drawn from these studies is that the messages conveyed in the nociceptive system set up by different painful stimuli, resulting in different temporospatial patterns of ascending activity, is differentially susceptible to alterations to different modes of TENS.

The neurochemical events associated with TENS are largely unknown. There is a suggestion that endogenous opioid release may mediate part of the pain-relieving effects but the evidence for this is conflicting. Some studies have reported that naloxone can reverse the effect of TENS.
in healthy volunteers (Chapman & Benedetti 1977). However, Woolf and colleagues found this not to be so in patients with acute pain (Woolf et al 1978). Other studies have found an elevation in endogenous opioid release following stimulation with TENS and found higher levels after stimulation at 85Hz of both plasma beta-lipotropin and beta-endorphin in the cerebrospinal fluid (CSF) compared with placebo (Facchinetti et al 1984). Similar elevations in CSF dynorphin (another endogenous opioid) have been found following high-frequency TENS and following stimulation with low-frequency TENS there is an increase in the CSF levels of Met-enkephalin-Arg-Phe (Han et al 1991). It has also been shown that the inhibitory neurotransmitter GABA is also released in response to the Aβ stimulation (Duggan & Foong 1985). To summarise therefore, it does appear that there is a release of endogenous opioids following TENS stimulation which is reversed by naloxone and that this may account for some of the analgesic effect.

4.2.2 Technical and practical aspects

TENS involves the transmission of electrical energy from an external stimulator to the peripheral nervous system via cutaneously placed conductive pads. Commercial machines offer at least 3 different pulse patterns: high frequency (HF, usually 50-120 Hz), low frequency (LF, 1-4 Hz) and bursts of high frequency delivered at low frequency (1-5) Hz i.e. acupuncture-like (AKU) TENS. In addition, pulse width and stimulus amplitude can be controlled. The pulse width can be varied from 50-500 μs, employing a current whose amplitude can be increased from 0-50 mA and whose frequency is generally 100 Hz. The pulse is produced by a pulse generator, which is then fed into an amplifier which amplifies the signal to a level where sufficient current is delivered to the electrodes (Woolf CJ 1989). The amount of current required depends on the impedance of the electrodes and the impedance of body tissue. Since the total impedance can change (e.g. by drying of the gel interface between electrodes and skin)
it is best to use a constant current amplifier, where the delivered current will not change with the changes in the impedance of the system. The TENS pulse width is sufficiently long in duration to excite $A\beta$ nerves at low voltage causing a painless tingling. If the frequency is reduced below 80 Hz and the amplitude is increased sufficiently to cause a painful form of tingling, $A\delta$ fibres are recruited. The aim of TENS is to deliver a sufficient charge to a pair of electrodes so that the current density produced by the resultant electric field is able to excite the afferent fibres in an adjacent nerve in a controllable manner. The stimulation must in addition be performed without damaging the skin. Disposable reusable self-adhesive electrodes are used.

In general, HF stimulation in the centre of the pain area is recommended as the first choice of stimulation with an intensity just below the pain threshold so that paraesthesias are felt in the painful region. If HF stimulation fails or is inconvenient, e.g. due to aggravation of pain in an area of tactile allodynia, LF or AKU TENS may be tried in an anatomically related area with normal sensibility. Regardless of the mode of TENS, a duration of stimulation of at least 30-45 minutes is recommended. The best case scenario is that TENS may relieve pain for several hours after termination of stimulation. A lot of patients will only report pain alleviation during stimulation only with no post stimulatory effect. They may still often volunteer to have a machine prescribed if other pain relieving measures have proven ineffective for their pain. Frequent follow ups of patients in a chronic pain setting are recommended to reinstruct patients if necessary and to carefully extract the benefits of stimulation.

4.2.3 Limitations

TENS is currently used in both acute and chronic pain settings. While it is quite popular, probably due to the fact that it is non-invasive and non-pharmacological, there are several
limitations to its use. Firstly, it has varying success rates (Campbell et al. 1982) and its effects diminish over time (Bates et al. 1980). The reason for the latter is unknown but it is suggested that the central nervous system production of neurotransmitters in response to TENS becomes habituated. Furthermore, as patients will always feel the tingling sensation when the machine is switched on, it is difficult to properly evaluate the response. It is not possible to undertake double blind controlled trials. Finally, some TENS machines are quite complex to use and difficult for some patients to understand how to use them correctly.

4.2.4 Methodology in research trials

The quality of methods used in clinical trials has been shown to be a key determinant of the eventual results (Carroll et al. 1996). Schulz and colleagues have demonstrated that trials that are not randomised or inadequately randomised exaggerate the estimate of treatment effect by up to 40% (Schulz et al. 1995). Studies which are not fully blinded can exaggerate the estimate of treatment effect by up to 17%. TENS can almost never be properly blinded, as patients always feel the tingling when the machine is switched on and bias is likely from this source alone (Deyo et al. 1990a).

The following are important methodological issues to be considered when evaluating and conducting TENS trials.

- Adequate (non-biased) selection of patients
- Description of diagnostic criteria
- Description of criteria for inclusion and exclusion
- Identical machines and administration routine for TENS and placebo TENS
- Blinded randomisation
- Blinding of patients and research team
• Assessment of compliance with treatment
• Description of withdrawals and reason for withdrawals
• Description of outcome measures
• Independent evaluation

4.2.5 Efficacy of TENS

In reviewing the available literature to date on TENS, I will consider TENS in acute pain, labour pain and lastly chronic pain.

Acute pain

Studies evaluating the analgesic effects of TENS have produced inconsistent results. For many studies, it was found that details regarding specific stimulation variables were lacking (White et al 2001). However, the main determinant of the results appears to be the quality of the methods (Carroll et al 1996). As mentioned above, studies which are not randomised or inadequately randomised can exaggerate the estimate effect by up to 40% (Schulz et al 1995). A systematic review of 46 studies on the use of TENS in acute postoperative pain found that only 17 were deemed to be well designed as in proper randomised controlled trials (Carroll et al 1996). Fourteen trials compared TENS with sham TENS and only one found a significant improvement in pain intensity with TENS but it was judged inappropriate by the reviewers (Warfield et al 1985). Seven of the 17 trials compared opiate plus TENS with opiate alone, four of which also included sham TENS. Only two were judged by their authors and by the reviewers to be positive (Pike PM 1978, VanderArk et al 1975). The first trial studied 40 patients after total hip replacement (Pike PM 1978). They found that patients with active TENS had significantly fewer injections of meperidine on the first postoperative day as well as higher scores on a global rating of treatment. The second trial recruited 100 patients having abdominal
and thoracic surgery and found that there was more success with active TENS used for 20
minutes three times per day (VanderArk 1975). In a postthoracotomy study, TENS-treated
patients demonstrated a benefit of lower pain scores, shorter recovery room stays and better
tolerance of physiotherapy on the first postoperative day (Warfield et al 1985. However, this
trial was rejected by the review (Carroll et al 1996), which judged their statistical analysis
inappropriate. The clear message from this review is that adequate randomisation is an
important quality standard in studies with pain outcomes.

Other studies have since looked at the effect of TENS postoperatively. More recent
randomised control trials of TENS have reported beneficial effects with regard to dental pain
(Estafan et al 1998), lithotripsy (Reichelt et al 1999), hemorrhoidectomy (Chiu et al 1999) and
hysterectomy pain (Hamza et al 1999) associated with a decrease in morphine consumption.
However, an earlier randomised single blind trial, looking at the effect of TENS on morphine
consumption found no difference in morphine consumption and no difference in morphine
plasma concentrations measured in patients who received either active or sham TENS
(McCallum et al 1988). These later trials have been randomised but because of the inherent
nature of TENS, they are all single-blinded.

TENS has also been shown to reduce the incidence of pulmonary complications after upper
abdominal surgery (Ali et al 1981). A randomised study particularly examining the effect of
TENS on postoperative pain due to elective caesarean section found a decrease in movement
associated incisional pain (Smith et al 1986). However, the main flaws with this study, apart
from the fact that it is single blind, was that half of the patients had their surgery performed
under general anaesthesia and half under epidural anaesthesia, therefore their levels of sedation
(which were not commented on) may have influenced results. Furthermore to produce any
analgesic effect, continuous therapy from 24 hours to 3 days seems to be required (Smith et al 1986) or regular therapy every 2 hours for 30 minutes (Chen et al 1998, Chiu et al 1999).

Therefore, while a large body of the early evidence for TENS reports favourable outcomes in terms of pain intensity (Carroll et al 1996), the bias in these studies is too great to allow for these to be counted as positive results. This demonstrates the importance of randomisation and also that the randomisation process is adequately described. Furthermore, double blinding with TENS is practically impossible and many earlier studies made no attempts at blinding. The later studies (after 1996) quoted were all single blinded, with explanations given of what patients may or may not feel. However, some of these do report reductions in morphine consumption postoperatively with improved sedation scores. On the whole however, there is limited data available to support a significant beneficial analgesic effect with TENS in postoperative pain.

Labour pain

TENS is quite widely used in obstetric units throughout the UK, particularly in early labour (Steer M 1993). A systematic review looking at the efficacy of TENS in labour pain did not find any compelling evidence for TENS having an analgesic effect (Carroll et al 1997). This review consisted of 8 reports involving 712 women. Seven different devices were used predominantly with individual titration. Five studies used sham TENS as the control group. Only one study made a significant attempt at blinding (Thomas et al 1988). This was also the only study to record a significant analgesic benefit, but this was only on retrospective post partum questioning. There was a variety of different pain measures used, some studies measured back pain separately, some measured pain at different stages of labour or different
stages of dilatation. No study recorded any difference in pain scores during labour between TENS and control. Information about analgesic benefits were recorded in 6 studies as the number of analgesic interventions. In two trials, women with TENS had significantly less analgesic interventions (Neisham et al 1982, Bundsen et al 1981). In total of the eight studies reviewed, 3 were judged to have a positive result and five a negative result (Carroll et al 1997). Another later trial not included in this review did not report any improvement in pain intensity with TENS, or amount of additional analgesia required following either sham TENS or active TENS (Van Der Ploeg 1996). This trial claimed to be double blinded but gave no details of how this was performed. A more recent trial found no difference between analgesic interventions between an active and control group (van der Spank et al 2000).

While evidence for an analgesic effect in labour is sparse, it has been noted to be a popular choice with patients (Thomas et al 1988). No adverse effects (maternal or foetal) have been reported. An argument for its use is that something that appears to do no harm, which may do some good is worth using. Further, large scale studies are needed to demonstrate whether or not there is a definite benefit of TENS associated with pain relief or sparing of other analgesic intervention.

Chronic pain

It is probably in the chronic pain clinic that TENS has its most widespread use (Carroll et al 2001). Again there are varying results as to its benefit and the majority of trials do not show a definite positive outcome (Milne et al 2001, Carroll et al 2001). Earlier studies with TENS in chronic back pain do show a reduction in pain intensity but they are not randomised or placebo controlled (Bates et al 1980, Fox & Melzack 1977, Melzack 1975). However, patients were monitored for a long period of time i.e. from 1 month to 2 years (Bates et al 1980, Melzack
However, when used to treat chronic pain related to musculo-skeletal disorders alone, treatment with TENS for a period of one month had no significant treatment effect over placebo (Deyo et al 1990b). Exercise was found, on the other hand to produce a temporary improvement in pain scores and reduction in pain frequency (Deyo et al 1990b). Other studies report short and long term benefits ranging from 50-80% and 6-44% respectively (Lampl et al 1998). Another study reported that the long term use of TENS in patients with chronic pain was associated with a 55% decrease in analgesic medication and 69% reduction in the use of physical/occupational therapy (Chabal et al 1998).

McQuay and colleagues reviewed 38 randomised controlled trials on chronic pain (McQuay et al 1997). They found that ten out of 24 trials comparing TENS with controls were regarded as having a positive outcome. However, TENS exposure in all these trials was low i.e. less than 4 weeks in 85% of trials. Johnson and colleagues recommend that TENS should be prescribed for at least 30 minutes use twice daily for at least a month before any beneficial effect may be felt (Johnson et al 1992). The length of treatment time with TENS in the literature rarely extends for longer than a month. When TENS is used to treat chronic pain states the onset of its analgesic effect is very slow (McQuay et al 1997). The reasons for its inconsistent responses may be due to several factors, including variable stimulations sites, frequencies, intensities and durations of electrical stimulation as well as the patient’s psychological profile (White et al 2001).

Milne and colleagues performed a review of TENS use in chronic low back pain (Milne et al 2001). Of five trials that fitted inclusion into this review, there was no difference between the active TENS group compared with placebo. The reviewers conclusions recommended that new trials on TENS should make use of standardised outcome measures and include data on how
TENS effectiveness is affected by four important factors: type of applications, site of application, treatment duration of TENS and optimal frequencies and intensities.

A further Cochrane Review found inconclusive results in reviewing the use of TENS in a variety of chronic pain settings (Carroll et al 2001). They reported that the trials published do not provide enough information on the stimulation parameters which are most likely to provide optimum pain relief, nor do they answer questions about long term relief.

To summarise therefore, there appears to be lack of evidence of effect with the use of TENS in chronic pain. Large randomised trials with definite stimulation parameters and sufficient treatment times are needed.

4.3 Spinal Cord Stimulation (SCS)

In 1967, Shealy reported the first use of an implantable device for direct spinal cord stimulation (Shealy et al 1967). This technique involved surgically implanting electrodes over the dorsal columns after laminectomy with the aim of activating pain-inhibiting mechanisms. It was initially labeled dorsal column stimulation. It was later discovered that stimulation applied to the ventral surface (Larson et al 1975) and stimulation by electrodes inserted into the epidural space was also effective in relieving pain (Campbell JN 1981). Presently, the term spinal cord stimulation is used to describe this technique. Its proposed mechanism of action is by modulation of perception of afferent nociceptive stimuli (North et al 1995). Since the introduction of SCS, the implanted systems have changed remarkably (Turner et al 1995). The first systems used monopolar electrodes with one channel of stimulation and a ground plate was also attached to the receiver/transducer. Stimulators are now available with quadripolar or
octapolar electrodes. “Multichannel” programmable systems have also been developed and the range in stimulation parameters is large (Turner et al 1995).

### 4.3.1 Mechanism of action

There are several mechanisms by which SCS is believed to exert its analgesic activity, including direct neural stimulation effects on the posterior columns, supraspinal mechanisms and neurochemical alterations in the central nervous system (North et al 1995). One of the proposed mechanisms is based on Melzack and Wall’s gate control theory of pain i.e. that the selective stimulation of larger fibres, which have a lower threshold than the smaller pain-mediating nerve fibres, closes the gate. This effect is supported by the observation that paraesthesias in the same distribution as pain appear to be a prerequisite for adequate analgesia from SCS. Patients feel paraesthesia even in phantom limbs, when the stimulator is activated.

This indicates a supraspinal action and there is also evidence for thalamic and sensory cortical effects (Larson et al 1974, Modesti & Wasak 1975). Evidence to support this is provided by an increase in blood flow to those areas as demonstrated on functional magnetic resonance imaging (MRI) (Kiriakopoulos et al 1997). Autonomic responses are altered in patients with spinal cord stimulators, as demonstrated by altered vascular dynamics in patients with peripheral vascular disease (Jacobs et al 1990). The analgesic effects in angina pectoris are thought to be due to altered sympathetic tone with vasodilation and a reduction in ischaemic pain (De Landsheere et al 1992). SCS has also been shown to be effective for pain states that are mediated through the sympathetic nervous system such as reflex sympathetic dystrophy (RSD) (North et al 1995). There is strong clinical evidence that dorsal column activation is a necessary condition for SCS at least in neuropathic pain. Previous anterolateral cordotomy does not prevent SCS but vibration sense (transmitted in the dorsal columns) must be preserved for SCS to be effective (Tesaye et al 1996). The anterior pretectal nucleus (APN), a rostral mid-
brain nucleus which has a rich excitatory input from the dorsal columns via the dorsal column nuclei, appears to have a central role (Rees & Roberts 1989). Mathematical and physiological models have shown that optimal electrode position and arrangement is based on bipolar stimulation and that the maximal effect is achieved with midline contacts parallel to the fibres of the dorsal columns (North et al 1995).

Neurochemical effects of SCS have also been investigated. Pain relief by SCS does not seem to be mediated through endogenous opioids. Naloxone does not reverse the effects of SCS (Freeman et al 1983) of the spinal cord. It is known that the concentrations of certain neurotransmitters and their metabolites are altered by SCS (Linderoth et al 1992). Serotonin, substance P and GABA have all been implicated but their exact role is unknown (North et al 1995). SCS is known to increase the release of GABA and suppresses tactile allodynia (Stiller et al 1996).

4.3.2 Insertion

A two-stage procedure is recommended (North et al 1995, Turner et al 1995, White et al 2001). Trial placement of the electrodes and functional testing with an external stimulator should be undertaken before permanent implantation to increase the probability of achieving a successful outcome (Kumar et al 1998). The stimulating electrodes are usually inserted percutaneously via an epidural needle under Xray guidance and positioned to obtain optimal paraesthetic coverage of the nociceptive areas. They must be ipsilateral (if the pain is unilateral) and posterior and usually rostral to the pain. However, a recent study showed that electrodes placed via a thoracic laminectomy were associated with significantly better long-term effectiveness than electrodes placed percutaneously in patients with chronic low back pain (Villavicencio AT et al 2000). These electrodes have larger surfaces, are insulated and can be sutured to the dura.
Power is supplied by an intracorpeal pulse generator (IPG) or by radiofrequency (RF). IPG's are less obtrusive, the parameters can be changed only by telemetry and they require replacement every few years at significant cost. RF systems are cheaper and are preferable where high outputs are required. For angina, the electrodes are placed between C7 and T2 (cardiac pain afferents enter the cord at T1-5). For lower limb peripheral vascular disease, T10 is the most commonly effective level. T8-9 is the level most likely to stimulate the lower back. Total selectivity cannot always be achieved. For example, it is rarely possible to stimulate the lower back or buttocks without some stimulation being felt in the legs. Afferents enter the dorsal columns laterally and have a lower threshold than the more medial fibres from the more caudal segments. Optimum electrode placement is a product of both rostrocaudal level and degree of laterality. If the cathode is place too far laterally, unwanted uncomfortable dorsal root (DR) stimulation will occur. The frequencies used in spinal cord stimulators are generally the same as TENS, i.e. rarely outside the range of 50-120 Hz most usually 80-100 Hz and the pulse width between 100 and 500 microseconds. The effective amplitude is usually in the range of approximately 2-6 volts at the receiver-transducer or IPG. Patterns of use vary from 1-2 hours per day, not every day to almost continuous use. Continuous, 24 hour stimulation is not recommended as it may encourage the development of tolerance (Simpson et al 1991). Permanent implantation is generally considered if patients report at least 50% pain relief while demonstrating increased levels of activity with stable or decreased levels of medication usage (North et al 1995). Permanent implantation of SCS devices are performed in the operating room under aseptic conditions. Once the appropriate location of the device is confirmed, analgesic and/or sedative drugs are given (North & Roark 1995).

The main complications associated with SCS are either technical or biological. The most frequently reported technical complications are electrode dislocation and breakage, lead
migration and breakage and pulse generation failures (Turner et al 1995). The most frequently reported biological complications are infection, cerebrospinal fluid leakage and pain at the incision, electrode or receiver site (Turner et al 1995).

4.3.3 Efficacy of SCS

The ‘failed back surgery syndrome’ (FBSS) is now the commonest indication for SCS insertion. This may be a diagnosis but it is not a unitary disease entity (Simpson BA 1999). SCS is currently used to treat inoperable and intractable chronic pain syndromes. The most favourable results have been seen in patients with peripheral vascular disease, complex regional pain syndrome and peripheral neuropathy (Kumar et al 1998, Turner et al 1995). In patients with failed conservative and surgical treatment of lower-limb ischaemia, SCS has been shown to increase skin blood flow, decrease pain and improve quality of life (Petrakis IE & Sciacca V 1999). Recently, SCS has been used to treat intractable angina pectoris (Fanniullo et al 1999) and chronic mesenteric ischaemia (Ceballos et al 2000). However, as mentioned above, the most common reason for implanting an SCS device is failure of lumbar or cervical surgery. Kumar and colleagues found that the patients who benefited most from SCS were those in whom the device was implanted within 3 years of their initial back operation (Kumar et al 1998). They reported that the success rate for SCS decreased from 93% for patients with less than a 3 yr interval between surgery and implantation to 9% for those exceeding a 12 yr interval. Furthermore North and colleagues in 1995 found a statistically significant advantage in favour of SCS over reoperation at the 6 month crossover point. At a mean follow-up of 7 yrs, 52% of patients who received a permanent SCS reported at least 50 % continued pain relief
(North et al 1993). These patients also reported improvements in activities of daily living and in analgesic use.

In a literature review of 39 case reports, after a mean follow-up of 16 months, only 59% of patients had >50% pain relief (Turner et al 1995). In a prospective multicentred study, of the 70 patients who completed a >1 yr follow-up evaluation, 55% had sustained improvements in pain and quality-of-life measures (Burchiel et al 1996). Of patients that were followed for longer, a mean of 5.5yr, of the 80% that received permanent devices, 59% continued to receive satisfactory pain relief at their last follow-up and of these 42% were now employed compared with only 20% before implantation (Kumar et al 1998). However, some authors feel that the ability to resume activities of daily living may be a more appropriate endpoint than return to work or alleviation of pain in this patient population.

It appears that the 3 main predictors of long term success include 1) percutaneous insertion of electrodes to determine that the stimulation-induced paraesthesia encompassed the topographic distribution of the patient’s pain 2) use of multipolar stimulators and dual leads to augment the range of stimulation and paresthesia coverage and 3) a positive trial stimulation before definitive SCS implantation (White et al 2001). Recently, a four contact array implanted via laminectomy was shown to provide more effective and sustained pain relief than a percutaneous four-contact electrode of the same design (North et al 1999). This was a prospective randomised, controlled trial comparing percutaneous and laminectomy electrodes of varying designs (North et al 1999).

However, because of the paucity of carefully controlled randomised studies, the efficacy of SCS remains controversial even after more than 30 years use. According to two systematic
reviews, the most favourable results have been observed in patients with peripheral vascular
disease, complex regional pain syndrome and peripheral neuropathy (Kumar et al 1998, Turner
et al 1995). In the review by Turner and colleagues, of 39 studies reviewed, there were no
randomised trials. All were case series with poor demographic and clinical details and short
term follow up, (Turner et al 1995). However it appears that there are few randomised
controlled trials to truly evaluate the efficacy of spinal cord stimulation on pain relief (North et
al 1994, North et al 1999). Tesfaye and colleagues performed a trial on patients who had
diabetic neuropathy (Tesfaye et al 1996). In the initial screening, patients were randomised to
receive either a placebo or active temporary electrode for 2 days and treatment was then
changed to the other electrode for a further 2 days. At the end of the trial period if there was an
improvement in their pain of greater than 50% on the VAS, a stimulator was inserted. Eight out
of ten patients had significant pain relief with their stimulator. Exercise tolerance was also
improved. There does seem to be a benefit this population of patients.

Finally, in properly selected patients, SCS has been shown to be cost-effective when used for
an average of 5.5yr (Bell et al 1997). These authors have suggested that as SCS lowers medical
care for FBSS, it can also lower medical costs. They also determined that in patients in whom
SCS therapy is clinically efficacious, the therapy could pay for itself in just over two years.
This is encouraging as SCS is often still perceived by some physicians as expensive, with little
benefit and hazardous complications. As SCS is an invasive and expensive analgesic
intervention with potentially serious side effects it therefore should be reserved only for the
management for severe, intractable chronic pain syndromes with careful patient selection.
There still remains a lack of randomised, prospective, controlled trials concerning its efficacy
and cost-effectiveness relative to other less invasive electroanalgesia modalities or even no
specific treatment at all (Turner et al 1995). As patients are always aware when the stimulator
is activated, trials cannot be double-blind. Nevertheless, given the large body of case reports stating effectiveness, more properly randomised controlled and comparison trials are needed. They should also include proper follow up assessments by independent observers for up to at least five years after SCS insertion, with uniform assessment of multiple outcome measures.

SCS appears to have a significant beneficial analgesic effects in severe refractory patients with chronic pain syndromes. The bulk of this evidence is based on case series and not on randomised controlled trials. While the procedure itself is invasive, it appears to offer benefits in carefully selected patients. More evidence is required though in the form of randomised controlled trials, not only to definitely prove this benefit but also to convince the people who hold the purse strings of the benefits of supporting this form of treatment.

Though TENS and spinal cord stimulation are by the far the most common forms of electroanalgesia currently available, there are other less well known methods available. They will be briefly discussed below and include Deep Brain Stimulation, Peripheral Nerve Stimulation, Percutaneous Electrical Nerve Stimulation (PENS), Transcutaneous Acupoint Electrical Stimulation, H wave Therapy, Interferential Current Therapy and Piezo-Electric Current Therapy.

4.4 Deep Brain Stimulation (DBS)

This technique involves stereotactic implantation of a stimulator and electrode guided by ventriculography, computerized tomography, or magnetic resonance imaging. Electrical stimulation is activated via percutaneously placed leads and the final electrode placement
depends upon a favorable response to direct stimulation. A multipolar electrode system allows for a number of bipolar stimulation combinations to be evaluated during the trial period. In common with SCS, the stimulator is only internalized if satisfactory pain relief is achieved during the trial period.

The most common targets of stimulation have been the periventricular and periaqueductal gray matter in the mesencephalic-diencephalic transition zone, thalamus, internal capsule and motor cortex. It is thought to act by decreasing pain transmission along the sensory-discriminative pathways and/or the release of endogenous endorphins. It is mainly used in the management of debilitating chronic pain syndromes after all other less-invasive therapeutic modalities have failed (including SCS). However, as there is quite a potential for serious intracranial complications (eg intracranial, haemorrhage, infection), this has limited its more widespread application as a treatment modality.

Over a 15 year experience using DBS for intractable pain syndromes, 78% of the 68 patients had the stimulating devices internalized, and of those 79% were receiving adequate pain relief after one year (Kumar et al 1997). It also provides effective analgesia in patients with stable neuropathic pain (Tasker et al 1995). However, patients with thalamic pain, spinal cord lesions and postherpetic lesions respond poorly to DBS. It is still considered investigational and has not yet found a clearly defined role in pain management (White et al 2001).

4.5 Peripheral Nerve Stimulation (PNS)
This technique was first reported over 30 years ago (Wall & Sweet 1967). Studies have demonstrated that electrical stimulation of peripheral nerves leads to inhibitory input to the pain pathways at the spinal cord level (Hannai 2000). It appears to have the best success rate in the treatment of neuropathic pain where the nerve lesion is distal to the site of stimulation. For lesions proximal to the stimulation site, the results have not been as successful (Campbell et al 1976).

4.6 Percutaneous Electrical Nerve Stimulation (PENS)

This was originally described for the treatment of intractable pain associated with chronic low back pain syndrome, cancer and other disorders. Electrical stimulation of the spine was achieved by using electrodes inserted percutaneously into the epidural space (North et al 1977). However, now the term has been used to describe a technique involving insertion of 32-gauge acupuncture needle into the soft tissues or muscles to electrically stimulate peripheral nerve fibres in the sclerotomal, myotomal, or dermatomal distribution corresponding to the patients symptoms. Its basis is related to both electroacupuncture (electrical stimulation of percutaneously placed needle probes positioned at classical Chinese acupoints) and transcutaneous electrical nerve stimulation (via cutaneous electrodes at the symptomatic dermatomes) (Ahmed et al 1998b). Recent PENS studies have demonstrated significant efficacy in the short-term management of back pain, sciatica, and diabetic neuropathic pain (White et al 2001). Like TENS, the response to PENS is influenced by the location, frequency and duration of the electrical stimulation (White et al 2001). The use of mixed stimulating frequencies (e.g. alternating 15 and 30 Hz) was more effective than either low or high frequencies alone (Ghoname et al 1999a).
4.6 Electroanalgesia

This has gained increasing acceptance in westernized medical practice. It is thought that its analgesic effects may be mediated through the central release of endogenous opioids (i.e. endorphins, enkephalins and dynorphins) by the body's pain modulation system (White et al 2001). It has been reported to be more effective than traditional acupuncture and compared favourably with PNS for pain relief. Short term success rates of up to 70% have been reported in patients with chronic low back pain, osteoarthritis and migraine (Ulett GA et al 1998).

4.8 Transcutaneous Acupoint Electrical Stimulation

This is a variant of TENS therapy that involves applying cutaneous electrodes at classical Chinese acupoints and stimulating with alternating high-and low-frequency electrical current (Wang et al 1997). It is thought that the combination of different stimulation frequencies will penetrate the soft tissues and be less discomforting at the skin surface (Goats GC 1990). It has been shown to be as effective as dermatomal stimulation in producing an analgesic-sparing effect after lower abdominal surgery (Chen et al 1998a). In this study TENS was shown to provide better postoperative analgesia applied at either the dermatomal level or the Zusanli acupoint than at a nonacupoint site.

4.9 H-Wave Therapy (HWT)

This is a form of electrical stimulation that produces a direct, localized effect on the conduction of underlying peripheral nerves (McDowell et al 1996). It is currently been promoted for the treatment for acute musculoskeletal injuries, postoperative pain and as a noninvasive form of local analgesia. The stimulating variables for HWT differ from TENS in that its signal
comprises a fixed pulse duration of approximately 16ms (vs 50-200μs), a frequency range of 2 to 60 Hz (vs 1-250 Hz), and a biphasic exponentially decaying (versus rectangular or square) waveform. It remains to be determined if these differences in the electrical stimulus produce differences in the analgesic response to HWT compared to TENS therapy. It has been reported to be effective in 76% of diabetic patients with peripheral neuropathic pain with an improvement in their neuropathic symptoms sustained for an average of 2 yrs (Julka et al 1998).

4.10 Peizo-Electric Current Therapy (PECT)

This is an investigational analgesic technique based on the principle that mechanical deformation of a motorized piezoelectric ceramic rod produces a burst of 10 electrical pulses (five positive and five negative) each lasting 2-3 ms. Each electrical burst lasts for 50 to 250 ms and generates a current of approximately 25 μA. At the skin this produces a “pricking” sensation associated with a neurogenic inflammatory response lasting 3-4 hrs. This reaction is indicative of stimulation of Aδ and C pain fibres, which can lead to depression of nociceptive afferent input via a neuromodulatory mechanism involving diffuse noxious inhibitory controls (Daniziger et al 1998). The extent of this process is directly related to the intensity of the applied stimulus and is alleged to be associated with the release of endogenous endorphins (Willer et al 1990).
4.11 Summary

There are many techniques which have been used over the years to produce electroanalgesia, ranging from noninvasive (eg TENS) to minimally invasive (PENS) to highly invasive (SCS, DBS). However, more widespread application of its use will depend on the results of well controlled, randomised long term studies. A more “indepth” understanding of the effect of different electrical stimulation patterns on the pain response may lead to further long term benefits with electroanalgesic therapy. Once the theoretical basis has been more clearly elucidated for electroanalgesia, it will be possible to optimize the efficacy of the above options for both acute and chronic pain. Given that the non-pharmacological, non-invasive therapy is often more attractive to patients, it behoves us as doctors to fully explore these therapies. Another new form of electroanalgesia, has recently become available, namely Transcutaneous Spinal Electoranalgesia (TSE). The next Chapter (5) describes the technique and reviews the limited evidence for its efficacy.
Transmission of pain from the periphery and its modulation at various sites within the central nervous system have been discussed in Chapters 1 and 2. An overall outline of the management of both acute and chronic pain is given in Chapter 3. Electrical methods to relieve pain by interference with impulses in the spinal cord and periphery have been portrayed in Chapter 4. However, recently a new form of electrical pain relief has become available. This technique, devised by Macdonald and Coates is called Transcutaneous Spinal Electroanalgesia (Macdonald & Coates 1995).

There is very little evidence available on the efficacy of TSE to date, though the devices are now widely distributed throughout pain clinics in the UK. The purpose of this chapter is to outline its development, the actual device and the limited evidence for its efficacy to date.

5.1 Development of TSE

The inventor’s aim was to see if spinal cord mechanisms could be directly affected via surface electrodes and also to reduce the cost and surgical risks of implanting electrodes in the immediate vicinity of the spinal cord as is performed in dorsal column stimulation. It is thought that with TENS only 33% of the applied current reaches tissues 5cms deep to the skin (Ericson 1984). The challenge was to provide a current of sufficient potential to reach the spinal cord from surface electrodes without causing distress to the patient. It was therefore decided to investigate the effects of pulses that have a sufficient voltage (100V or more) to penetrate tissues. The pulses were so brief in duration (typically 4μs), that action potentials were not produced in peripheral nerves. Therefore no tingling (in contrast with TENS) was felt on the skin surface. When the surface electrodes were placed directly over the spinal cord, widespread analgesia was noticed (Macdonald & Coates 1995).
Chapter 5

Figure 1

Transcutaneous Spinal Electroanalgesia Device (TSE).

The exact mechanism of action of the device is unknown as is its effect on the CNS and no work has been done to elucidate this. However, unpublished reports suggest it affects the performance of voltage-gated channels in the CNS.

5.2 TSE device

It comprises a patented signal generator which supplies electrical pulses having rapid rising and falling phases at parameters of pulse width, frequency and amplitude such that analgesic effects are produced in the central nervous system when the electrodes are placed over the spinal cord. Each pulse is too brief to cause an action potential in peripheral nerves so no stimulation is felt by the patient. The TSE device has an output pulse which is variable in amplitude, approximately 250 V and has a pulse width of 4 μs. The first TSE devices were designed to
give pulses of a substantially rectangular wave pulse. The shape of this wave with TSE is always consistent. This a major difference between TSE and TENS. With TENS the shape of the output wave is dominated by the load impedance of the body. TENS operating at a voltage of 10 V excites Aβ fibres. If the voltage is increased to 15 V, Aδ fibres are recruited and this exceeds the patients pain threshold and produces a pricking sensation. If the TENS voltage is increased to 35 V, pain tolerance is reached. The inventors found that when square waveform TSE was performed at frequencies of 5 kHz or more, occasionally patients developed a painless erythema under the electrodes. Placing a capacitor in series with one of the outputs produces a differentiated waveform that reduces tissue warming. This differentiated waveform, incorporated in the present TSE devices allows for more effective analgesia at higher frequencies and does not heat the tissues or cause burns.

5.2.1 Electrode placement

The current TSE devices employ a single pair of electrodes, typically of size 4x4 cm. In order to treat total body pain, one electrode should be placed on the skin of the mid-line of the back overlying the spinous process where the spinal cord arises and the second is placed on the skin overlying the termination of the spinal cord under the spinous process of T12. However as it is not easy to keep an electrode in position over C1, as hair tends to be in the way, it is better to place it over T1. At this position however, it is claimed analgesia is not produced in the cervical and cranial segments. For pain in these regions the inventors recommend placement of the electrodes overlying the transverse processes of C4/5 on each side of the neck, thus allowing the current to reach the spinal cord at the cervical level.
5.2.2 TSE sensations

When using the first TSE machines with a square waveform at a frequency of 100Hz, a sensation of tingling could be elicited at typically 80 V. But in trained subjects, a painless feeling of continuous light pressure could be felt at 55 V (a sub-threshold level for tingling). This only occurred when the electrodes were placed directly over the spinal cord with the anode over T1 and the cathode over T12. As this sensation was only reported when electrodes were placed over the spinal cord and in no other area of the body it was called ‘spinal cord sensations’ (Macdonald & Coates 1995). However, these sensations were found not to be palpable in patients using TSE devices with higher frequencies and with a capacitor in series irregardless of where the anode and cathode were placed (Macdonald & Coates 1995).

5.3 Evaluation of TSE

In summary, the inventors claimed that when electrodes are placed on the skin overlying the spinal cord, changes take place that tend to produce widespread analgesia. This occurs even when stimulation is sub-threshold for peripheral nerves. They have called this new method transcutaneous spinal electroanalgesia to distinguish it from other electrical methods that produce their effects by stimulating peripheral nerves.

The inventors performed 3 trials to evaluate whether or not this form of stimulation is an effective means of producing analgesia (Macdonald & Coates 1995).

They included

1. an open pilot study with 100 patients

2. a study of 16 out of the above 100 patients who presented with unilateral tenderness
3. a randomised double-blind, cross-over clinical trial on 8 subjects with TSE and a control (TENS)

**Study 1**

This included 100 patients with chronic pain (average duration 4.7 yrs) and average severity of pain on the Visual Analogue Scale was 5 cm. The diagnoses of the patient's pain ranged from musculoskeletal, visceral to neuropathic origins. The anode was placed overlying T1 and cathode over T12. A 4 µs square wave was employed at a frequency of 600 Hz. This pilot study showed that TSE produced long term 60% or more relief after five of six weekly treatments in 63% of patients whose pain was of relatively recent origin (2.6 years). However, 30% of patients whose pain was of longer duration (on average 12 years duration) did not develop this cumulative effect and required daily treatment to produce continuous comfort. There were no side effects or interactions with drug regimens reported. There is no information given on whether or not patients were able to reduce their daily medication intake. Nor is the reader told how this reduction in pain relief was actually measured (i.e. was a VAS used or a McGill score?).

**Study 2**

16 out of the above 100 patients had unilateral tenderness. They were noticed to have lower pain pressure threshold on the tender side compared to the non-tender side as measured by a pressure threshold meter (Fisher 1988). Following 60 minutes of TSE treatment (performed with a 4 µsec pulse at 600 Hz) the ratio of thresholds of the tender side compared to the non-tender side was significantly reduced (p<0.001) when measured with the pressure threshold meter.
Study 3

This trial was a double-blind randomised cross-over study to compare the effects of one 20 minute treatment of the new method TSE (frequency 10 kHz, pulse duration 1.5 μs requiring an amplitude 180 V to reach tingling threshold) with a 20 minute treatment of TENS (frequency 100 Hz, pulse duration 200 μs requiring an amplitude of 10 V to reach tingling threshold). It is important to note that both TENS and TSE were producing a tingling sensation. The TSE devices used were the earlier ones which do not place the capacitor in series and therefore some patients were noted to feel sensations at the site of electrode placement. On each occasion the patient was linked to both devices via a junction box designed to allow only one type of stimulation. Each box was coded by a trial coordinator who was not present during the investigation. Neither the patient nor the practitioner knew which type of treatment was being administered. As this was a crossover trial the patient received each type of treatment at a weeks interval. Inclusion and exclusion criteria ensured that all patients had suffered continuous musculoskeletal pain for a year or more. As the first eight patients recruited into this trial had a significant reduction in their pain with TSE compared with TENS the trial was terminated and no further patients were recruited. This pain reduction was demonstrated by a decrease in pain intensity as demonstrated on the McGill Questionnaire and, an increase in pain threshold and a decrease in the surface area of the body occupied by the pain. As mentioned above, these studies were performed with square waveform TSE, which is different to the TSE devices used in this thesis. The parameters and details of the current machines used in this thesis are outlined below.

Towell and colleagues have demonstrated that TSE has elevated mood and reduced mechanical pain tolerance in healthy subjects, compared with a control TSE machine (Towell et al 1997). This trial employed square waveform TSE devices operating at frequency of 600 Hz. Subjects
felt elated and more relaxed following active TSE treatment. This was not a double-blind or
crossover trial. In this thesis I have examined the effect of TSE on thermal sensation, pain and
mood in a double blind crossover design.

In summary, there is a small amount of sparse evidence demonstrating an analgesic benefit
associated with TSE. However, the trials are either large and not placebo-controlled or very
small comparing the TSE treatment to TENS but not to placebo TSE. Clearly more work is
needed to fully evaluate these devices. In 1995, Macdonald and Coates did not think that TSE
masks acute pain. They included anecdotal examples to support this, e.g. a patient who had
used TSE for years at home for chronic pain still felt the onset of angina. They also claimed
that TSE is of no benefit in labour. Anxiety they say will decrease the effectiveness of TSE.
However TSE’s role in both acute pain and chronic pain has yet to be fully examined. In this
thesis I have attempted to do this. I have also looked for an effect of TSE on thermal sensation
and pain thresholds in healthy volunteers.

All the trials performed in this thesis have used TSE devices with a differentiated waveform at
a frequency of 2.5 kHz. The investigators have gradually increased the frequency of the device
from 100 Hz to 600 Hz to 2 kHz. What they have noticed in unpublished reports is that
increasing the frequency appears to shorten the treatment time for analgesia.

5.4 Indications and contraindications for TSE

TSE has been used to treat frequently occurring chronic and chronically recurring painful
conditions, including migraine, cervical spondylosis, upper and lower limb pains, thoracic,
abdominal pains and sciatica. Chronic visceral pains such as pancreatitis may also improve.
The only acute condition it has been found to relieve to date is herpes zoster (Macdonald &
Coates 1995). Recently, the inventors have produced a new device operating at a frequency of 50 kHz. It remains to be fully evaluated but its effect in acute pain is currently under investigation.

**[Chapter 5]. [Table 1] Parameters of the TSE device used in this thesis.**

<table>
<thead>
<tr>
<th>Wave form</th>
<th>differentiated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse width</td>
<td>4μs</td>
</tr>
<tr>
<td>voltage</td>
<td>300V</td>
</tr>
<tr>
<td>Charge per pulse over a 1 KΩ load</td>
<td>&lt;0.8μC</td>
</tr>
<tr>
<td>Frequency</td>
<td>2.5kHz</td>
</tr>
<tr>
<td>Location of electrodes</td>
<td>Skin overlying the spinal cord</td>
</tr>
<tr>
<td>Average treatment time</td>
<td>30 mins</td>
</tr>
<tr>
<td>Average duration of relief after 1st treatment</td>
<td>8 hours</td>
</tr>
</tbody>
</table>

TSE is contraindicated in patients with cardiac pacemakers. Furthermore, its effects on foetal maturation are unknown therefore long-term use is not advisable in pregnancy.

It is important to mention that the above parameters and settings in Table 1 of this chapter are not changed by the user of the machine. Patients simply activate an on / off switch and the
above current at a frequency of 2500 Hz is transmitted at all times. Therefore, this device is simpler for patients to use than a TENS machine, all that is required for treatment is switching on of the device. The average treatment time of 30 minutes twice daily has been put forward by the inventors of the device as this is what they have found to be most beneficial in the treatment of patients chronic pain in anecdotal reports. Until this thesis there has been no work with TSE in postoperative patients.

For the purposes of all trials described in this thesis, I have used the suggested treatment time of 30 minutes throughout. In the three chronic pain trials, the inventors recommended that two 30 minute treatments of TSE per day would be required for patients with chronic pain as this is what they have anecdotally report to have benefitted the majority of patients that have used their device. I have abided by their recommendation.

5.5 Summary

TSE is a new form of non-invasive electroanalgesia, which appears to exert its analgesic effect by interfering with pain transmission in the spinal cord. Its exact mechanism is unknown but it is thought by its inventors to affect voltage gated ion channels in the spinal cord. However, its analgesic effect has not yet been fully evaluated, though the machines are widely distributed throughout pain clinics in the UK. In this thesis, I have attempted to undertake this, by examining TSE in both acute and chronic pain patients and also in healthy volunteers.
Chapter 6

Methodology

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6.13 Data analysis 135
This chapter contains a description of all study methodologies, methods of measurement, power calculations and methods of statistical analysis used in this thesis. Although the details of methods are individually stated in Chapters 7-12 inclusive, many of the methods (e.g. pain measurement techniques) were common to more than one study so they are therefore described in this chapter.

6.1 Ethical considerations

Each study was given ethical approval by the Leicestershire Research Ethical Committee and approved by the Leicester Royal Infirmary Research and Development Department for indemnification by the Leicester Royal Infirmary NHS Trust. For patients in the two acute pain studies i.e. looking at the effect of TSE on postoperative pain (Studies 1 and 2 Chapters 7 & 8), who were presenting for elective surgery, the trials were discussed with them when the date of surgery was confirmed. In the three chronic pain studies (Studies 3,4 and 5, Chapters 9,10 and 11), involvement was discussed at an outpatient visit and each patient had least a two-week wait before enrolment in these trials. In the case of the volunteer study (Study 6, Chapter 12), hospital personnel were recruited by means of a flyer and specific appointments were made on subsequent days. All participants were informed that they could withdraw from the study at any time and written, informed consent was obtained before formal inclusion into any of the studies. Verbal assent was also obtained from any surgeons and anaesthesitists responsible for the patients care.
6.2 Patient selection and recruitment

6.2.1 Criteria for patient inclusion

Participants were adults > 18yrs presenting for elective surgery, chronic pain patients or healthy volunteers. The American Society of Anaesthesiologists (ASA) grading system for physical status (American Society of Anesthesiologists 1963) was used to classify healthy women for the two acute pain studies (Studies 1 and 2). The patient groups in these studies were healthy women ASA grade 1 and 2 who were undergoing elective laparoscopic sterilization and elective caesarean section. Patients in the three chronic pain studies (Studies 3, 4 and 5) were male and female with chronic back pain, chronic lumbar radiculopathy and stable chronic neck pain whose pain was associated with a visual analogue score > 4 on a 10 cm line. In the volunteer study, healthy males and females between the ages of 18 and 65 yrs were recruited.

6.2.2 Criteria for patient exclusion

Patients and volunteers were excluded from all studies if they had a cardiac pacemaker in-situ, as the effect, if any, of TSE on a demand pacemaker is not known. They were also excluded if they had skin lesions on the back in the area of proposed electrode placement or local skin hypersensitivity. Patients were excluded from the two acute pain studies if they were being currently treated for an ongoing pain state and if they had a known hypersensitivity to the study analgesics. They were also excluded from Study 2 if they were on anticoagulation therapy as this would interfere with the placement of an epidural catheter. In the three chronic pain studies patients were excluded if vertebral collapse, cancer or rheumatoid arthritis was a cause of their pain. In Study 6, volunteers were excluded if they were being treated for a chronic pain state, or showed any clinical signs of neuropathy or altered sensation on clinical examination.
6.3 Randomisation and blinding

In all studies, randomisation was performed using a sealed envelope technique. Advanced Pain Management Limited (APM) very kindly provided us with a number of trial machines (XPain-TSE Lancashire UK) and coded leads. Half the coded leads were active and half were controls. When either a dummy or active lead was connected to a trial machine, the appearance of the machine was the same, i.e. the on/off light was always activated so that neither the patient nor investigator knew which machine was in use. When the dummy device was switched on, current activated the indicator light but not the control leads. Patients were randomly allocated to receive either a dummy or active lead, which was put in an envelope with the patient number on it by an anaesthetist not directly involved with the trial. These envelopes were opened prior to treatment and the lead attached to the trial machine.

6.4 Measurement of pain, sedation, mood, quality of life, thermal thresholds

The measurement of pain and sedation in all studies was assessed using a number of scales. These included Visual Analogue Scales, Categorical Pain Scores and the Short Form McGill Questionnaire. Quality of Life was assessed using the SF-36 Health Survey. Mood in Study 6 was assessed using the Positive and Negative Affect Schedule. Thermal Sensation and Pain was measured by the technique of Quantitative Sensory Testing. These are all described in the following sections.

6.5 Measurement of pain and sleep interference using visual analogue scales

The most common visual analogue scale (VAS) consists of a 10-cm horizontal line with the two endpoints labeled “no pain” and “worst pain ever” (Joyce et al 1975). The patient is
required to place an X on the 10-cm line at a point, which corresponds to the level of pain intensity they are currently feeling. The distance in cm from the low end of the VAS to the patient’s mark is used as a numerical index of the severity of pain.

VAS have been shown to be sensitive to pharmacological and non-pharmacological procedures which may alter the experience of pain (Price et al 1986) and also to correlate highly with pain measured on verbal and numerical rating scales (Ohnhaus & Adler 1975). Its other main advantages include its ratio scale properties (Price et al 1983). This allows investigators to calculate percentage differences between VAS measurements obtained at different points in time. Other advantages include, ease and brevity of scoring (Jensen et al 1986) and its simplicity providing that clear instructions are given to the patient. Its main disadvantage is that it assumes pain is a unidimensional experience, which can be measured with a single item scale and does not differentiate between the sensory and affective components of pain (Melzack R 1975). Pain can refer to an endless variety of qualities, which the scale categorises under a single label. This issue is addressed below with the development of the McGill Questionnaire (Melzack R 1975). Furthermore, some patients may also have difficulty completing the scale because of perceptual-motor problems or difficulty comprehending instructions.

The change in VAS for pain was used as the primary outcome measure in the three chronic pain studies (Studies 3,4 and 5) where we looked for a change in the quality of the pain perceived by the patient as determined by the visual analogue scale. This was similar to the method used previously by Ghoname and colleagues (Ghoname et al 1999a). VAS at rest and on movement were also used in the 2 acute pain studies (Study 1- every 15 minutes for 1st hour, then half hourly for 2 hours and Study 2-hourly for 1st hour and then hourly for 6 hours) to assess pain intensity. It is similar to methods used by Campbell and colleagues in assessing
postoperative pain (Campbell et al 2001). Visual analogue scales for pain have been widely used in research trials in acute and chronic pain. Therefore, we considered it to be a suitable form of measurement for our trials. The 10 cm VAS was also adapted to measure quality of sleep in a similar method used successfully by Rowbotham and colleagues and Backonja and colleagues when assessing sleep interference due to pain. (Rowbotham et al 1998, Backonja et al 1998). Sleep interference is rated on a scale that describes how pain has interfered with the patients sleep during the past 24 hours with the endpoints of the scale labelled “did not interfere” to “unable to sleep due to pain”.

6.6 Methods of assessment of categorical variables

In the two acute pain studies (Studies 1 and 2), which examined the treatment effect of active TSE on time to first analgesic request postoperatively, two ordinal rating scores were employed to assess pain and sedation postoperatively. These categorical pain scores consisted of a 4 point scale (0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain) and a 5 point categorical scale to assess sedation (0=wide awake, 1=drowsy, responds to verbal communication, 2=asleep, awakes with verbal communication, 3=asleep, awakes with mild physical stimulation and 4=asleep, unresponsive to mild physical stimulation). These scales for pain and sedation were similar to those used previously in studies of postoperative pain (Ready et al 1994, Goodchild et al 2001). In the studies outlined in this thesis, the scores were recorded postoperatively initially at 15 minute intervals for the first hour and half hourly for a further 2 hours (Study 1) and thereafter half hourly for first hour, (Study 2) followed by hourly for 6 hours postoperatively by an investigator who was blinded to the type of TSE treatment (active or control) that the patient received. These categorical scales were recorded at the same time points as the VAS postoperatively. In a recent study by Lines and colleagues, a high degree of
correlation was demonstrated between VAS and the standard categorical four-grade scale in assessing headache pain (Lines et al 2001). There is also evidence to suggest that if a patient records a baseline VAS in excess of 3 cm (30 mm) they would probably have at least moderate pain on a 4-point categorical scale (Collins et al 1997), because when a visual analogue scale is used alone it is unclear which point on the scale represents at least moderate baseline pain intensity. These categorical scales were used because they are simple and easy to use for the patient and also because they correlate well with the VAS.

6.7 Short Form McGill Pain Questionnaire (SF-MPQ)

In the three chronic pain studies (Studies 3, 4 and 5) the Short-Form McGill Pain Questionnaire is used as a measure of the patients pain intensity (Melzack R 1987) (see appendix 2). This questionnaire was given to patients to fill out at the beginning and end of each weekly treatment session to determine whether treatment with active or control TSE produced any difference in pain intensities. It is a widely used now in chronic pain studies (Rowbotham et al 1998, Backonja et al 1998) and has the advantage of being easier to administer than the standard McGill Pain Questionnaire (Melzack R 1975).

The SF-MPQ was developed for use in research when there is limited time to obtain information from patients and when more information is desired than that provided by intensity measures such as the VAS or the overall present pain intensity index (PPI) (Melzack 1975). We opted to use it as our patients were also filling out a longer score (SF-36 Questionnaire) at the same time. The SF-MPQ takes about 2-5 minutes to complete compared with 10 minutes for the longer form. The present pain intensity index is recorded as a number from 1 to 5, in which each number is associated with the following words: 1, mild; 2, discomforting; 3,
distressing; 4 horrible; 5, excruciating. Both the VAS and the PPI provide data on pain intensity only and no data on the qualities of the pain. In the development of the SF-MPQ, the most frequently used set of words were chosen from the sensory and affective categories of the standard form. They were divided into the two descriptive categories of the sensory and affective components of pain. The most common sensory words were throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender and splitting. In the affective category, the most frequently used words are tiring-exhausting, sickening, fearful, and cruel-punishing. These 15 descriptors were selected on the basis of their frequency of endorsement by patients with a variety of acute, intermittent and chronic pains. Each descriptor is ranked by the patient on an intensity scale of 0=none, 1=mild, 2=moderate, 3=severe. The sensory and affective components can be therefore examined individually or as a total score. In our studies, this form was completed at the beginning and end of each weekly treatment (control or active TSE) session by the patient.

The SF-MPQ has been shown to correlate very well with the LF-MPQ (Melzack 1987). It has also been shown to be sensitive to clinical change brought about by various therapies, analgesic drugs, TENS machines and epidural agents in labour (Melzack 1987, Steilian et al 1992). Furthermore it may also be used to discriminate between different pain syndromes (Melzack 1987). There has also been shown to be consistency among young, middle-aged and elderly patients in their ability to complete the questionnaire effectively (Gagliese & Melzack 1997). This is important as in all three chronic pain studies outlined in this thesis we recruited patients of all ages.
6.8 Positive and Negative Affect Schedule (PANAS)

This is the personality scale used in Study 6 to detect change of mood in healthy volunteers. It was developed by Watson and colleagues (Watson et al 1988) as a brief measure of both positive and negative mood. Trait measures of Negative Affectivity (NA) and Positive Affectivity (PA) assess the predisposition of the individual to experience negative or positive mood states.

The schedule consists of 20 adjectives used to describe different feelings and emotions (see appendix 2). Ten adjectives describe negative moods (distressed upset, guilty, scared, hostile, irritable, ashamed, nervous, jittery and afraid) while the other ten describe positive moods (interested, excited, strong, enthusiastic, proud, alert, inspired, determined, attentive and active). Subjects rate their feelings and indicate the extent to which the word describes their feelings on a five-point scale, from “very slightly or not at all” to “extremely”. The rating is as follows; 1=very slightly or not at all, 2=a little, 3=moderately, 4=quite a bit 5=extremely (Appendix 3). The scale is self-administered and takes about five minutes to complete. The scores are obtained by adding item scores (1 to 5) for the ten PA adjectives and the other ten adjectives for the NA score. Total NA and PA scores therefore range from 10 to 50. In Study 6 we performed this test before and after 30 minutes of TSE treatment with both investigator and volunteer blinded as to the type of TSE treatment (active or placebo). The change in mood before and after each treatment session was calculated. These were then analysed to determine if there was a difference in mood following active or control TSE treatment (Section 6.13)

Validity of this scale has been demonstrated by Watson and colleagues (Watson et al 1988). Further evidence of validity has been demonstrated by correlation of the PANAS with other
personality scales eg the Hopkins Symptom Checklist (Derogatis et al 1974). I chose this scale after advice from our psychology colleagues as I wanted to use a scale that would be sensitive in assessing changes in both positive and negative mood states in healthy volunteers. An earlier study had shown an elevation in mood in healthy subjects following active TSE treatment (Towell et al 1997). This study used the Nowlis Adjective Checklist (Nowlis 1965) to detect change in mood. This is a checklist of positive and negative adjectives which volunteers completed before and after each treatment session. This study found that healthy volunteers felt more “relaxed” and “leisurely” after TSE treatment. We elected to use the newer and more robust scale to determine if TSE could produce a change in mood.

6.9 Short Form 36 Health Survey (SF-36)

The Short Form 36 Health Survey (SF-36) was used in Studies 3, 4, and 5 to assess the benefit if any of TSE treatment on quality of life. This questionnaire has been also used in other chronic pain studies to demonstrate a change in quality of life after certain treatments (Rowbotham et al 1998, Backonja et al 1998 and Ghoname et al 1999a). In the first two studies, the effect of the anticonvulsant agent gabapentin on quality of life was assessed in patients with diabetic neuropathy and postherpetic neuralgia and demonstrated that as the patients pain improved, there was also an improvement in their quality of life scores. Ghoname and colleagues demonstrated in a crossover trial of similar design to ours an improvement in overall quality of life scores in patients who received active percutaneous electrical nerve stimulation (PENS) therapy (Ghoname et al 1999a).

The SF-36 Health Questionnaire was developed from the RAND Corporations Health Insurance Experiment (HIE) and the subsequent Medical Outcomes Study (MOS) as a measure
which is sensitive to health differences in general populations (Ware et al 1980). The aim of
the questionnaire was “to develop a general health survey that is comprehensive and
psychometrically sound, yet short enough to be practical for use in large scale studies of
patients in practice settings” (Ware et al 1980). Initially, the short form 20 General Health
Survey (SF-20) was developed but this had several limitations, the main one being the length of
time that was required for completion. The authors then produced a substantially shortened
version i.e. the SF-36 Health Survey.

The SF-36 Health Survey is a self-administered questionnaire containing 36 items which takes
about 10 minutes to complete (See Appendix 2). It measures health on eight multi-item
dimensions, covering functional status, well-being and overall evaluation of health (Table 1).
Scores on each of the domains are gained by summing item responses and with the use of a
scoring algorithm transforming these raw scores on to a scale from 0 (poor health) to 100 (good
health). Evidence from its use within the UK suggests that respondents find it easy to complete,
as response rates in postal surveys using the questionnaire are high (Brazier et al 1992).

Aims of the dimension of the Questionnaire

Physical functioning: This scale consists of ten questions about physical activity where subjects
are asked to rate their limitations in performing certain activities. It allows for detection of
small differences in function (Ware and Sherbourne 1992). Low scores indicate subjects are
limited a lot in performing activities including bathing and dressing and high scores indicate no
limitations of performance of these activities.

Role functioning: This scale has been designed to capture role limitations due to physical health
(four items) and emotional health (three items). Again, low scores indicate problems with work
or other daily activities as a result of physical or emotional health and high scores indicate that neither physical or emotional health does not interfere with these activities.

### [Chapter 6]. [Table 1] Dimensions of the SF-36 health survey questionnaire

<table>
<thead>
<tr>
<th>Area</th>
<th>Dimension</th>
<th>No of Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional Status</td>
<td>Physical functioning</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Social functioning</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Role limitations (physical Problems)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Role limitations (emotional problems)</td>
<td>3</td>
</tr>
<tr>
<td>Wellbeing</td>
<td>Mental health</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Vitality</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>2</td>
</tr>
<tr>
<td>Overall evaluation of health</td>
<td>General health perception</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Health change *</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>36</strong></td>
</tr>
</tbody>
</table>

* This item is not included in the eight dimensions

**Social functioning:** This scale was designed to determine the extent to which physical or emotional health problems limit interaction with others and the extent of changes in levels of social activity due to changes in health. Low scores indicate extreme interference with normal social activities due to physical or emotional problems. High scores on the other hand indicate no difficulty in performing normal social activities.

**Mental Health:** This is a five item scale which was constructed from questions in the Mental Health Inventory (Ware and Sherbourne 1992). Low scores indicate feelings of nervousness and depression all of the time and high scores indicate a subject who feels happy and calm.
Energy/Vitality: This is a four item scale of vitality (energy level and fatigue) which was also constructed from the Mental Health Inventory. Low scores indicate a subject who feels tired and worn down all the time whereas high scores indicate a person who is full of energy.

Bodily Pain: These two questions ask about intensity of bodily pain and the degree to which pain interferes with normal functional abilities. This was adapted from the Wisconsin Brief Pain Questionnaire (Daut et al 1983). Low scores indicate severe and limiting bodily pain and high scores indicate no pain or limitations because of pain.

General Health Perceptions: This is a five item scale to assess the individuals perception of their own health. High scores indicate that subjects believe their personal health is excellent whereas low scores indicate the opposite.

The validity and reliability of the SF-36 in patient populations has been confirmed in the United States (McHorney et al 1993) and the UK (Brazier et al 1992). The questionnaire has been applied across a wide range of patient groups, including arthritis (Husted et al 1997), stroke (Andresen et al 1996) lupus (Strand et al 1999), traumatic brain injury (Colantio et al 1998), epilepsy (Jacoby et al 1999).

In our trials the SF-36 Questionnaire was completed at the beginning and end of each treatment session by the patient. The scores for each of the 8 dimensions were then calculated by the algorithm (Appendix 3). The change in quality of life scores before and after treatment were then calculated and these were analysed as described in this Chapter Section 6.13.
6.10 Quantitative Sensory Testing (QST)

In Study 6 (Chapter 12), the method of quantitative sensory testing is used for measurement of thermal sensation and pain thresholds. This was performed using the TSA 2001 (Medoc, Advanced Medical Systems, Ramat Vishai, Israel). I set out to determine if TSE would affect heat and cold sensation and heat and cold pain thresholds in healthy volunteers by the method of quantitative sensory testing.

[Chapter 6][Figure 1] This picture shows the quantitative sensory testing machine with the thermode and patient response device in the upper left of the photograph connected to the laptop computer which displays the results of testing.
Quantitative sensory testing allows physiological measurement of sensory neurological function (Dyck PJ 1993) and is used in the examination of chronic neuropathic pain patients (Yarnitsky et al 1997, Attal et al 1998). It consists of a Peltier thermode attached to the thermosensory device and the results are displayed on a connected laptop computer. The Peltier thermode (30cm x 30cm) was attached to the thenar eminence of the dominant hand by means of an elastic velcro tape. The thermostimulator operates by the Peltier principle (Kenshalo et al 1966). By passing an electrical current through two dissimilar semiconductors, heat is displaced in the direction of the current. The plate increases in temperature when the current flows towards it and decreases when the current flows away. The opposite side of the system is buffered by water at 25°C, which acts as a heat sink or heat source depending on the direction of the current. Current direction can be reversed at any time by two switches, one controlled by the subject and one by the examiner. Current intensity determines the rate of change of temperature. The temperature at the surface of the stimulator probe is measured through a thermacouple made of dissimilar wires whose voltage difference varies in response to temperature. Stimulation temperature range was 0°C to 50°C and the rate of increase or decrease of temperature was 1°C per second.

Skin adaptation temperature was always 32°C as demonstrated in previous studies (Attal et al 1998, Yarnitsky et al 1997). This temperature is within the “neutral zone of adapting temperature” (31°C-36°C) at which any thermal sensation induced by application of the probe rapidly vanishes by adaptation (Darian-Smith 1984). The interstimulus interval was 10 seconds. Sensation and pain thresholds were measured through the methods of limits (Furhstorfer et al 1976). To detect the heat and cold sensation threshold, subjects were asked to press a button when they first perceived the heat and cold sensation. This then switched off the desired temperature change and the thermode temperature returns to baseline (32°C) awaiting the next
stimulus. For heat and cold pain thresholds, volunteers were asked to press the button when the
temperature change became uncomfortable. They were told not to tolerate the painful stimulus.
The heat and cold sensation threshold and heat and cold pain threshold was taken as a mean of
four consecutive readings.

All sessions were held in the same room at the same time of day and carried out by the same
investigator who was blinded to the type of TSE treatment the volunteer was undergoing. Each
volunteer had one training run 30 minutes prior to the actual testing session. In Study 6, QST
was performed prior to and following 30 minutes of TSE treatment. Each volunteer had 2
treatment sessions one with the active device and one with the control device in a random
order. All volunteers completed a second session at a minimum interval of 4 days. The mean
change in thermal threshold was calculated as the mean change (baseline minus post test) of
heat and cold sensation and heat and cold pain following both active or inactive TSE treatment.

6.11 Data collection, storage and display

Data for all studies were collected by the author and manually entered onto SPSS (Statistical
Package for the Social Sciences, SPSS Inc Version 9.0, 1998.) spreadsheets on computers in
the University Department of Anaesthesia, Critical Care and Pain Management, Leicester
Royal Infirmary and handled in accordance to the Data Protection Act 1998.

Data display

Data were exported in GraphPad Prism (GraphPad Software Inc, Version 2.0, 1995) for
graphical display or displayed in SPSS when appropriate.
6.12 Study power and sample size calculations

The power of a study is a measure of the likelihood of a statistical test to detect a specified difference between two variables. If $\beta$ is the probability of making a Type II error i.e. failing to demonstrate a statistically significant difference between groups where one exists, the power of a study is the probability of not making a Type II error, and can be defined as power = $(1-\beta)$. (Bourke, Daly et al 1985).

Study 1

When this study was designed there was no published data on the effect of TSE in acute pain. The incidence of request for postoperative analgesia following laparoscopic sterilisation in our institution is 85%. We hypothesized that reducing the incidence of these requests to 50% would constitute a clinically useful affect. It was calculated that with a study power of 80% ($\alpha=0.05$, $\beta = 0.2$), 23 patients would be required per group. A total of fifty patients were recruited for this study (25 per group).

Study 2

We had no current data relating to time to first analgesic request with the use of TSE for postoperative pain relief following elective caesarean section. However, based on previous data, (Dahlgren et al 1997) it was calculated that with 21 patients per group, the study would have a 90% power to demonstrate an increase in time of 30 minutes to first analgesia request ($\alpha=0.05$, $\beta= 0.1$).
Studies 3, 4 and 5

These were the three chronic pain studies looking at the effect of TSE on chronic back pain, chronic lumbar radiculopathy and chronic neck pain. Again, we had no data looking at the effects of TSE in these three groups of patients. However, based on data (Ghoname et al 1999a) where a standard deviation of 1.5 cm was found to be clinically significant on the VAS, it was calculated that 20 patients would need to be recruited to detect a clinically significant difference of 1.3 cm in pain intensity in the VAS for a power of 80% and α error of 0.05. Therefore, a total of 20 patients were recruited into each of these three randomised double blind crossover trials.

Study 6

The power calculation for this study was based on data from an earlier study looking at the effect of TSE treatment on mechanical tolerance changes and mood in healthy volunteers (Towell et al 1997). In order to have an 80% chance of excluding a false positive result and assuming significance at the 0.05 level, it was calculated that 16 volunteers would need to be recruited to detect a 20% change in threshold from baseline. Therefore, 20 volunteers in total were recruited in this study.

6.13 Data analysis

Data distribution

The distribution of the data was analysed using the one sample Kolmogorov-Smirnov goodness of fit test to determine the normality of its distribution. Appropriate non-parametric or parametric tests were then performed.
**Patient and volunteer characteristics**

Ages and body mass indices when measured were compared using Student’s t-test in all studies.

**Categorical variables**

Ordered categorical variables were compared using Chi-squared tests. When small numbers were present in each group, Fisher’s exact test was performed.

**Analysis of repeated measures**

In studies 1 and 2, which examined the effect of TSE treatment on postoperative pain relief, following laparoscopic sterilisation and elective caesarean section, analysis of the visual analogue scores between the two groups (active and control) was carried out using general linear model analysis of variance for repeated measures (with treatment group and time as between- and within-group factors).

In the three chronic pain studies, 3,4 and 5, the measures of the daily visual analogue scores and sleep interference scores were summarized by the area under the curve (AUC). To determine whether there was any statistical significance in the above scores following active or control TSE treatment, a paired Student’s t-test was used to analyse this difference.

**Analysis of time to analgesic request**

This type of analysis was required in Studies 1 and 2 to determine whether TSE treatment made a difference in the time to first analgesic request postoperatively. A survival analysis was performed to determine the probability of patients not requiring postoperative analgesia. Group
comparisons were then made using the log rank test. This data was displayed using a Kaplan-Meier survival plot.

*Analysis of difference in thermal thresholds, mood, SF-MPQ and SF-36 Questionnaires*

These variables were measured in the three crossover trials. Therefore, the data were examined for normality. Data were then analysed using a paired Student’s t-test or Wilcoxon signed-rank test depending on the distribution.
Chapter 7

Efficacy of Transcutaneous Spinal Electroanalgesia in Postoperative Acute Pain Management: Laparoscopic Sterilisation (Study 1)

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<tr>
<th>Section</th>
<th>Page</th>
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<td>7.2 Methods</td>
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<tr>
<td>7.3 Results</td>
<td>141</td>
</tr>
<tr>
<td>7.4 Discussion</td>
<td>144</td>
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<tr>
<td>7.5 Conclusion</td>
<td>145</td>
</tr>
</tbody>
</table>
7.1 Introduction

The effect of TENS in acute postoperative pain has been examined so far with conflicting results (Carroll D et al 1996, Chen et al 1999) (Chapter 4). The review by Carroll and colleagues in 1996 showed, that out of 46 studies on the use of TENS postoperatively, only 17 were of a randomised controlled design to merit inclusion for review, and no reported benefit of TENS over placebo was shown (Carroll D et al 1996). The main fault found with these studies was lack of, or inadequate randomisation as the degree of exaggeration of treatment effect when randomisation is inappropriate can be as much as 40% (Schulz et al 1995). More recent randomised trials with TENS have reported beneficial effects postoperatively with a reduction of morphine consumption, less incidence of postoperative sedation and lower pain scores (Hamza et al 1999b, Chiu et al 1999, Chen et al 1999, Wang et al 1997). However, as the sensation of TENS is always perceived by the patient, these trials are all of a single-blind design.

There are no studies to date looking at the effect of TSE in acute postoperative pain. I therefore proposed to investigate the clinical efficacy, of a TSE device in this setting. Unlike conventional TENS treatment, the TSE electrodes do not induce tingling or painful skin sensations. The active treatment was easily blinded using placebo electrodes (control treatment) (Chapter 6, Section 3).

The results of this study were presented at the Annual Meeting of the American Society of Anesthesiology in New Orleans in October 2001 and published in abstract form in Anesthesiology (Heffernan et al 2001b).
7.2 Methods

Following local ethics committee approval, the informed consent of fifty women scheduled to undergo elective laparoscopic sterilisation was obtained for this prospective randomised double-blind placebo-controlled clinical study. Women (25-41 yrs) with American Society of Anesthesiologists physical status I & II (ASA I & II) were included. Exclusion criteria and statistical analysis were as stated in Chapter 6, Section 2.2 & 13.

Patients were randomised to one of two groups (n=25) per group. Group 1 received a control treatment and Group 2 received an active treatment. The trial was double-blind, neither the patient nor the investigator knew which treatment was being applied. The incidence of request for postoperative analgesia following laparoscopic sterilisation in our institution is 85%. We hypothesized that reducing the incidence of these requests to 50% would constitute a clinically useful effect. With a study power of 80%, it was calculated that 23 patients would need to be recruited per group. A total of 50 patients were recruited (25 per group).

Study Interventions

Patients were fitted with the skin electrodes and leads for use with the TSE device prior to induction of anaesthesia. Anaesthesia was standardised in all patients and included fentanyl 1.5 μg/kg, propofol 1-2 mg/kg and atracurium 0.5 mg/kg for induction and maintained with isoflurane 1% and 60% nitrous oxide in oxygen. A laryngeal mask airway was inserted and the lungs ventilated to normocapnia. Antiemetic prophylaxis was provided with ondanestron 4 mg intravenously. At the end of surgery, a suppository of diclofenac 100 mg was administered.
On reversal of anaesthesia, when patients first opened their eyes to verbal command, the TSE machine was activated. This was taken as time zero. Treatment time for all patients was 30 minutes. A blinded investigator observed patients for three hours postoperatively. Requirement for postoperative analgesia, time to first analgesic request, visual analogue scores at rest and on movement, categorical pain scores, categorical sedation scores, analgesic consumption were recorded. These recordings were initially made every 15 minutes for the first hour and afterwards every 30 minutes (Chapter 6, Section 5). Supplemental analgesia was provided if required in the form of morphine 10 mg intra-muscularly for severe pain and codeine 16 mg and paracetamol 1g for moderate to mild pain. At the end of the observation period, patients were asked following questions.

1. Did they feel any abnormal skin sensations at or underneath the sites of electrode placement? Yes/No.
2. Overall how would they have rated their pain control? Poor, fair, good or excellent.
3. Would they be interested in having TSE for supplemental analgesia following a future operation? Yes/No.

Any adverse events were also recorded e.g., nausea, vomiting, skin tingling or irritation.

7.3 Results

All patients completed the study. There were no significant differences in age or weight between the two groups (Table 1). 80% of patients in the active group requested postoperative analgesia compared with 85% of patients in the control group. This difference was not significant (P=0.3). The mean time to first analgesic request in the active treatment group was 85.7 minutes (95% confidence intervals 71.4-167 minutes) compared with 119.2 minutes in the control group (95% confidence intervals of 44.61-126.75 minutes). This difference was not statistically significant (P=0.1), (Figure 1). There were no statistically significant differences in
the visual analogue scores at rest and on movement between the two groups. However there was a trend towards lower visual analogue scores in the active group (Tables 2&3, Figure 2&3).

[Chapter 7].[Table 1] Patients' characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>TSE</th>
<th>P value (Confidence Intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>33.6(3.89)</td>
<td>34.2 (4.9)</td>
<td>0.49 (-3.3,1.6)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.5 (9.1)</td>
<td>65.5(6.3)</td>
<td>0.38 (-6.4,2.3)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD), n=25 per group. There were no significant differences between the ages and weights of patients in the two groups.

[Chapter 7].[Table 2] VAS for pain at rest

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>Visual Analogue Scores</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (cm)</td>
<td>TSE</td>
</tr>
<tr>
<td>30</td>
<td>5.6 (1.8)</td>
<td>4.6 (2.2)</td>
</tr>
<tr>
<td>60</td>
<td>4.9 (2.3)</td>
<td>4.3 (2.4)</td>
</tr>
<tr>
<td>90</td>
<td>4.1 (2.3)</td>
<td>3.45 (2.2)</td>
</tr>
<tr>
<td>120</td>
<td>3.5 (2.5)</td>
<td>2.89 (2.06)</td>
</tr>
<tr>
<td>150</td>
<td>2.7 (2.2)</td>
<td>2.55 (2.0)</td>
</tr>
<tr>
<td>180</td>
<td>2.81 (2.3)</td>
<td>2.3 (1.8)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD).

The above table shows the VAS scores at rest in the control and TSE group. There is a significant variation over time i.e. decrease in VAS at rest over time in both groups, but there is no difference between groups (general linear model analysis of variance for repeated measures), (P=0.96), (Figure 2).
There were no significant differences in categorical pain scores or categorical sedation scores at any time point. Two patients in each group complained of nausea and vomiting, which was treated with cyclizine 50 mg intra-muscularly. This did not delay their discharge. There was no significant difference in postoperative analgesia required by either group. This technique was well tolerated by both groups of patients. 60% of women in the active group expressed an interest in using TSE following any future surgery compared to 66% in the control group, this was not statistically significant \( P = 0.38 \). One woman in the control group felt sensations i.e. tingling at the skin surface compared to none in the active group. There was no difference in patients overall perception of their pain control between the two groups \( P = 0.57 \) (Table 4).

### [Chapter 7].[Table 3] VAS for pain on movement

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>Visual Analogue Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>30</td>
<td>5.7 (2.1)</td>
</tr>
<tr>
<td>60</td>
<td>4.7 (2.1)</td>
</tr>
<tr>
<td>90</td>
<td>4.2 (2.4)</td>
</tr>
<tr>
<td>120</td>
<td>3.5 (2.8)</td>
</tr>
<tr>
<td>150</td>
<td>2.7 (2.2)</td>
</tr>
<tr>
<td>180</td>
<td>2.7 (2.3)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD).

The above table shows the VAS Scores on movement in the control and TSE group. There is a significant variation over time i.e. decrease in VAS on movement over time in both groups, but there is no difference in VAS on movement between groups (general linear model analysis of variance for repeated measures), \( P = 0.74 \), (Figure 3).
[Table 4] Patient’s rating of their own pain control

<table>
<thead>
<tr>
<th>Rating of pain control</th>
<th>control</th>
<th>TSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>poor</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>fair</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>good</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>excellent</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>total</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

Data expressed as numbers. There was no difference between the two groups in patients overall rating of their own pain control (P=0.57).

7.4 Discussion

In this study, there was no difference in the incidence of requests for postoperative analgesia between the two groups. Nor was there any difference in time to first analgesic request between the two groups. These findings are also reflected in the fact that there are no differences in visual analogue scores at rest or on movement between the control and active groups. Furthermore, there were no differences in categorical pain scores or sedation scores at any time point. Therefore the data suggests that the use of transcutaneous spinal electroanalgesia does not appear to have any effect on the incidence of request for postoperative analgesia, time to first analgesic request or on pain scores following laparoscopic sterilisation.

There is no work in the literature looking at the effect of TSE on postoperative pain. The only published work to date examines the effect of TSE in chronic pain and on pain thresholds in healthy volunteers (Macdonald & Coates 1995, Towell et al 1997). However, Macdonald and colleague state in their article, based on anecdotal evidence, that TSE does not mask acute pain.
e.g. angina or the pain of acute appendicitis. Postoperative pain is not mentioned. The use of TENS has been examined postoperatively. The main conclusion of a review by Carroll and colleagues on the use of TENS in postoperative pain was that there was a lack of randomisation in the trials reviewed and also a huge difficulty in adequately blinding TENS treatment (Carroll et al 1996). Recently, there have been a number of randomised controlled trials looking at the effect of TENS on postoperative pain following hysterectomy, myomectomy and haemorrhoidectomy (Chiu et al 1999, Wang et al 1997, Chen et al 1997, Hamza et al 1999b). They have demonstrated a decrease in postoperative opioid analgesic requirements and a decrease in opioid related side effects. However, unlike this study, these are all single-blind trials.

TSE is a relatively new means of providing analgesia, which had not previously been examined in acute pain. Since, it operates at a higher frequency to TENS, its inventors believe it to be more efficacious to TENS and have demonstrated lower pain scores in comparison to TENS, albeit in only 8 patients (Macdonald & Coates 1995). Furthermore, as no tingling is felt at the skin surface when the machine is switched on, it is easily blinded by means of control electrodes and a device with the ‘on’ switch lighting. While a positive result was not found in this trial with this device, its use was popular with patients, 60% of patients in the active group and 66% in the control group expressing an interest in using it again following any future surgery. There will be further discussion of this and subsequent findings in Chapter 13.

7.5 Conclusion

This randomised double-blind placebo-controlled trial demonstrates that 30 minutes of treatment with transcutaneous spinal electroanalgesia has no effect on requests for
postoperative analgesia, time to first analgesic request, pain scores or total analgesic consumption in women undergoing laparoscopic sterilisation. However I decided that, as this is the first trial looking at the effect of TSE postoperatively, another trial was needed to verify or dispute the above results. I then decided to examine its effect in women undergoing elective caesarean section.
Kaplan-Meier Survival Curve for time to first analgesic request for both groups. There is a longer time to first analgesic request in the TSE group (119 minutes) compared to 85.68 minutes in the control group. This difference is not statistically significant (P=0.1).
The above graph shows the VAS Scores at rest in the control and TSE group. There is a significant variation over time i.e. decrease in VAS at rest over time in both groups, but there is no difference in pain scores between groups (P=0.96) (general linear model analysis of variance for repeated measures).

Data expressed as mean (SEM).
Data expressed as mean (SEM).

The above graph shows VAS on movement in the control and TSE group. There is a significant variation over time i.e. decrease in VAS on movement over time in both groups, but there is no difference between groups (P=0.74).
Chapter 8

Efficacy of Transcutaneous Spinal Electroanalgesia in Acute Postoperative Pain Management following Elective Caesarean Section (Study 2)

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8.5 Conclusion 158
8.1 Introduction

The use of TENS has been examined following elective caesarean section with mixed results (Reynold's et al 1987, Hollinger JL 1986 and Smith et al 1986). None of the above studies were double-blinded and only one was randomised (Smith et al 1986) which as discussed in Chapter 6 can lead to an overestimation of the treatment effect (Schulz et al 1995). Smith and colleagues found that TENS was more effective than placebo TENS (identical stimulator to active TENS, but current only activates indicator light and not electrode leads) in reducing movement-associated incisional pain (Smith et al 1986). However, deep pain was not amenable to TENS treatment and there were no significant differences in analgesic intake observed following either TENS or placebo TENS. Reynolds and colleagues demonstrated no difference in narcotic use or hospital stay after TENS (Reynolds et al 1987). The retrospective chart review demonstrated a lower opioid requirement following TENS but no shorter hospital stay (Holliger et al 1986).

The effect of TSE following caesarean section has not been examined before. We therefore proposed to determine the effect if any of TSE treatment on acute postoperative pain following elective caesarean section. As in all studies, the active treatment mode was blinded using placebo electrodes (Chapter 6 Section 3).

The results of this study were presented at the Joint European Society of Regional Anaesthesia and European Society of Obstetric Anaesthesia Meeting in Warsaw in September 2001 and published in abstract form in The International Monitor (Heffernan et al 2001a)
8.2 Methods

Following local ethics committee approval, the informed consent of forty two women scheduled to undergo elective caesarean section was obtained for this prospective randomised double-blind placebo-controlled clinical study. Women (22-38 yrs) ASA physical status I or II were included who were having an second elective caesarean section with a healthy singleton pregnancy. Exclusion criteria and statistical analysis were as stated in Chapter 6, Sections 2.2 and 13).

Patients were randomised to one of two groups (n=21) per group. Group 1 received a control treatment and Group 2 received an active treatment. The trial was double-blind, neither the patient nor the investigator knew which treatment was being applied. Based on previous data (Dahlgren et al 1997), for the study to have a 90% power, 21 patients per group would need to be recruited to increase the time to first analgesic request by 30 minutes.

Study Interventions

Patients were fitted with the electrodes and leads over the spine at approx T1 and T12 for use with the TSE device prior to induction of anaesthesia. Anaesthesia was standardised in all patients and consisted of a combined spinal epidural technique, 2.5 ml of 0.5% heavy bupivacaine and 20 µg fentanyl were administered into the intrathecal space. An epidural catheter was then placed in the epidural space for administration of postoperative diamorphine. The spread of local anaesthetic was assessed prior to surgery, a dermatomal level of T4 to S4 was demonstrated before allowing surgery to proceed. All patients received diclofenac 100 mg rectally at the end of surgery. When patients first requested analgesia,
diamorphine 2.5 mg was administered epidurally. Postoperatively, all patients were prescribed diclofenac 100 mg 12 hourly and codeine 16 mg, paracetamol 1 g on a PRN basis. When the last stitch was in place the TSE machine was activated for 30 minutes treatment. This TSE treatment was repeated again 3 hours later for a further 30 minutes. Time to first analgesic request, visual analogue scores at rest and on movement, categorical pain scores, categorical sedation scores, analgesic consumption, and adverse events were recorded by a blinded observer. These were made every 30 minutes for each hour after commencement of TSE treatment and then hourly for 6 hours (Chapter 6, Sections 5 & 6). The total analgesic consumption over 24 hours was also recorded for the two groups. At the end of the 24 hour period, all patients were asked the following questions.

1. Did they feel any abnormal skin sensations at or underneath the sites of electrode placement? Yes/No.
2. Overall, how would they have rated their pain control? Poor, fair, good or excellent.
3. Would they be interested in having TSE for supplemental analgesia following a future operation? Yes/No

8.3 Results

One patient in the active treatment group failed to fully complete the study as following the second application of TSE treatment and oral codeine and paracetamol, she was still in severe pain, which necessitated epidural bupivacaine for its relief. There were no significant differences with regard to patients' ages, body mass indices and surgical times between the two groups (Table 1).
There was no difference in the mean time to first analgesic request between the two groups. The mean time to first analgesic request in the control group was 120 minutes (95% confidence interval 100-139.6 minutes) and 119 minutes (95% confidence interval 102-136.8 minutes) in the active treatment group (P=0.66). Pain visual analogue scores at rest and on movement were very low post-operatively in both groups.

**[Chapter 8],[Table 1] Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>TSE</th>
<th>P Value</th>
<th>Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>31.5 (4.1)</td>
<td>31 (4.7)</td>
<td>0.7</td>
<td>(-2.2,3.3)</td>
</tr>
<tr>
<td>BMI (kgm(^2))</td>
<td>27.8 (5.0)</td>
<td>27.9 (3.2)</td>
<td>0.9</td>
<td>(-2.7,2.6)</td>
</tr>
<tr>
<td>Duration surgery</td>
<td>58 (13.3)</td>
<td>57.9 (8.8)</td>
<td>0.9</td>
<td>(-7,7.2)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD), n=21 per group. There were no significant differences between age, body mass index and duration of surgery between the two groups.

There were no differences in VAS at rest or on movement between the groups (Table 2,3, Figures 2,3), data analysed using general linear model analysis of variance for repeated measures. There were no differences in categorical pain scores and categorical sedation scores at any time point between the two groups. TSE did not make any difference to the requirement of postoperative analgesia (P=0.368) over the first 24 hours postoperatively in either group (Table 4). 85% of the patients who received active TSE expressed a preference in using this technique again following any future surgery compared to 71% of the control group. This difference was not statistically significant (P=0.14). No patient in either group felt any tingling at the skin surface. There were no significant differences between the two groups in patients' overall perception of their pain control (P=0.345) (Table 5). Only one patient in the active
treatment group complained of nausea and vomiting, this was at one hour post operatively and was treated with cyclizine 50 mg intramuscularly.

[Chapter 8][Table 2] VAS at rest (cm)

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Control</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.87 (0.99)</td>
<td>0.17 (0.47)</td>
</tr>
<tr>
<td>1</td>
<td>1.5 (1.21)</td>
<td>0.83 (1.81)</td>
</tr>
<tr>
<td>2</td>
<td>2.8 (2.1)</td>
<td>1.97 (1.9)</td>
</tr>
<tr>
<td>3</td>
<td>3.7 (2.62)</td>
<td>4.06 (1.97)</td>
</tr>
<tr>
<td>4</td>
<td>2.4 (2.7)</td>
<td>3.9 (1.92)</td>
</tr>
<tr>
<td>5</td>
<td>2.4 (1.5)</td>
<td>2.44 (1.73)</td>
</tr>
<tr>
<td>6</td>
<td>2.4 (1.98)</td>
<td>2.81 (1.6)</td>
</tr>
<tr>
<td>24</td>
<td>2.78 (2.3)</td>
<td>1.99 (1.65)</td>
</tr>
</tbody>
</table>

[Chapter 8][Table 3] VAS on movement (cm)

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Control</th>
<th>TSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1.1 (1.2)</td>
<td>0.47 (0.8)</td>
</tr>
<tr>
<td>1</td>
<td>2.1 (1.6)</td>
<td>1.5 (2.3)</td>
</tr>
<tr>
<td>2</td>
<td>3.4 (1.8)</td>
<td>3.6 (2.3)</td>
</tr>
<tr>
<td>3</td>
<td>3.8 (2.3)</td>
<td>5.08 (2.3)</td>
</tr>
<tr>
<td>4</td>
<td>1.1 (1.1)</td>
<td>1.1 (0.48)</td>
</tr>
<tr>
<td>5</td>
<td>3.1 (2.0)</td>
<td>3.9 (1.7)</td>
</tr>
<tr>
<td>6</td>
<td>3.4 (2.3)</td>
<td>2.8 (1.90)</td>
</tr>
<tr>
<td>24</td>
<td>3.6 (2.1)</td>
<td>3.1 (1.6)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD).

There were no significant differences in VAS for pain at rest or on movement between control and TSE groups (general linear model analysis of variance for repeated measures).
### Requests for post operative analgesia

<table>
<thead>
<tr>
<th>No of requests for postoperative medication</th>
<th>Control</th>
<th>TSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>20</td>
</tr>
</tbody>
</table>

Data expressed as numbers.

There was no difference between the two groups in requests for postoperative analgesia (P=0.368).

### Patients rating of their own pain control

<table>
<thead>
<tr>
<th>Patient's rating</th>
<th>Control</th>
<th>TSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Fair</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Good</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Excellent</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>20</td>
</tr>
</tbody>
</table>

Data expressed as numbers.

There was no significant differences between the two groups in patients overall rating of their pain control (P=0.345).

The only other adverse event reported was that of pruritus and while there was no significant differences in its incidence between the two groups, it occurred most commonly in the active treatment group (Table 6).
Table 6: Incidence of Pruritus Postoperatively

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Control No of Patients</th>
<th>Active No. of Patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>4</td>
<td>0.343</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0.606</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>0.488</td>
<td></td>
</tr>
</tbody>
</table>

Data expressed as numbers.

While there are no significant differences in the incidence of pruritus across the two groups there, it occurred predominantly in the active TSE group. Pruritus only occurred at the time points shown.

8.4 Discussion

TSE did not reduce the time to first analgesic request, in fact the times to first analgesic request in both groups are almost the same. The visual analogue scores for pain were very low in both groups postoperatively, this reflects the very low level of postoperative pain that this patient group demonstrate. There were also no significant differences in visual analogue scores at rest (P=0.947) or on movement (P=0.983), postoperatively when analysed using general linear model analysis of variance for repeated measures (Tables 2,3 & Figures 2,3). This technique was also popular with patients with 85% of patients in the active group expressing an interest in using it again following future surgery compared to 71% in the control group. The main adverse effect reported is that of pruritus, which was reported predominantly, but not significantly in the active group (Table 6). The pruritus observed was a generalized predominantly affecting the upper trunk and arms and it is known to be a complication associated with opioid administration (Colbert et al 1999).
These results compare with the results of our earlier randomised double blind study (Chapter 7) in that there is no difference in time to first analgesic request associated with active TSE treatment. There is no difference between groups in the VAS at rest and on movement, however the VAS in both groups increase with time (Figure 2,3). As this effect appears to occur in both groups, both at rest and on movement, it is thought to be due to the diminishing effect of spinal anesthesia. As in our earlier study, there is no difference in categorical pain and sedation scores and in total analgesic consumption between the two groups.

TENS has yet to be shown to have a definitive analgesic effect in postoperative analgesia following elective caesarean section. It has already shown a reduction in cutaneous associated pain following caesarean section but this was not a double blind trial (Smith et al 1986).

8.5 Conclusion

The results of this study demonstrate that treatment with TSE following elective caesarean section show no reduction in time to first analgesic request or reduction in pain scores postoperatively. These results concur with the results of our earlier study in Chapter 7.
Kaplan-Meier Survival Curve for time to first analgesic request for both groups. There were no significant differences in time to first analgesic requests between the two groups (P=0.6).
Data expressed as mean (SEM).

There were no significant differences in VAS at rest between the two groups (general linear model analysis of variance for repeated measure), (P=0.947).
Data expressed as mean (SEM).

There were no significant differences in VAS on movement between the two groups (P=0.983). At four hours, all patients in both groups have had epidural diamorphine and a second 30 minute application of TSE which may explain the decrease in VAS on movement. Furthermore, the effect of spinal anaesthesia would have worn off. The subsequent increase in VAS on movement may be due to the lack of analgesic effect from the TSE machine in combination with increased mobility associated with decreased spinal anaesthesia.
Chapter 9

Efficacy of Transcutaneous Spinal Electroanalgesia in Patients with Chronic Lumbar Back Pain (Study 3)

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9.2 Methods 164
9.3 Results 165
9.4 Discussion 167
9.5 Conclusion 168
9.1 Introduction

It is in the management of chronic pain that TENS probably has its most widespread use (Chapter 4, Section 4.2.5). However, results in this area are somewhat conflicting (Bates et al 1980, Deyo et al 1990b, Chabal et al 1998). When it is used to treat chronic pain, its onset of analgesic effect is thought to be very slow (McQuay et al 1997). The reason for this may be as stated in Chapter 4 (Section 4.2.5), i.e. variable stimulation sites, frequencies, durations of electrical stimulation as well as the patient’s psychological profile (White et al 2001). It is believed that more randomised controlled trials with standard outcome measures, treatment times and stimulation parameters are needed before the efficacy of TENS in chronic pain can be properly evaluated (Carroll et al 2001, Milne et al 2001).

Before the advent of transcutaneous spinal electroanalgesia, spinal cord stimulation afforded another way of treating very severe, disabling, chronic pain conditions. However, this is a costly invasive procedure for which strict patient selection appears to be the key to its success (Turner et al 1995). The most common indication for this procedure is FBSS (North et al 1995) but it is not the majority of patients attending the chronic pain clinic with back pain that fall into this category.

The development of transcutaneous spinal electroanalgesia may provide clinicians with another method of simulating spinal cord stimulation without the huge cost and invasive procedure (Macdonald & Coates 1995). To validate this method the investigators performed the three trials as described in Chapter 5, Section 3 and showed that it produced 60% relief after five weekly treatments in 63% of chronic pain patients whose pain was of relatively recent origin (2.6yrs) (Macdonald & Coates 1995). They also compared TSE with TENS in patients with a
one year history of musculoskeletal pain and found that TSE produced a decrease in SF-MPQ scores, reduction in referred area of pain and an increase in pain threshold (Macdonald & Coates 1995). However, this was a very small study population of only 8 patients and involved only one twenty-minute session with TENS and TSE.

In the next three trials, the clinical efficacy of TSE in the chronic pain population has been evaluated. The three main subgroups of patients that would be referred for TENS treatment at the chronic pain clinic at the Leicester Royal Infirmary have been chosen. These are patients with chronic lumbar back pain, chronic lumbar radiculopathy and chronic neck pain.

The results of this trial (Chapter 9) have been accepted for presentation at the World Congress on Pain in San Diego, August 2002.

9.2 Methods

Following local ethics committee approval, the informed consent of 20 patients with chronic lumbar pain greater than six months duration (45 to 70 yrs) was obtained for this prospective randomised double-blind placebo-controlled crossover clinical trial. Exclusion criteria and statistical analysis were as stated in Chapter 6, Sections 2.2 & 13. Based on data from (Ghomane et al 1999a), it was calculated that 20 patients would need to be recruited to detect a clinically significant difference of 1.3 cm in pain intensity in the visual analogue scale for a study power of 80%. This was a three week trial during which the patient received either control or active TSE treatment for week 1, had a “washout period” of no treatment for week 2 and a further week of either control or active treatment for the final week. Each patient therefore received both control and active TSE treatment in a random order. Both investigator
and patient were blinded at all stages of the trial. Randomisation was by the sealed envelope technique. The dummy device used placebo electrodes, i.e. when the device was activated no current was passed (Chapter 6, Section 3).

**Study Interventions**

Correct use of the device was demonstrated to each patient and they were instructed to use it for 30 minutes treatment twice daily (morning and evening) at home. This is the treatment time and time gap recommended by its inventors (Macdonald & Coates 1995). The electrodes were positioned directly over the spine at the levels of T1 and T12. Following seven days treatment, they then returned to the clinic and commenced the seven day "washout" period during which they no treatment. They then returned after a further seven days and were given a different device for the final seven day period. VAS for pain and sleep interference, Short Form McGill Questionnaires and Short Form-36 quality of life questionnaire were filled out at the beginning and end of each treatment section. Repeat VAS assessments of pain and sleep interference were filled out daily by patients. Finally, patients were asked to record their medication history over the three weeks.

9.3 Results

All patients fully complied with the study protocol throughout the study period. Twenty patients, 6 male and 14 women (mean age 58.1yrs SD 8.3) were recruited into this randomised double-blind placebo-controlled crossover trial. There was a greater change in VAS (difference between the beginning and end of treatment) following control TSE treatment than following active TSE treatment (P= 0.01) (Table 1,Figure 1). Control treatment demonstrated significantly lower area under the curve also, compared with the area under the curve for active
There was no difference in sleep interference during either week (P=0.72) (Figure 3).

[Table 1] Change in VAS pain, AUC for VAS for pain and sleep interference scores following control and active TSE treatment

<table>
<thead>
<tr>
<th></th>
<th>Control Mean (SD)</th>
<th>Active Mean (SD)</th>
<th>P (CI of difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in VAS pain (cm)</td>
<td>-1.9 (1.9)</td>
<td>0.4 (2.2)</td>
<td>0.01 (-3.93, -0.65)*</td>
</tr>
<tr>
<td>AUC VAS pain scores (cm day)</td>
<td>25.5 (9.3)</td>
<td>31.8 (10.1)</td>
<td>0.02 (-10.2, -0.93)†</td>
</tr>
<tr>
<td>AUC VAS sleep interference (cm day)</td>
<td>24.1 (12.7)</td>
<td>23.4 (14.3)</td>
<td>0.72 (-2.8, 4.1)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD).

* P<0.05. There was a greater change in VAS score for pain following control TSE treatment.

† P<0.05. The Area under the Curve for VAS for pain following control TSE treatment was significantly lower than that following active TSE treatment. There was no difference in the VAS for sleep interference as summarized by the Area under the Curve (P=0.72).

[Table 2] Change in Short Form McGill Pain Scores

<table>
<thead>
<tr>
<th></th>
<th>Control Change Mean (SD)</th>
<th>Active Change Mean (SD)</th>
<th>P value (CI's of difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Sensory (No)</td>
<td>-2.5 (6.5)</td>
<td>-1.65 (7.3)</td>
<td>0.69 (-5.2, 3.5)</td>
</tr>
<tr>
<td>Change in Affective (no)</td>
<td>-1.00 (2.0)</td>
<td>-0.35 (3.7)</td>
<td>0.47 (-2.4, 1.6)</td>
</tr>
<tr>
<td>Total Change (no)</td>
<td>-3.5 (7.4)</td>
<td>-2.0 (10.1)</td>
<td>0.60 (-7.3, 4.3)</td>
</tr>
<tr>
<td>PPI (no)</td>
<td>-0.65 (1.9)</td>
<td>-0.1 (0.9)</td>
<td>0.13 (-1.2, 0.18)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD). There was no difference in Short Form McGill Scores following control or active TSE treatment.
### Table 3: Change in quality of life components following control and active TSE treatment.

<table>
<thead>
<tr>
<th>Component</th>
<th>Change Control</th>
<th>Change Active</th>
<th>P value (CI of difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function</td>
<td>2.5 (0,5)</td>
<td>0 (-5.8.75)</td>
<td>0.59 (-5.0,10.0)</td>
</tr>
<tr>
<td>Role physical</td>
<td>0 (-25,18.75)</td>
<td>0 (0.25)</td>
<td>0.58 (-25.0,12.5)</td>
</tr>
<tr>
<td>Role mental</td>
<td>0 (0,0)</td>
<td>0 (0,44)</td>
<td>0.57 (-33.5,16.5)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>0 (-11,11)</td>
<td>0 (-11.75,11)</td>
<td>0.244 (-5.5,27.5)</td>
</tr>
<tr>
<td>Mental health</td>
<td>0 (-4.0,11.0)</td>
<td>2 (-7,7)</td>
<td>0.837 (-8.0,12.0)</td>
</tr>
<tr>
<td>Energy</td>
<td>0 (0,13.75)</td>
<td>-2.5 (-13.75,5)</td>
<td>0.248 (-5.0,20.0)</td>
</tr>
<tr>
<td>Pain</td>
<td>0 (-11,11)</td>
<td>0 (-11,11)</td>
<td>0.281 (-5.5,16.5)</td>
</tr>
<tr>
<td>General perception health</td>
<td>0 (-5,5)</td>
<td>-2.5 (-6.5,10)</td>
<td>0.861 (-10,7.5)</td>
</tr>
</tbody>
</table>

Data expressed as median (IQR).

There were no significant differences in any of the changes of the components of the quality of life scores following either active or control TSE treatment.

There were no differences in sensory or affective components or present pain intensity scores of the SF-MPQ following either control or active TSE treatment (Table 2).

There were no differences in the change of any of the quality of life components of the SF-36 questionnaire following control or active TSE treatment (Table 3). Patients’ analgesic requirement during either week is displayed in Table 4.

### 9.4 Discussion

The data suggest that control TSE brings about a greater reduction in the visual analogue scale for pain and that a placebo effect is prevented by active TSE. There is also a significant difference in the area under the curve of the visual analogue scale for the control group.
However there is no significant difference in the change in McGill Pain Scores following control or active TSE treatment. Nor was any difference in quality of life demonstrated.

This work is in contrast to earlier work by Macdonald and Coates with TSE (Macdonald & Coates 1995). They have found in patients with a long history of chronic pain that TSE significantly reduces their pain and also produced a marked reduction in McGill Pain Scores. However, their studies were small and not limited to a specific painful condition as I have done. Results with TENS have shown reductions in pain scores, however earlier studies were not randomised (Bates et al 1980). The two other studies looking at the effect of TSE in chronic lumbar radiculopathy and chronic neck pain (Chapters 10, 11) provide conflicting results to this study; while not demonstrating an improvement with active TSE, no difference was found following either treatment.

In properly selected patients, spinal cord stimulation is considered cost effective when used for an average of 5.5 years (Bell et al 1997). It has been demonstrated to have good results in chronic pain, particularly neuropathic pain (Turner et al 1995, Tesafaye et al 1996). However there still remains a lack of randomised, prospective, controlled trials concerning its efficacy and cost-effectiveness relative to less invasive modalities.

9.5 Conclusion

The data show that treatment with a placebo TSE device has reduced the pain intensity in patients with chronic lumbar back pain and no effect with active treatment. However, there has been no difference demonstrated in McGill pain scores or quality of life. These results contrast to the following 2 studies (Chapter 10,11).
[Chapter 9].[Figure 1]

Data expressed as mean (SEM).

There was a greater change in the VAS for pain following control treatment (P=0.01).
### Patients' analgesic requirement expressed as number of tablets during control and active TSE treatment

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Control</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>28</td>
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<td>7</td>
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<td>8</td>
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<td>10</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>11</td>
<td>98</td>
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<tr>
<td>20</td>
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</tr>
</tbody>
</table>

Data expressed as numbers.

The above table shows the number of analgesic tablets required by each patient during each week with either active and control TSE treatment.
Data expressed as mean (SEM).

This graph shows the VAS for pain over the seven day period following control and active TSE treatment. When summarised by Area under the Curve, they were significantly lower for the control group compared with the active group (paired Student’s t-test) (P=0.02).

[Chapter 9], [Figure 2]
Data expressed as mean (SEM).

There were no significant differences in VAS for sleep interference following control or active TSE treatment when summarised by the Area under the Curve (P=0.72).
Chapter 10

Efficacy of Transcutaneous Spinal Electroanalgesia in Chronic Lumbar Radiculopathy (Study 4)

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<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
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<td>10.1 Introduction</td>
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<tr>
<td>10.2 Methods</td>
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</tr>
<tr>
<td>10.4 Discussion</td>
<td>177</td>
</tr>
<tr>
<td>10.5 Conclusion</td>
<td>179</td>
</tr>
</tbody>
</table>
10.1 Introduction

The objective of this study was to determine if transcutaneous spinal electroanalgesia has a beneficial effect in a group of chronic neuropathic pain patients i.e. patients with a radicular element to their back pain. Again, these patients are another large subgroup of patients attending our pain clinic referred for TENS therapy. There is some evidence to demonstrate that TENS is effective in some types of neuropathic pain, namely postthoracotomy pain and diabetic neuropathy (Carroll & Badura 2001, Somers & Somers 1999). Furthermore, the best results with spinal cord stimulation have been shown with patients with peripheral neuropathy (Kumar et al 1998). A recent study published in the Lancet has demonstrated effective analgesic relief and improved exercise tolerance in patients with diabetic neuropathy following the insertion of spinal cord stimulators (Tesaye et al 1996). However, the effects of TSE on neuropathic pain have not yet been examined.

The results of this study have been presented at the European Society of Anaesthesiologists Meeting in April 2002 and published in abstract form in the European Journal of Anaesthesia (Heffernan et al 2002a).

10.2 Methods

Following local ethics committee approval, the informed consent of 20 patients with chronic lumbar radicular (unilateral or bilateral leg pain) greater than six months duration was obtained for this prospective randomised double-blind placebo-controlled crossover clinical trial. Exclusion criteria and statistical analysis were as stated in Chapter 6, Sections 2.2 & 13. The
calculation for power determination was based on the same study as used in Chapter 9 (Ghoname et al 1999a). This was a three week trial during which the patient received either control or active TSE treatment for week 1, had a “washout period” of no treatment for week 2 and a further week of either control or active treatment for the final week. Each patient therefore received both control and active TSE treatment in a random order. Both investigator and patient were blinded at all stages of the trial. The dummy device used placebo electrodes i.e when the device was activated no current was passed (Chapter 6, Section 3).

Study Interventions

Prior to commencing the trial, use of the TSE device was demonstrated to each patient. Each patient was shown how to apply the electrodes in the midline over the spinous processes at the levels of T1 and T12. They were asked to wear the TSE machine for 30 minutes treatment twice daily, which is the recommended treatment time as per the inventors (Macdonald & Coates 1995). Following seven days treatment, they then returned to the clinic and commenced the seven day “washout period” during which they had no treatment. Following this, they returned again and were given a different device for the final seven day period. VAS Scores for pain (neuropathic leg pain) and sleep interference, Short Form McGill Questionnaires and the Short Form Quality of Life Survey (SF-36) were filled out at the beginning and end of each treatment session. Repeat VAS assessments of pain and sleep interference were filled out daily by patients. Finally, patients were asked to record their medication history over the three weeks.

10.3 Results

Twenty patients were recruited into this study and all completed the three week trial period, recording pain and sleep scores following twice daily usage of the machine. There were nine
males with a mean age of 56 yrs (SD 9.72) eleven females with a mean age of 48 years (SD 13.1). There was no difference in the change (difference between beginning and end of treatment) in visual analogue scales for pain following control or active TSE treatment (P=0.88) (Table 1, Figure 1). No differences in the area under the curves for pain or sleep interference following either type of TSE treatment were found also (Table 1, Figure 2 &3). There were no significant differences in either the sensory and affective categories and the present pain intensity index of the Short Form McGill Questionnaire following either control or active TSE treatment (Table 2). There was a significant difference in the change of the social functioning component of the quality of life questionnaire following active TSE treatment P=0.01 (Table 3).

[Chapter 10][Table 1]  Change in VAS pain, AUC of VAS for pain and sleep interference scores following control and active TSE treatment

<table>
<thead>
<tr>
<th></th>
<th>Control Mean (SD)</th>
<th>Active Mean (SD)</th>
<th>P (CI of difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in VAS pain (cm)</td>
<td>-0.5 (1.5)</td>
<td>-0.6 (1.7)</td>
<td>0.88 (-0.9,1.1)</td>
</tr>
<tr>
<td>AUC VAS pain scores (cm day)</td>
<td>33.4 (12.4)</td>
<td>30.8 (12.3)</td>
<td>0.32 (-2.3,6.7)</td>
</tr>
<tr>
<td>AUC VAS sleep interference (cm day)</td>
<td>29.0 (15.3)</td>
<td>26.4 (14.7)</td>
<td>0.23 (-1.8, 6.8)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD).

There were no differences in change in VAS, AUC pain score and AUC sleep score following either active or control TSE treatment.
[Chapter 10]. [Table 2] Change in SF-MPQ Scores

<table>
<thead>
<tr>
<th></th>
<th>Control Change Mean (SD)</th>
<th>Active Change Mean (SD)</th>
<th>P value (CI's of the difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Sensory (no)</td>
<td>-0.32 (3.5)</td>
<td>-2.78 (5.03)</td>
<td>0.06 (-0.09,5.0)</td>
</tr>
<tr>
<td>Change in Affective (no)</td>
<td>-0.47 (2.3)</td>
<td>-1.05 (2.4)</td>
<td>0.36 (-0.9,2.1)</td>
</tr>
<tr>
<td>Total Change (no)</td>
<td>-0.74 (4.2)</td>
<td>-3.95 (6.6)</td>
<td>0.06 (-0.3,6.1)</td>
</tr>
<tr>
<td>PPI (no)</td>
<td>-0.32 (1.2)</td>
<td>-0.11 (0.94)</td>
<td>0.27 (-0.3,1.1)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD).

While the mean change in all the above components of the McGill Score was greater in the active group, they did not reach statistical significance.

There was no difference in the change of any of the other quality of life components of the SF-36 questionnaire i.e. physical functioning, role physical, role mental, mental health, energy, pain or health perception following either control or active TSE treatment (Table 3).

10.4 Discussion

The data suggests that one weeks treatment with TSE does not produce any reduction in pain intensity as measured on a visual analogue scale for pain for patients with chronic lumbar radiculopathy. This is also demonstrated by no change in McGill Scores and no change in Present Pain Intensity Indices when active TSE treatment is compared with control TSE treatment. There was however a significant difference in the social functioning component of the quality of life score following active TSE treatment. This is the component of the SF-36 questionnaire that determines the extent to which health problems limit normal social interactions. This is likely to be a real difference, rather than it occurring by chance (P=0.01).
What effect this would have for patients when everything else remains the same remains unknown.

[Chapter 10]. [Table 3] Change in quality of life components following control and active TSE treatment.

<table>
<thead>
<tr>
<th></th>
<th>Change</th>
<th>Control</th>
<th>Change</th>
<th>Active</th>
<th>P value (CI's of difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function</td>
<td>2.5 (-5, 13.75)</td>
<td>2.5 (-8.75, 9)</td>
<td></td>
<td>0.59 (-6.0, 14.5)</td>
<td></td>
</tr>
<tr>
<td>Role physical</td>
<td>0 (0,0)</td>
<td>0 (-18.75, 0)</td>
<td></td>
<td>0.65 (-12.5, 25.0)</td>
<td></td>
</tr>
<tr>
<td>Role mental</td>
<td>0 (0,0)</td>
<td>0 (0,25.5)</td>
<td></td>
<td>0.95 (-33.5, 33.5)</td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>0 (-11.0)</td>
<td>11 (0,30.5)</td>
<td></td>
<td>0.01 (-28.0, -5.5)</td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>2 (-11.15)</td>
<td>10 (-4.23)</td>
<td></td>
<td>0.6 (-14.0, 10.0)</td>
<td></td>
</tr>
<tr>
<td>Energy</td>
<td>0.5 (-8.75, 10)</td>
<td>0 (-21.25, 13.75)</td>
<td></td>
<td>0.88 (-14.0, 10.0)</td>
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<tr>
<td>Pain</td>
<td>5.5 (0.19, 25)</td>
<td>5.5 (-8.25, 11)</td>
<td></td>
<td>0.71 (-11.0, 13.0)</td>
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<td>General health perception</td>
<td>0 (-2.13.25)</td>
<td>3 (-9.5, 10)</td>
<td></td>
<td>0.89 (-10.0, 12.0)</td>
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</tbody>
</table>

Data expressed as median (IQR).

* P<0.05 There was a greater mean change in the social functioning component of the SF-36 Questionnaire following active TSE treatment. There was no statistical significance between any of the other components.

While earlier work has demonstrated a reduction in chronic pain associated with TSE (some of the patients studied had evidence of radicular pain), it has not looked specifically at the pain associated with chronic lumbar radiculopathy (Macdonald & Coates 1995). TENS has been used before and been shown to be effective in patients with neuropathic pain, namely postthoracotomy pain and diabetic neuropathy (Carroll & Badura 2001, Somers & Somers 1999). However, the first study by Carroll and colleagues is neither randomised nor is there any placebo group for comparison (Carroll & Badura 2001). Somers and colleague have
demonstrated effective reduction in painful diabetic neuropathy with a case report in a patient whose pain was significantly improved with TENS therapy (Somers & Somers 1999). As mentioned earlier the best results with spinal cord stimulation have been shown in patients with neuropathy but there is a lack of randomised trials to demonstrate clear results (Turner et al 1995).

10.5 Conclusion

While we have failed to demonstrate a reduction in pain intensity in patients with chronic lumbar radiculopathy as demonstrated on the visual analogue scale following the use of TSE, it does appear to demonstrate an improvement in the social functioning component of the quality of life survey. This is in contrast to the studies outlined in Chapter 8 and 10.
[Chapter 10]. [Table 4] Patients' analgesic requirement during the trial

<table>
<thead>
<tr>
<th>Patient No</th>
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</thead>
<tbody>
<tr>
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<td>32</td>
</tr>
</tbody>
</table>

Data expressed as numbers.

The above table shows the number of analgesic tablets taken by each patient during the control and active week of the trial. Looking objectively at the numbers there does not seem to be any difference in number of tablets taken during either week.
Mean change (SD) in VAS for pain following control or active TSE treatment. This is not significant (P=0.88)(paired Student's t test).
Data expressed as mean (SEM). There were no significant differences in VAS Scores for pain following control or active TSE treatment when summarised by the Area under the Curve (P=0.32)
There was no difference in the VAS for sleep interference when summarised by the Area under the Curve following either control or active TSE treatment ($P=0.23$).
Chapter 11

Efficacy of Transcutaneous Spinal Electroanalgesia in Chronic Nociceptive Neck Pain (Study 5)

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
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<tbody>
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<td>11.2 Methods</td>
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<td>11.3 Results</td>
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<tr>
<td>11.4 Discussion</td>
<td>188</td>
</tr>
<tr>
<td>11.5 Conclusion</td>
<td>190</td>
</tr>
</tbody>
</table>
11.1 Introduction

This final subgroup of patients with chronic pain was studied as they are the third largest patient population requiring TENS treatment at our pain clinic. There is little work in the literature looking at the effect of TENS in chronic neck pain specifically. Two studies have compared placebo TENS to acupuncture in patients with chronic neck pain (Petrie & Langley 1983, Petrie & Hazlmann 1986). In both studies acupuncture proved superior to placebo TENS. A meta-analysis of the conservative management of mechanical neck pain found no improvement with TENS over other treatments (physical therapies, collar, rest) (Aker et al 1996). Treatment with a different form of electrotherapy, PENS in chronic neck pain, demonstrated short term improvement in pain intensity in patients with chronic neck pain (White et al 2000). However the effect of TSE treatment has yet to be evaluated in this group of patients. The study objective therefore was to determine whether twice daily treatment with TSE would reduce pain intensity.

The results of this study were presented at the Anaesthetic Research Society Meeting in Nottingham in November 2001 and published in abstract form in the British Journal of Anaesthesia. (Heffernan et al, 2002b).

11.2 Methods

Following local ethics committee approval, the informed consent of 20 patients with chronic nociceptive neck pain greater than six months duration (25 to 65 yrs) was obtained for this prospective randomised double-blind placebo-controlled crossover clinical trial. Exclusion criteria and statistical analysis were as stated in Chapter 6, Sections 2.2 & 13. The calculation
for power determination was based on the same study as used in Chapter 9, Section 12 (Ghoname et al a). This was a three week crossover trial of the same design as the previous two chronic pain trials in Chapters 9 & 10. Each patient therefore received both active and control TSE treatment for a period of one week separated by a one week “washout” of no treatment. Both investigator and patient were blinded at all stages of the trial. The dummy device used placebo electrodes, when the device was activated no current was passed (Chapter 6.3).

**Study Interventions**

Patients were shown how to use the TSE device. They were instructed to wear the electrodes over the transverse processes of C4/5 and to use the device for 30 minutes twice daily. This is the treatment time recommended by its inventors (Macdonald & Coates 1995). Following seven days treatment, they then returned to the clinic and commenced the seven day “washout” period during which they received no treatment. After the “washout period”, they returned to the clinic and were given a different TSE device for the final seven days. The following scores were filled out at the beginning and end of each treatment session, VAS for pain and sleep interference, Short Form McGill Questionnaire and Short Form Quality of Life Survey (SF-36) (similar to Studies 3,4, Chapters 9 & 10). Repeat VAS assessments of pain and sleep interference were filled out daily by patients. Patients also recorded their medication history over the 3 weeks.

**11.3 Results**

Twenty patients (13 female, 7 male) completed the study, mean age 49.8 (10.5) yrs. All completed pain, sleep scores and used the machine twice daily. There was a no difference in the change in VAS (i.e. difference between beginning and end of treatment) for pain following
either control or active TSE treatment (P=0.12) (Table 1, Figure 1). There were no significant differences in the area under the curves for pain and for sleep interference scores following either treatment (Table 1), (Figure 2,3).

[Chapter 11]. [Table 1] Change in VAS pain, AUC for VAS pain and sleep interference scores and Short Form McGill Pain Scores

<table>
<thead>
<tr>
<th></th>
<th>Control Mean (SD)</th>
<th>Active Mean (SD)</th>
<th>P (CI of difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in VAS pain (cm)</td>
<td>-0.06 (1.7)</td>
<td>-1.2 (2.27)</td>
<td>0.12 (-0.3,2.5)</td>
</tr>
<tr>
<td>AUC VAS pain scores (cm day)</td>
<td>27.4 (12.8)</td>
<td>26.8 (11.2)</td>
<td>0.64 (-2.2,3.5)</td>
</tr>
<tr>
<td>AUC VAS sleep interference (cm day)</td>
<td>25.0 (13.6)</td>
<td>22.7 (12.4)</td>
<td>0.42 (-3.2,7.7)</td>
</tr>
<tr>
<td>Change in McGill Score (no)</td>
<td>-1.35 (9.01)</td>
<td>-4.25 (9.2)</td>
<td>0.12 (-3.7, 9.5)</td>
</tr>
<tr>
<td>Change in PPI (no)</td>
<td>0.15 (1.0)</td>
<td>-0.7 (1.5)</td>
<td>0.09 (-0.1, 1.8)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD).

There were no significant differences in change in VAS scores, AUC pain score and AUC sleep interference score following either active or control TSE treatment. There were also significant differences in the change in SF-MPQ Scores following control and active TSE treatment.

There were no significant differences in change in McGill Score and change in present pain intensity index (PPI) following control or active TSE treatment (Table 1). There were no significant differences in any of the quality of life components of the SF-36 Questionnaire (physical functioning, role physical, role mental, social functioning, mental health, energy, pain and health perception), (Table 2). Patients analgesic requirement (expressed as number of tablets) during the week in which they had control TSE and the week in which they had active TSE is shown, looking objectively at the numbers there does not appear to be any difference in amount of medication used in either week (Table 3).
[Chapter 11]. [Table 2] Change in quality of life components following control and active TSE treatment.

<table>
<thead>
<tr>
<th></th>
<th>Change median (IQR)</th>
<th>Control</th>
<th>Change median (IQR)</th>
<th>Active</th>
<th>P value (CI of difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function</td>
<td>0 (-8.8,5.0)</td>
<td>5 (-1,15)</td>
<td>0.09 (-22.5,1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role physical</td>
<td>0 (0,25.0)</td>
<td>0 (0,25)</td>
<td>0.84 (-12.5,12.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role mental</td>
<td>0 (0,33.0)</td>
<td>0 (0,33)</td>
<td>0.66 (-17,33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>0 (-8.3,9)</td>
<td>11 (0,22)</td>
<td>0.17 (-27,5.5)</td>
<td></td>
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</tr>
<tr>
<td>Mental health</td>
<td>5 (-6,16)</td>
<td>8 (3,3,16)</td>
<td>0.60 (-10,8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy</td>
<td>2.5 (-5,1)</td>
<td>5 (-10,23.8)</td>
<td>0.78 (-20,5)</td>
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</tr>
<tr>
<td>Pain</td>
<td>5.5 (0,19.25)</td>
<td>5.5 (0,22)</td>
<td>0.94 (-11,11)</td>
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<tr>
<td>General health perception</td>
<td>0 (-5.8,8.75)</td>
<td>0 (-10,20.3)</td>
<td>0.91 (-12.5,8.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data expressed as median (IQR)

There were greater changes in physical functioning, social functioning, mental health, energy, and general health perception associated with active TSE treatment but they were not statistically significant.

11.4 Discussion

The data shows that treatment with a TSE device does not appear to reduce pain intensity in this subgroup of patients. This is demonstrated by the fact that there was no difference in the change in VAS (Table 1, Figure 1). Further evidence to support this, is shown by no difference in the area under the curve for the VAS pain scores, no change in McGill Scores and no change in present pain intensity indices following either control or active treatment. Sleep interference was also not reduced. Finally there was no change in the any of the eight components of the quality of life score following either control or active TSE treatment.
[Chapter 11][Table 3] Patients analgesic requirement during both control and active TSE treatment week

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Control</th>
<th>Treatment</th>
</tr>
</thead>
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</tr>
<tr>
<td>19</td>
<td>54</td>
<td>60</td>
</tr>
<tr>
<td>20</td>
<td>42</td>
<td>48</td>
</tr>
</tbody>
</table>

Data expressed as numbers.

The above table shows the number of tablets taken by each patient during the weeks in which they had control and active TSE treatment.

There is little work to date looking at the effect of TSE in chronic pain. Mcdonald and Coates have demonstrated a reduction in McGill pain scores and reduction in size of the painful area as shown associated with TSE when compared to TENS treatment (Mcdonald & Coates 1995).
Only eight patients were recruited into this trial and only two complained of chronic neck pain. Furthermore, this was a crossover trial and each patient only received one twenty minute session with each treatment. The use of TENS in chronic neck pain has also been demonstrated to be inconclusive (McQuay et al 1997).

11.5 Conclusion

This is the first trial to date looking at the efficacy of transcutaneous spinal electroanalgesia in patients with chronic nociceptive neck pain. There was no reduction in pain intensity, sleep interference or improvement in quality of life following treatment with active TSE. Therefore we have failed to demonstrate a clinically significant benefit of TSE in this population of pain patients attending a chronic pain clinic.
[Chapter 11],[Figure 1]

Data expressed as mean (SD).

There are no significant differences in the change in visual analogue scale for pain following active or control TSE treatment (P=0.12).
Data expressed as mean (SEM).

There were no significant differences in VAS for pain following control or active TSE treatment (P=0.64).
This graph shows the mean VAS for sleep interference for the seven day period following control and active TSE treatment. There were no significant differences in sleep interference following either control or active TSE treatment (P=0.42).

[Chapter 11],[Figure 3]

Data expressed as mean (SEM).
Chapter 12
The Effect of Transcutaneous Spinal Electroanalgesia on Thermal Sensation and Pain Thresholds in Healthy Volunteers (Study 6)

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12.1 Introduction

It is known that descending impulses in the spinal cord and also stimulation by Aβ fibres can interfere with pain transmission and perception by the patient (Chapter 1). It is by that mechanism that TENS is thought to operate (Chapter 4). Prior studies have looked at the effect if any of TENS on other modes of sensory perception in healthy volunteers (Golding et al 1986, Johnson et al 1989) and results are somewhat conflicting. TENS has been shown to produce a significant reduction of both the early and late components of somatosensory evoked potentials which the authors suggested was due to a disrupting effect of TENS on general sensory integration attentional mechanisms (Golding et al 1986). Associated with this, there was a significant reduction in subjective rating of stimulus intensity and an elevation of sensory detection threshold. Finally Ekblom and Hansson have demonstrated no change in heat or cold sensitivity with TENS (Ekblom & Hansson 1987).

Another study found that TENS, at a frequency of less than 80 Hz, significantly elevated the ice pain threshold but had no effect on ice pain tolerance (Johnson et al 1989). Heat pain thresholds also appear to be increased (Woolf et al 1979). Marchand and colleagues demonstrated that TENS also increased the heat pain threshold (Marchand et al 1991). In a study by Towell and colleagues, a single treatment of TSE operating at a frequency of 625 Hz lowered mechanical pain tolerances and improved mood (Towell et al 1997).

Therefore, to date, the picture is somewhat confusing as to the effect of TENS and TSE on the sensations of mechanical pressure and temperature. The objective of the following study was to determine whether a single application of transcutaneous spinal electroanalgesia had any effect on thermal thresholds (both sensation and pain) and mood in healthy volunteers.
The results of this study were presented at the Anaesthetic Research Society Meeting in July 2001 and published in abstract form in the British Journal Anaesthesia in October 2001 (Heffernan et al 2001c).

12.2 Methods

Following local ethics committee approval, the informed consent of 20 healthy volunteers (9 male, 11 female), whose ages ranged from 24 to 58 years was obtained for this prospective randomised double-blind placebo-controlled crossover clinical trial. Exclusion criteria and statistical analysis were as stated in Chapter 6, Sections 2.3 and 14. The power calculation for this study was based on data from an earlier study looking at the effect of TSE treatment on pressure pain thresholds and mood in healthy individuals (Towell et al 1997) (Chapter 6, Section 13). In order to have an 80% chance of excluding a false positive result and assuming significance at the 0.05 level, it was calculated that 16 volunteers would need to be recruited to detect a change of 20% of threshold from baseline. Twenty volunteers in total were recruited.

Volunteers attended for investigation on 2 separate occasions separated by a minimum of 4 days. They each had a treatment session with a control or active TSE machine in a random order. Randomisation was by the sealed envelope technique, with the active and control electrodes placed in a sealed envelope by an anaesthetist not involved with the study (Chapter 6, Section 3). Both volunteer and investigator were blinded at all times. All volunteers completed both sessions.
**Study Interventions**

A history and clinical examination were taken from each volunteer and they were excluded if there was a history or clinical evidence of sensory loss or neurological disease. For determination of the sensory thresholds, the method of quantitative sensory testing was used which is described in Chapter 6, Section 10. The thenar eminence of the dominant hand was used. The TSE electrodes were fitted onto either side of the base of the neck over the transverse processes of C4 and 5, which is the recommended position when treating pain in head, arms and neck (Macdonald & Coates 1995). Each volunteer received 30 minutes of TSE treatment with a quantitative sensory test before and after each treatment on two separate occasions. They also completed the Positive and Negative Affect Schedule before and immediately after each session. The quantitative sensory testing was carried out by the same investigator at all times. The mean change in threshold was calculated as discussed in Chapter 6, Section 10 and shown in Table 1, Figure 1. Scores for the Positive and Negative Affect Schedule were calculated as discussed in Chapter 6, Section 8 and shown in Table 2.

12.3 Results

Twenty volunteers (mean age 38.1yrs SD 10.7) were recruited. Sixteen studies were performed on the right arm and four on the left. One female volunteer complained of pain in her right arm following QST testing on that side. All volunteers completed the study protocol.

There were no significant differences in the mean changes (baseline minus post test) in the QST results of heat and cold sensation and heat and cold pain following either active or control TSE treatment (Table 1, Figure 1). There was also no significant differences in either Positive
or Negative Affect following either active or control TSE treatment. (Table 2). Confidence intervals of the changes are shown in Tables 1 and 2 also.

**[Chapter 12],[Table 1] Temperature changes following control and active TSE**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change °C Active TSE</th>
<th>Change °C Control TSE</th>
<th>Significance P value &amp; (95% CIs of the difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold sensation</td>
<td>0.05 (0.7103)</td>
<td>0.1212 (0.81)</td>
<td>0.779, (-0.4, 0.5)</td>
</tr>
<tr>
<td>Warm sensation</td>
<td>-0.01 (1.22)</td>
<td>0.2750 (0.7651)</td>
<td>0.403, (-0.41, 0.93)</td>
</tr>
<tr>
<td>Cold pain</td>
<td>-1.22 (3.1)</td>
<td>-0.6 (3.7)</td>
<td>0.502, (-1.03, 2.4)</td>
</tr>
<tr>
<td>Heat pain</td>
<td>-0.1180 (1.7)</td>
<td>0.61 (3.06)</td>
<td>0.829, (-1.5, 1.8)</td>
</tr>
</tbody>
</table>

*Data are expressed mean (SD).*

There were no significant differences between active and control treatments in any of the measured variables shown above. The confidence intervals of the differences are also shown.

**[Chapter 12],[Table 2] Change in mood**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change Active TSE Median (IQR)</th>
<th>Change Control TSE Median (IQR)</th>
<th>P value (95% CI's)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Affect</td>
<td>0.5 (0, 2.75)</td>
<td>0 (-2, 2)</td>
<td>0.309 (-2.5, 1)</td>
</tr>
<tr>
<td>Negative Affect</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0.829 (-0.5, 0.5)</td>
</tr>
</tbody>
</table>

*Data expressed as median (IQR).*

There were no significant differences in change in mood following active or control TSE.
12.4 Discussion

The data demonstrate that there were no changes in either heat or cold sensation, heat or cold pain following either control or active TSE treatment. Furthermore, despite all testing being carried out at the same time each day i.e. afternoon, there were no changes in mood either.

The confidence intervals in Table 1 and 2 are tight. They are tightest for the changes in heat and cold sensation and comparable to those demonstrated in other studies (Wang et al 1999, Jamal et al 1985). The detection of these variables is specific. They are slightly wider for the change in heat and cold pain thresholds, which is recognized in the literature as the measurement of pain is subjective (Fruhstorfer et al 1976). The measurement of the cold pain threshold is often omitted in studies for this reason. Wider confidence intervals are demonstrated particularly for the change in positive affect, which may be expected as mood is more variable.

These data differ to an earlier study, which demonstrated a reduction in mechanical pain tolerance and an elevation in mood following TSE treatment in healthy volunteers (Towell et al 1997). There are slight differences in our study. The authors measured mechanical pressure tolerance not change in thermal sensation and pain thresholds, i.e. differing sensations transmitted by different nerve fibres (Towell et al 1997). Their study was also randomised and double blinded but it was not of a crossover design. Furthermore, the TSE devices used by Towell and colleagues were the earlier devices, which operate with a square wave, at a lower frequency and not a differentiated wave as the newer devices in this study.
12.5 Conclusion

We have demonstrated that TSE has no effect on thermal sensation, pain thresholds and mood in healthy volunteers.
Data expressed as mean (SD).

There were no significant differences in change in temperature in heat or cold sensation and heat and cold pain following control or active TSE treatment.
Chapter 13
Discussion

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13.1 Summary of findings

The preceding sections have outlined the efficacy of transcutaneous spinal electroanalgesia in acute and chronic pain and also its effect in healthy volunteers. The first published work on TSE was in 1995 by Macdonald and Coates but only relates to its use in chronic pain (Macdonald & Coates 1995). Since then, the only other published work relates to its effects on mechanical pressure tolerances and mood in healthy volunteers (Towell et al 1997). Like TENS, whose effect in chronic pain remains inconclusive (Carroll et al 2001, Milne et al 2001), the use of TSE is becoming more widespread within the UK, probably because it is relatively non-invasive, non-pharmacological and free from adverse side effects. As has been alluded to earlier, chronic pain itself is a huge drain on public resources and patients are extremely difficult to treat effectively (Elliott et al 1999).

The work presented in this thesis includes the first independent work evaluating TSE in both acute and chronic pain and also in healthy volunteers. As the use of TSE is now becoming more common and with only limited data available to date on the technique, it needed to be further evaluated. While no significant analgesic benefit with TSE has been found in any of these trials, it may be that these trials have asked too much of this machine. Further work needs to be done evaluating those patients with chronic pain whose pain is not severe enough to warrant referral to a chronic pain clinic. The purpose of this chapter is to discuss these issues, interpret the findings of these six studies and outline possible future studies.
Overall my data suggest that TSE has no effect in reducing pain intensity in both acute and chronic pain. It also appears to have no effect on heat and cold sensation thresholds, heat and cold pain thresholds or mood in healthy volunteers.

In Study 1 (Chapter 7), treatment with TSE did not reduce the requirement for postoperative analgesia (P=0.3). While the mean time to first analgesic request in the TSE treatment group was shorter than the control group (87.7 minutes compared to 119.2 minutes), unfortunately this difference was not significant (P=0.1). Further evidence of this lack of analgesic effect is shown by no difference in the visual analogue scores for pain both at rest and on movement, no difference in categorical pain scores and analgesic consumption between the two groups.

Further evidence of no effect in acute pain is seen also in Chapter 8, where TSE has shown no difference in time to first analgesic request (P=0.66). There is no difference in pain scores at rest and on movement between the two groups also. Nevertheless it remains a popular choice with patients with 85% of patients who received active TSE expressing an interest in using the treatment again (Study 2, Chapter 8).

Unfortunately, the results with chronic pain have been somewhat disappointing. No reductions in pain intensity were demonstrated with TSE in the three subgroups of patients studied, chronic lumbar pain, chronic lumbar radiculopathy and chronic nociceptive neck pain. This is particularly so in Study 3 (Chapter 9) where control TSE was found to provide better pain relief (P=0.01). Further evidence of this is also provided by a decrease in area under the curve (P=0.02) also. Quality of life was also examined in these three trials and the only difference found was a significant improvement in the social functioning component of the SF-36 questionnaire following active TSE in patients with chronic lumbar radiculopathy (Chapter 10).
This is the part of the questionnaire that determines the extent to which health problems limit normal social interactions, while their pain intensity may still be same, they may at least be able to engage in more social activities and therefore enjoy life more. No other changes following active TSE in quality of life were found.

In the final study outlined in Chapter 12, TSE was examined in relation to its effect on thermal sensation and thermal pain threshold in healthy volunteers. Again no significant difference was found in those parameters following both active and control TSE treatment. This is in contrast to earlier work by Towell and colleagues which showed a reduction in pressure tolerance and an elevation in mood following active TSE (Towell et al. 1997). However, in the study in Chapter 12, a different TSE device has been used.

Therefore, TSE has failed to demonstrate a clinically significant benefit in patients in a chronic pain clinic, which is in contrast to earlier work (Macdonald & Coates 1995). It does not appear to have a significant benefit in the reduction of postoperative pain either, while noted to be popular with patients. Finally, it has been shown not to affect heat and cold sensation thresholds, heat and cold pain thresholds and mood in healthy volunteers.

13.2 Study design

All 6 trials in this thesis were randomised controlled trials. This is extremely important because, as mentioned earlier, Schulz and colleagues have demonstrated that studies that are not randomised or which are inadequately randomised can exaggerate the estimate of treatment
effect by up to 40% (Schulz et al 1995, Chalmers et al 1977). Randomisation also excludes selection bias. Furthermore studies that are not fully blinded can exaggerate the treatment effect by up to 17% (Schulz et al 1995, Carroll et al 1996, Carroll et al 1997).

All of the trials are double blinded, which would exclude observer bias. TSE is much easier to blind and more user friendly compared with TENS. This is achieved by identical placebo TSE devices, the current of which activates the indicator light, but not the control electrode leads. Furthermore, there are no settings on a TSE machine as the frequency is non-adjustable (different to TENS), all that is required of patients for treatment is switching on of the device.

Data in all these trials were compared with controls. Considering that 20-30% of clinical improvement can be explained by placebo effects, it is important to control for placebo responses in evaluating the effectiveness of an analgesic procedure (Josphe 1978). Some earlier trials using TENS have not used any control group (Bates et al 1980, Wolf et al 1981). The controls used in other studies were not placebo TENS but different treatments entirely e.g. heat treatment (Deyo et al 1990b). As the patient always feels the tingling when a TENS machine is activated, it is difficult to have a placebo TENS i.e. no tingling and maintain blinding. Attempts have been made at this in certain studies but patients have been told they may or may not feel sensations when the machine is activated which may not be very precise (Chen et al 1998, Hamza et al 1999b).

Finally all the studies presented in this thesis have been powered to have at least an 80% chance of excluding a false positive result. Apart from the volunteer data, there was no suitable TSE data for use in power analyses, hence all studies have been powered against PENS in chronic pain for the chronic pain studies (Ghoname et al 1999a) data in our own institution for
study one (Chapter 7) and data from a study on analgesia in elective caesarean section (Dahlgren et al 1997), (Study 2, Chapter 8).

All three of the chronic pain trials use a crossover trial design. That is, where the subjects receive both the test and control treatments in a random order. This type of trial has the advantage over a parallel group design, because as subjects act as their own controls, the number of subjects required is considerably less (Campbell & Machin 1999). Therefore all data from these studies was analysed using paired testing.

The quality of the data in all the trials in this thesis will now be discussed. In the first of the two acute pain trials (Chapter 7 – Study 1) the primary outcome measure was whether or not the patients required analgesia. In Chapter 8 (Study 2) the primary outcome measure was the time to first supplemental analgesic request. However, in both of these trials, VAS at rest and on movement and categorical pain scores were also recorded. Carroll and colleagues state in a review of TENS in labour pain that as TENS is considered to produce pain relief that the most important outcome measure should be a lower pain intensity or greater pain relief (Carroll et al 1997). They also state that the subsequent need for analgesic interventions is a secondary outcome measure. A reduction of pain intensity by TSE is the primary outcome measure in our three chronic pain trials outlined in Chapters 9,10 and 11. However, TSE has not been investigated in an acute setting before. It was thought that the outcome measures chosen in Chapter 7 and 8 were important and relevant because of this. That is why they were chosen as primary outcome measures and not the ones stated above by Carroll and colleagues (Carroll et al 1997). Pain intensity was not overlooked though, VAS at rest and on movement and also categorical pain scores were recorded. Few trials in the literature record both VAS at rest and on movement with regard to TENS in postoperative pain. Furthermore, good correlation
between VAS and categorical pain scores has been also been demonstrated (Lines et al 2001, Collins et al 1997).

There was no difference in VAS between control and active groups, though a trend towards lower scores is observed in the active treatment group (Chapter 7, Study 1). It may be that expecting TSE to rule out the requirement for postoperative analgesia with just 30 minutes treatment was expecting too much of the device. In Study 2 (Chapter 8), all the values for VAS at rest and on movement are very low at all times postoperatively. This is indicative of the very low level of pain experienced after this type of surgery.

In the three chronic pain studies (Chapters 9, 10 and 11), as well as measuring pain intensity on the visual analogue scale, the SF-MPQ was also used. This was used to give information on the actual quality of the pain i.e. the difference between the sensory and affective components of the pain. It proved useful in confirming whether or not there was a difference in pain quality associated with the use of TSE to a certain extent. For example in the studies on chronic lumbar radiculopathy and chronic nociceptive neck pain (Chapter 10, 11), where no difference in the change in VAS following both active and control TSE was demonstrated, there were likewise no differences in the McGill Scores found. Contrastingly, in Chapter 9, where control TSE produced a significantly greater reduction in pain intensity demonstrated by the change in visual analogue scores and also by the area under the curve, this significance was not reflected in McGill scores.

Some studies in chronic pain have looked at the treatment effect with relation to function, e.g. VAS of activity where “0” = no activity due to pain and “10” = maximal activity (Ghoname et al 1999a, Hamza et al 1998a). It was decided in the chronic pain studies not to use this as a measure, but to use the Short Form 36 quality of life questionnaire instead, which would give
more relevant specific information. This as described earlier (Chapter 6, Section 9) measures health on 8 multi-item dimensions, covering functional status, well-being and overall evaluation of health, so it was thought to give a broader overall evaluation (Brazier et al 1992).

In the final study outlined in Chapter 12 which looks at the effects of TSE on heat sensation and pain thresholds in healthy volunteers, no difference was found following either control or active TSE treatment. The confidence intervals in this study are tight and as expected. They are tightest for the changes in heat and cold sensation and comparable to that demonstrated in other studies (Wang et al 1999, Jamal et al 1985). The detection of this variable is specific compared with the detection of pain thresholds. They are slightly wider for the change in heat and cold pain thresholds which is recognized in the literature, (Fruhstorfer A et al 1976). Wider confidence intervals are demonstrated for the change in positive and negative affect, which may be also be expected as mood is more variable. To counteract this all volunteers were examined at the same time of day i.e. the afternoon.

In summary, to outrule overestimation of a treatment effect, all 6 trials outlined in this thesis are randomised placebo controlled double blind trials, four of which have a crossover design and are therefore designed to the strictest requirements of research methodology (Schulz et al 1995). All have been powered to exclude the chance of finding a false positive result. In the two acute pain trials, as well as measuring pain intensity, outcome measures have been chosen that were thought to truly assess the impact of TSE on postoperative pain, which had never been done before. In the three chronic pain trials, it was thought that the best way of doing this was to look at pain intensity on the VAS, which apart from one study correlates well with the
McGill Pain Score. Finally, the SF-36 Health Questionnaire was used for its detailed assessment on quality of life and function.

13.3 Limitations of the data

While trial design was considered to be of a high quality with strict inclusion and exclusion criteria for patients, the data have some limitations.

In the first trial outlined in Chapter 7, it was found that there was no significant difference in patients' requirement for postoperative analgesia whether they were in the control or active TSE group (P=0.3). While laparoscopic sterilisation is performed routinely as a day case in procedure in our institution and throughout the UK, it is quite a painful operation compared with other day case procedures. Maybe the outcome measure that was chosen was requesting too much of the TSE device, i.e. that it may obviate the requirement for postoperative analgesia completely (even though patients had been given analgesia intraoperatively). This could be reflected in the fact that TSE did not demonstrate a difference in time to first analgesic request or in any other variable recorded. There is a trend towards lower VAS on movement in the active treatment group which is not significant. This may indicate that if this study had been performed on a group of patients undergoing a less painful procedure, e.g. one that was not laparoscopic, a difference may have been found. It would be interesting to see if collection of data for a longer period of time i.e. up to 24 hours postoperatively on pain scores and analgesic consumption. This could be done by telephone for day case procedures. Also, if the TSE device had been applied for a second 30 min treatment, prior to discharge, would it have detected a difference?
The same rationale could also be applied to the second study, which is outlined in Chapter 8. While patients did have two applications of the device compared with the previous study, they were undergoing a more extensive procedure and still no difference was found. Again, the question remains that if they had more applications of the device in the first 24 hours postoperatively, would that have detected a difference? Recent studies assessing TENS postoperatively, apply the device every 2 hours for 30 minutes (Hamza et al 1999b, Chen et al 1998). As TSE is reported to be superior to TENS (MacDonald & Coates 1995), it may not have been needed as frequently as the above two studies, but maybe more frequently that it was applied in Studies 1 and 2. Furthermore, this procedure is a more extensive procedure it may have been that too much was again being expected of the device for it to actually significantly decrease the time to first analgesic request. The pain scores throughout this study are quite low at all times nevertheless, this is a patient group which expect no pain, as it interferes with looking after the baby. All patients following elective caesarean section in this institution are very comfortable. Again, if patients undergoing a different procedure were examined e.g. total abdominal hysterectomy and treated with more sessions of the TSE device, it would then be interesting to see whether or not a difference could be found.

Data from the three chronic pain studies, demonstrated quite a degree of variability. This is most obvious in the quality of life data in Chapters 9,10 and 11. While there was only one significant value found between each of the three trials, i.e. the social functioning component of the chronic lumbar radiculopathy study (Chapter 10), some of the median changes were quite large though not statistically significant. The main reason to explain this variability is that people are different and what may limit one person may not limit another and interfere with enjoyment of life. By using a crossover design in these studies, this was minimised as much as possible. There is quite a degree of variability demonstrated in the McGill Scores in those three studies, particularly in the measurement of the sensory component of the McGill Score but it is...
not as great as the variability of the quality of life data. It is important also to remember that these are chronic pain patients whose pain is at least of 6 months duration but some was for as long as 10 years. Some patients would have undergone numerous other therapies before enrolling in these trials, e.g. TENS, acupuncture, injections, physiotherapy and various different medications. Therefore, their pain was of quite a severe nature. However, patients who demonstrated a significant psychological overlay were not enrolled.

In the final study outlined in Chapter 12, there is again a degree of variability. This is mostly demonstrated with the change in mood in both the positive and negative affect. To minimise this, or to keep this degree of variability as small as possible, all measurements were made at relatively the same time of day (afternoon), and while no significant differences have been found, some variability is seen. Mood, however is variable.

13.4 Comparison with the literature

In comparing the data outlined in this thesis with other data, a difficulty was encountered. Namely, I could find no other data relating to the use of TSE in acute pain. Therefore, I have compared the data in the two acute pain studies with data on TENS postoperatively. There is a small amount of data available on the use of TSE in chronic pain, which this work is compared with. Thereafter these data have been compared to studies using TENS in chronic pain. Spinal cord stimulation is also commented on. Finally, there are a small number of studies in the literature looking at TSE and TENS in healthy volunteers and their effects on sensation and pain thresholds, which are compared with the data in Chapter 12 (Study 6).
13.4.1 Acute pain

Similar to other studies reviewed, there are no differences in demographic data between control and active TENS groups studied (Chen et al 1998, Wang et al 1997, Chiu et al 1999, Hamza et al 1999, McCallum et al 1988). However, our data is confined to women who are all undergoing the same procedure, i.e. laparoscopic sterilisation and elective caesarean section. This is different to data in some studies in which the analgesic effect of TENS was examined in patients undergoing different procedures, e.g. women undergoing different gynaecological procedures, which may introduce some variability into the intensity of postoperative pain. Hysterectomy can be quite a varied procedure depending on whether oophorectomy is also performed and whether or not the indication is malignancy, which is not clear in these trials (Hamza et al 1999b, Chen et al 1998, Solomon et al 1980).

The studies outlined in this thesis have found no difference in pain intensity as outlined by the VAS or categorical pain scores postoperatively. This correlates to some other studies on the use of TENS postoperatively (Hamza et al 1999b, Wang et al 1997). Two studies do not even refer to actual pain scores postoperatively (McCallum et al 1988, Chen et al 1998). Other studies have found a reduction in pain scores in the active TENS groups (Chiu et al 1999). In all of the above studies quoted, the primary outcome measure has not been a reduction in requirement in postoperative pain relief or time to first analgesic request as in our studies but it is a reduction in analgesic consumption (morphine or hydromorphone) as measured on the PCAS (Chiu et al 1999, Chen et al 1998, Hamza et al 1999b, Wang et al 1997). All but one demonstrates a reduction in analgesic requirement as measured on the PCAS (McCallum et al 1988). This however was also the only study to measure morphine plasma concentrations and no difference was found between PCAS and morphine concentration in the two groups (control and active TENS). A review of TENS in postoperative pain states that the most common primary outcome measures were analgesic consumption and pain score measurements (Carroll et al 1996). Our
primary outcome measures in the two acute pain studies (Chapter 7 and 8) outlined above were different, as TSE had never been evaluated in a postoperative setting before, and it was decided to fully evaluate whether it could make a difference or not. Secondly, the trial designs in Chapter 7 and 8, did not allow for measurement of morphine consumption on a PCAS.

All of these studies found lower sedation scores as expected with less PCAS usage in the active TENS groups. There was no difference in sedation scores outlined in Studies 1 and 2 between the active and control TSE groups, while patients all received intraoperative (fentanyl either intravenously or intrathecally) and postoperative (morphine intramuscularly and diamorphine epidurally) opioid. This was to be expected, especially as in Study 2, Chapter 8, a regional anaesthetic technique was used.

Comparable with other studies using TENS, the use of TSE is popular with patients with 60% of patients who received active TSE in Chapter 8 and 85% in Chapter 9 expressing an interest in its use following any future surgery. This is comparable with other work (Chiu et al 1999, Chen et al 1998, Hamza et al 1999b, Wang et al 1997). There was no difference in patients overall perception of their pain control (Table 4 Chapter 7, Table 5 Chapter 8). This is also comparable with the above studies (Chiu et al 1999, Chen et al 1998, Hamza et al 1999, Wang et al 1997). A study specifically examining the effect of TENS on postoperative pain due to elective caesarean section found a decrease in movement associated incisional pain as measured on the McGill Pain Score compared with controls but not in visceral pain (Smith et al 1986). There was no difference in analgesic consumption between the two groups, which is comparable with our data (Chapter 8). However, unlike the study in Chapter 8, the analgesic technique was not standardised with half of the patients receiving surgery under general anaesthesia and half under epidural anaesthesia (Smith et al 1986). Furthermore, in Chapter 8 where patients received TSE treatment for two thirty minutes sessions and it produced no
analgesic benefit, these patients had TENS therapy for three days continuously postoperatively and it only produced a change in movement associated incisional pain but no difference in pain from internal structures or somatic pain associated with decreased peristalsis.

It is interesting to note that out of 46 reports of trials with TENS reviewed postoperatively, 19 are eliminated initially because they are not randomised, only 2 out of the remaining are judged by the reviewers to have a positive outcome, i.e. analgesic benefit associated with TENS (Carroll et al 1996). These were randomised placebo trials on patients undergoing hip replacements, abdominal and thoracic surgery who reported significant pain relief and decreased analgesic consumption associated with active TENS treatment (Pike et al 1978, VanderArk et al 1975). The work outlined in Chapters 7 and 8 is the first known work on TSE in an acute pain situation and it has not produced any significant analgesic benefit. However, unlike a lot of the earlier work on TENS, both trials are randomised double-blind placebo-controlled trials. TSE is a relatively new form of therapy available to physicians for use in both acute and chronic pain (Macdonald & Coates 1995). This is the first known work subjecting the technique to rigorous evaluation by the strictest of research methodology and probably more is required.

13.4.2 Chronic lumbar back pain

In the study in Chapter 8, it was shown that placebo TSE decreased pain intensity and active TSE did not as demonstrated on the visual analogue scale (P=0.01). However, there were no significant differences determined by change in McGill scores following active or control TSE treatment or change in quality of life scores. Looking objectively at the number of analgesic medications required by either group, no differences during either week can be seen. Firstly,
these data are conflicting with the very limited amount of data already available on TSE (Macdonald & Coates 1995). This work demonstrated as stated earlier, that TSE produced a significant decrease in the McGill Score following treatment and this was also significant when compared with TENS. However, these are very limited data as firstly it only relates to 8 patients (2 of whom complained of neck pain), secondly there is no control group and finally only one 20 minute TSE session is compared with one 20 minute TENS session. Visual analogue scales are not referred to as a measurement of pain intensity for this data. As this trial only refers to one session of either TSE or TENS treatment, no medication record has been made. In a larger trial performed by Macdonald and colleague of 100 patients with varying aetiologies of chronic pain, TSE has been shown to produce 60% or more pain relief over a period of five weeks. However, all the trials in chronic pain in this thesis are only of 3 weeks duration, during which patients only had active treatment for 1 week. It should be remembered that the TSE devices used by Macdonald and colleague are slightly different to the ones used in all trials outlined in this thesis. They operated with a lower frequency of 625 Hz compared with a frequency of 2,500 Hz in the TSE devices of this thesis. It is worth noting that the patients who underwent the trial outlined in Chapter 9 were patients attending the chronic pain clinic at the Leicester Royal Infirmary for some time. All had pain of greater than 6 months duration, but 2 had chronic pain of greater than 10 years duration. It would be very interesting to perform a similar trial in patients with chronic pain, still under the care of their general practitioner, whose pain has not yet warranted their attendance at a pain clinic.

There is quite a difference in the available evidence for the efficacy of TENS in chronic low back pain (Milne et al 2001, Carroll et al 2001, Marchand et al 1993, Deyo et al 1990b). I could not find a trial where TENS actually worsened pain intensity compared to placebo. However, there a number of trials which show a reduction in pain intensity with placebo TENS (Jensen et al 1985, Deyo et al 1990b, Marchand et al 1993). None of these were of a crossover design as
in Chapter 9. However all monitored patients for longer periods of time, from one month (Deyo et al 1990b) to six months (Marchand et al 1993). Earlier studies with TENS in chronic back pain, while they show a reduction in pain intensity are not randomised or have a placebo (Bates et al 1980, Fox & Melzack 1976, Melzack 1975). Two crossover trials of percutaneous electrical nerve stimulation are also included for comparison (Ghoname et al 1999a, Ghoname et al 1999c). In these trials PENS was compared to sham PENS, TENS and exercise. PENS was significantly more effective in reducing pain intensity on the VAS unlike the trial in Chapter 9 (Study 3). These trials are also included as the authors also measured quality of life on the SF-36 questionnaire and while TENS, sham PENS and PENS all produced significant improvements in quality of life in contrast with our data, the improvement was greatest with PENS. However, while these were crossover trials, patients received each mode of treatment for 3 weeks which is longer than the treatment period in the trials outlined in Chapters 9, 10 and 11.

Data on spinal cord stimulation will be compared in the discussion on neuropathic pain as that is where the best results with that technique have been seen. Therefore, with the limited amount of TSE data available, the data in Chapter 9 differs significantly, but only small numbers of patients are available for comparison using older TSE devices (Macdonald & Coates 1995). However, future trials would need to re-examine TSE to determine its effectiveness in chronic back pain but possibly for a longer period of time than one week (Section 13.5)

13.4.3 Chronic lumbar radiculopathy

As stated earlier there is very little data available on TSE to compare with the data in Chapter 10. However this data differs from that of Macdonald & Coates in that some of the initial patients they examined had evidence of neuropathic pain and demonstrated long term (60% or
more) relief after 6 weekly treatments (Macdonald & Coates 1995). In our study, no difference in pain relief was found following active or control TSE treatment after one weeks treatment. While a difference in the social functioning component of the SF-36 Questionnaire was found following active TSE, there is no available TSE data to compare with this.

There is some data available on the effects of TENS with neuropathic pain. The earlier studies are not randomised and have no control for comparison (Bates et al 1980, Wolf et al 1981). Patients with postherpetic neuralgia demonstrated a reasonable response with a third using their TENS machines after one year and a quarter after 2 years (Bates et al 1980). However, the outcome measure used in this trial was the length of time for pain relief and not pain intensity. While the trial in Chapter 10 is of a shorter duration, very specific outcome measures are examined e.g. change in pain intensity as determined by the VAS and McGill Scores. Another trial a year later which again is non-randomised and not placebo controlled found a reduction in the Present Pain Intensity component of the McGill Score immediately following treatment with TENS in patients with peripheral neuropathy and radiculopathy (114 patients), (Wolf et al 1981). However, this effect was found to decrease with time, and was not significant at one month follow up. This differs from our data in that, even after one weeks treatment with active TSE, no improvement in pain on the PPI has been demonstrated.

Trials using PENS have examined neuropathic pain of varying causes, namely sciatica (Ghoname et al 1999b), acute herpes zoster (Ahmed et al 1998a) and diabetic neuropathy (Hamza et al 2000). Two of these trials are of a crossover design (Ghoname et al 1999b and Hamza et al 2000). These two trials demonstrate a reduction in pain intensity associated with active PENS treatment compared with control PENS treatment. The trial examining the effect of PENS on acute herpes zoster is a single blind trial, in which the control group receive
antiviral medication instead of control PENS. As well as patients in the active group demonstrating a reduction in pain intensity, their herpetic lesions are also reported to heal quicker (Ahmed et al 1998a). The other two studies also examine quality of life and demonstrate a significant improvement in quality of life following active PENS treatment (Ghomane et al 1999b, Hamza et al 2000). In Chapter 10, it is only the social functioning component that demonstrates a significant change in quality of life following active TSE, the changes in the other 7 components of the questionnaire are insignificant. However, patients in study 4 (Chapter 9), only received treatment for one weeks duration as compared to 3 weeks duration in the above two studies. It must also be remembered that PENS is a different therapy i.e. electrodes are inserted into the subcutaneous tissue to exert an analgesic effect, (Chapter 4, Section 6). Furthermore the trials outlined for comparison above are all single blind and patients will always feel whether or not stimulation is occurring. With TSE, all the trials are double blind.

Spinal cord stimulation has had its best results in the management of neuropathic pain. However, it is not a treatment which is considered lightly and for every patient with chronic lumbar radiculopathy. Firstly, it is significantly more expensive to either TENS, TSE or PENS therapy. It is an invasive procedure, which also involves either general anaesthesia or sedation for the patient. Finally, electrodes are left in the epidural space which have been known to act as a source of infection, migrate or break (White et al 2001). Randomised controlled trials are lacking in the literature for this form of pain relief yet a prospective multicentre study found that at one year follow up 55% achieved sustained reductions in pain and improvements in quality of life (Burcheil et al 1996). Initial results from a randomised crossover trial show a significant advantage for SCS over reoperation when patients reach the crossover point (North et al 1994). This was a study where the primary outcome measure was the frequency of
crossover to the alternative procedure, (SCS or reoperation) if the results of the first have been unsatisfactory after 6 months. Clearly spinal cord stimulation is to be considered for those patients in whom all other forms of therapy have failed and who are aware and accepting of the risks.

13.4.4 Chronic neck pain

As stated earlier there is very little data available to compare the results in Chapter 11 with other work in TSE. The data in this thesis found no reduction in pain or significant changes in quality of life following active TSE treatment. The initial work in TSE demonstrates a 60% relief or more with long term TSE treatment (Macdonald & Coates 1995). Included in this data are some patients with chronic neck pain. However, this trial was of a longer duration 5-6 weeks compared with treatment duration in Study 5 (Chapter 11) i.e. one weeks treatment. Furthermore 2 out of the 8 patients that demonstrated a reduction in McGill scores following TSE treatment had chronic neck pain (Macdonald & Coates 1995). This contrasts with no significant differences with McGill Score results following control or active TSE treatment in Chapter 11, but in the inventors study, only one session of TSE was used. Furthermore, in that study, no measurement of quality of life was undertaken (Macdonald & Coates 1995).

There is very little work in the literature to compare with these results. A randomised single-blind placebo-controlled crossover trial looking at the effect of PENS stimulation in patients with chronic neck pain found a significantly greater reduction in pain associated with stimulation in the neck region compared to sham stimulation and stimulation in the back (White et al 2000). All treatments modalities were associated with a reduction in quality of life scores
but the greater reduction was seen with PENS stimulation in the neck region. These results contrast with the results outlined in Chapter 10 where no reduction in pain intensity and no difference in quality of life has been found. However, treatment in this trial with each modality was for a period of three weeks, whereas in Chapter 11 it is only for one week.

A systematic review of randomised controlled trials for acupuncture in chronic neck pain has found that the literature is lacking in adequate results (White & Ernst 1999). Out of 32 possible studies, 18 were excluded because they were non-randomised or had no placebo control. Only 8 were judged to be of high enough quality to be reviewed, and of those five had negative results. The authors conclude that there is not enough available evidence to judge acupuncture efficacious in the treatment of chronic neck pain and more randomised clinical trials are needed.

In summary, there does not appear to be enough available data in the literature on TSE in chronic nociceptive neck pain for proper comparison. Secondly, the results in Chapter 11 differ to results in a crossover trial using PENS (a different form of therapy), (White et al 2000). However the trial period for each modality in that trial was 2 weeks longer than Study 5.

13.4.5 Temperature and pain thresholds

The study with TSE in healthy controls outlined in Chapter 12 found no change in thermal sensation, pain or mood following active TSE. This is in contrast to an earlier study by Towell and colleagues, which showed lower mechanical pain tolerances and an elevation in mood in
healthy volunteers following active TSE treatment (Towell et al 1997). There are some differences with this study. Firstly, the study outlined in Chapter 12 (Study 6) is of a crossover design and used TSE machines, which use a frequency of 2500 Hz. However, Towell and colleagues used lower frequency machines, which do not have a differentiated waveform and their trial was not of a crossover design. Secondly, a different sensation is measured, I looked at thermal sensation and pain, they looked at mechanical pressure tolerance. Physiologically different nerve fibres are involved and this may explain the differences in findings. Finally, in both studies different questionnaires were used to evaluate mood, in Chapter 11 the PANAS is used whereas Towell and colleagues used an older form of mood evaluation, the Nowlis adjective checklist (Nowlis et al 1965). In Chapter 12 the confidence intervals for the differences are displayed which are thought to be quite tight (reasons outlined in Chapter 12, Section 12.4), however no data on confidence intervals is displayed by Towell and colleagues (Towell et al 1997).

A study of TENS in both healthy volunteers and patients, measuring thresholds using the method of quantitative sensory testing was carried by Ekblom and colleagues (Ekblom & Hansson 1987). They also found no difference in thresholds with volunteers compared with patients who had chronic pain. Mood however was not evaluated.

13.5 Future work

While the results outlined in this thesis fail to demonstrate significant effects of TSE treatment, further work is required for proper evaluation of this new technique. In the area of acute pain, a trend toward to lower pain scores was observed in the active treatment group. The design of
these trials (Chapter 7, 8) may have asked too much of this device. Trials that may show some effectiveness of the device could maybe include shorter procedures that are in themselves less painful e.g. removal of ganglions, dilatation and curettage. Laparoscopy itself is quite a painful procedure. Patients could also be monitored for a longer period of time by telephone after they return home to evaluate their pain intensity and also analgesic consumption. This was not done in Study 1 (Chapter 7). TSE stimulation could also be provided for a longer period of time for both short and longer procedures postoperatively.

In the area of chronic pain, a few recommendations can be made for future work. Firstly, it could be suggested to perform these trials on patients who are being treated in a GP setting for their chronic pain. These patients’ pain may not be quite as severe as patients in the trials in Chapter 9, 10 and 11, who have had pain for quite a number of years and have undergone a number of other failed therapies. Furthermore, these trials could be repeated with longer treatment times e.g. 2-3 weeks as in the other trials quoted above, particularly to gain a more comprehensive evaluation of quality of life.

13.6 Conclusion

This thesis has failed to demonstrate any reduction in pain intensity associated with the treatment of TSE after surgery and in chronic pain in appropriately powered studies. TSE has not demonstrated any effect on thermal sensation, pain or mood in healthy volunteers.
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Chapter 15 APPENDICES

Appendix 1. Leicestershire Research Ethics Committee (LREC) reference numbers for the studies in this thesis.

Study 1 (Chapter 6) LREC reference number 5861
Study 2 (Chapter 7) LREC reference number 6114
Study 3 (Chapter 8) LREC reference number 6081
Study 4 (Chapter 9) LREC reference number 6082
Study 5 (Chapter 10) LREC reference number 6079
Study 6 (Chapter 11) LREC reference number 6110
Appendix 2 Publications arising from this thesis

Abstracts


Heffernan AM, Rowbotham DJ. Efficacy of Transcutaneous Spinal Electroanalgesia in Patients with Chronic low back pain. This study is accepted for presentation at the World Congress Meeting next year (2002).

All the above studies will be submitted for publication early in 2002.
Appendix 3.

Questionnaires used in this thesis

Short Form McGill Pain Questionnaire

Short Form 36 Health Survey

Positive and Negative Affect Schedule
Patient's name: ___________________ Date: ___________________

**SHORT-FORM Mc GILL PAIN QUESTIONNAIRE**
© Dr Ronald Melzack, 1984

Please indicate whether any of the terms given below accurately describe your pain - if so, please mark, by circling, its severity (you can select as many or as few of the terms as you think are appropriate)

<table>
<thead>
<tr>
<th>Term</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throbbing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Shooting</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Stabbing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sharp</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cramping</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Gnawing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Hot-burning</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Aching</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Heavy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Tender</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Splitting</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Tiring - exhausting</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sickening</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Fearful</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Punishing-Cruel</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Total score: _______ / 45 (max)**

**Visual Analogue Scale**

Please rate the severity of the pain you are experiencing at present by making a vertical mark across the line below:

No Pain ____________________________________________ Worst possible Pain

**Present Pain Intensity Score**

Please also tick one of the descriptions below to approximately indicate the intensity of your pain at present

0  No Pain  
1  Mild  
2  Discomforting  
3  Distressing  
4  Horrible  
5  Excrutiating  
Dear Dr. Melzack,

My name is Dr. Anne Heffernan and I am a Clinical Research Fellow working with Professor David Rowbotham at the Leicester Royal Infirmary, Leicester, England.

I am writing to you for permission to use your Short Form McGill Questionnaire for three studies in chronic pain patients. They involve giving three subgroups of chronic pain patients Transcutaneous Spinal Electroanalgesia Devices, these are similar to TENS machine. We hope to measure any change in their quality of pain. If you require any other information about the study we will be happy to send it to you.

Best wishes,

Yours sincerely,

Anne M. Heffernan MB FFARCSI

Email: amh26@le.ac.uk

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6/11/00

Dear Dr. Heffernan,

You have my permission to use the SF-MPQ for the above studies.

With best wishes,

Ronald Melzack
General Health Questionnaire SF-36

Please answer the 36 questions of this health survey completely, honestly, and without interruptions.

General Health

In general, would you say your health is: (select one Circle)

☀ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

Compared to one year ago, how would you rate your health in general now? (Select one Circle)

☀ Much better now than 1 year ago ☐ Somewhat better now than 1 year ago

☀ About the same ☐ Somewhat worse now than 1 year ago ☐ Much worse now than 1 year ago

Limitations of Activities

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (Select one circle on each line)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Yes, Limited a Lot</th>
<th>Yes, Limited a Little</th>
<th>No, Not Limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Lifting or carrying groceries</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Climbing several flights of stairs</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Climbing one flight of stairs</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Bending, kneeling, or stooping</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Walking more than a mile</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Walking several blocks</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Walking one block</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Bathing or dressing yourself</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
### Physical health problems

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Select one circle on each line)

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut down the amount of time you spent on work or other activities</td>
<td>O</td>
</tr>
<tr>
<td>Accomplished less than you would like</td>
<td>O</td>
</tr>
<tr>
<td>Were limited in the kind of work or other activities</td>
<td>O</td>
</tr>
<tr>
<td>Had difficulty performing the work or other activities (for example, it took extra effort)</td>
<td>O</td>
</tr>
</tbody>
</table>

### Emotional health problems

During the past 4 weeks, 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)? (Select one circle on each line)

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut down the amount of time you spent on work or other activities</td>
<td>O</td>
</tr>
<tr>
<td>Accomplished less than you would like</td>
<td>O</td>
</tr>
<tr>
<td>Didn't do work or other activities as carefully as usual</td>
<td>O</td>
</tr>
</tbody>
</table>

### Social activities

During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? (Select one Circle)

- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

### Pain

How much bodily pain have you had during the past 4 weeks? (Select one Circle)

- None
- Very Mild
- Mild
- Moderate
- Severe
- Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Select one Circle)
**Energy and Emotions**

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. (Select one circle on each line)

<table>
<thead>
<tr>
<th>How much of the time during the past 4 weeks...</th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you feel full of pep?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Have you been a very nervous person?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Have you felt so down in the dumps that nothing could cheer you up?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Have you felt calm and peaceful?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Did you have a lot of energy?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Have you felt downhearted and blue?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Did you feel worn out?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Have you been a happy person?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Did you feel tired?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

**Social activities**

**During the past 4 weeks**, **how much of the time** has your **physical health or emotional problems** interfered with **your social activities** (like visiting with friends, relatives, etc.)? (Select one Circle)

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time
### General Health

How true or false is each of the following statements for you? (Select one circle on each line)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Definitely True</th>
<th>Mostly True</th>
<th>Don't Know</th>
<th>Mostly False</th>
<th>Definitely False</th>
</tr>
</thead>
<tbody>
<tr>
<td>I seem to get sick a little easier than other people</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>I am as healthy as anybody I know</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>I expect my health to get worse</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>My health is excellent</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

---

**Total Score: ________________________________**
SF-36 SCORING SYSTEM

The instructions given below are for scoring the eight dimensions of the U.K. SF-36 reproduced in this manual. They show:

- which items compose each dimension;
- the coding system for each item. Important note: not all items in a domain are coded in the same manner. For example, in the mental health dimension items 9d and 9h are coded in the reverse manner to 9b, 9c and 9f;
- the scoring algorithms for each dimension.

If you are interested in creating the summary scale scores (the Physical Component Summary (PCS) and the Mental Component Summary (MCS)) from UK SF-36 data then please see page 39.

1. Coding items:

Physical function

3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j  Yes, limited a lot = 1
Yes, limited a little = 2
No, not limited at all = 3

Role limitation due to physical problems

4a, 4b, 4c, 4d  Yes = 0
No = 1

Role limitation due to emotional problems

5a, 5b, 5c  Yes = 0
No = 1
Social functioning

6

Not at all = 5
Slightly = 4
Moderately = 3
Quite a bit = 2
Extremely = 1

9j

All of the time = 1
Most of the time = 2
A good bit of the time = 3
Some of the time = 4
A little of the time = 5
None of the time = 6

Mental health

9b, 9c, 9f

All of the time = 1
Most of the time = 2
A good bit of the time = 3
Some of the time = 4
A little of the time = 5
None of the time = 6

9d, 9h

All of the time = 6
Most of the time = 5
A good bit of the time = 4
Some of the time = 3
A little of the time = 2
None of the time = 1

Energy/vitality

9a, 9e

All of the time = 6
Most of the time = 5
A good bit of the time = 4
Some of the time = 3
A little of the time = 2
None of the time = 1

9g, 9i

All of the time = 1
Most of the time = 2
A good bit of the time = 3
Some of the time = 4
A little of the time = 5
None of the time = 6
<table>
<thead>
<tr>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
</tr>
<tr>
<td>None = 6</td>
</tr>
<tr>
<td>Very mild = 5</td>
</tr>
<tr>
<td>Mild = 4</td>
</tr>
<tr>
<td>Moderate = 3</td>
</tr>
<tr>
<td>Severe = 2</td>
</tr>
<tr>
<td>Very severe = 1</td>
</tr>
</tbody>
</table>

| 8    |
| Not at all = 5 |
| A little bit = 4 |
| Moderately = 3 |
| Quite a bit = 2 |
| Extremely = 1 |

<table>
<thead>
<tr>
<th>General health Perception</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>Excellent = 5</td>
</tr>
<tr>
<td>Very good = 4.4</td>
</tr>
<tr>
<td>Good = 3.4</td>
</tr>
<tr>
<td>Fair = 2</td>
</tr>
<tr>
<td>Poor = 1</td>
</tr>
</tbody>
</table>

| 10a, 10c                      |
| Definitely true = 1          |
| Mostly true = 2              |
| Not sure = 3                 |
| Mostly false = 4             |
| Definitely false = 5         |

| 10b, 10d                      |
| Definitely true = 5           |
| Mostly true = 4               |
| Not sure = 3                  |
| Mostly false = 2              |
| Definitely false = 1          |

<table>
<thead>
<tr>
<th>Change in health</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
</tr>
<tr>
<td>Much better now = 5</td>
</tr>
<tr>
<td>Somewhat better = 4</td>
</tr>
<tr>
<td>About the same = 3</td>
</tr>
<tr>
<td>Somewhat worse = 2</td>
</tr>
<tr>
<td>Much worse = 1</td>
</tr>
</tbody>
</table>
2. Calculating dimension scores

Physical function (PF)
\[ PF = 3a + 3b + 3c + 3d + 3e + 3f + 3g + 3h + 3i + 3j \]
Physical function score = \((PF-10)/20\) * 100

Role limitation due to physical problems (RP)
\[ RP = 4a + 4b + 4c + 4d \]
Role limitation due to physical problems score = \((RP/4)*100\)

Role limitation due to emotional problems (RE)
\[ RE = 5a + 5b + 5c \]
Role limitations due to emotional problems score = \((RE/3)*100\)

Social functioning (SF)
\[ SC = 6 + 9j \]
Social functioning score = \((SC-2)/9)*100\)

Mental health (MH)
\[ MH = 9b + 9c + 9d + 9f + 9h \]
Mental health score = \((MH-5)/25)*100\)

Energy/vitality (EV)
\[ EV = 9a + 9e + 9g + 9i \]
Energy/vitality score = \((EV-4)/20)*100\)

Pain (P)
\[ P = 7 + 8 \]
Pain = \((p-2)/9)*100\)

General health Perception (GHP)
\[ HP = 1 + 10a + 10b + 10c + 10d \]
General health perceptions = \((GHP-5)/20)*100\)

Change in health (CH)
\[ CH = 2 \]
Change in health score = \((CH - 1)/4)*100\)

Notes: (see over)
Friday, June 30, 2000

Dr. Anne M Heffeman
Leicester Royal Infirmary
University Department of Anaesthesia
University Department of Anaesthesia & Pain Manage
Leicester Royal Infirmary
Leicester, Leicestershire LE1 5WW
GB

Regarding your project: Quantitative Sensory Testing to evaluate gabapentin in chronic neuropathic pain

Dear Anne:

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We have added you to our mailing list and encourage you to visit our two Web sites www.qmetric.com and www.amlhealthy.com for the most up-to-date information on our scientific products and services.

Sincerely,

http://mail.cfs.le.ac.uk/exchange/forms/IPM/NODE/read.asp?command=open&obj=00000030/06/2000/2F4BBf
John E. Ware, Jr., Ph.D.
President and Chief Executive Officer
QualityMetric, Inc.

Executive Director, Health Assessment Lab

Research Professor of Psychiatry
Tufts University School of Medicine

Adjunct Professor of Health and Social Behavior
Harvard University School of Public Health
This scale consists of a number of words that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent:

Use the following scale to record your answers.

1  2  3  4  5
very slightly a little moderately quite a bit extremely
or not at all

interested

distressed

excited

upset

strong

guilty

scared

hostile

enthusiastic

proud

irritable

alert

ashamed

inspired

nervous

determined

attentive

jittery

active

afraid

*Insert appropriate time instructions above from page 27