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CAN PRE-EMPTIVE AND CONTINUED
TRANSCUTANEOUS ELECTRICAL NERVE
STIMULATION (TENS) IMPROVE THE
MANAGEMENT OF POST-OPERATIVE KNEE PAIN?

BY

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2001
Can Pre-emptive and Continued Transcutaneous Electrical Nerve Stimulation (TENS) Improve the Management of Post-operative Knee Pain?

By

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A thesis Submitted to the Research and Postgraduate Studies Office for the Degree of Doctor Philosoph

Department of Rehabilitation Sciences

THE HONG KONG POLYTECHNIC UNIVERSITY

Supervisor: Professor Christina WY Hui-Chan

September 2001
STATEMENT OF SOURCES

The idea of the present investigation originated from Prof. Christina W.Y. Hui-Chan and the planning of the experiments results from discussions between the author and Prof. Hui-Chan, my supervisor.

All experiments in the present investigations were completed solely by the author.

The author declares that the work presented in this thesis is, to the best of the author's knowledge and belief, original, except as acknowledged in the text, and that the material has not been submitted, either in whole or in part, for a degree at this University.

Wang Ninghua

September 2001
Abstract of the thesis entitled 'Can pre-emptive and continued transcutaneous electrical nerve stimulation improve the management of post-operative knee pain?' submitted by Ninghua Wang for the doctoral degree of philosophy at The Hong Kong Polytechnic University in September 2001.

ABSTRACT

Introduction. Research in human studies showed that TENS applications, repeated for 60 min 5 times a week over a 2-week period, produced cumulative antinociceptive effects on acute experimental electrical pain (Liu and Hui-Chan 1994), chronic low back pain (Cheing and Hui-Chan 1996) and chronic osteoarthritic knee pain (Cheing and Hui-Chan 1998). It should be noted that no study to-date has investigated the possible cumulative analgesic effect of repeated TENS applications on acute thermal pain, or more importantly the use of pre-emptive and continued daily TENS on the post-operative pain after total knee replacement. This thesis set out to investigate this subject matter through 3 inter-related studies with the following objectives.

Objectives. First, to determine if the inhibitory effect of TENS applied to the acupuncture points, was specific to pain as measured by the heat pain threshold, when compared with tactile sensibility as measured by the vibration threshold. In this thesis, we did not attempt to compare the effects of TENS to the acupuncture points and non-acupuncture points. Second, to examine whether TENS applications to the acupoints, repeated twice daily for 3 days, produced more cumulative analgesic effects on the heat pain threshold than placebo stimulation in older normal subjects who could be more susceptible to placebo effects. Third, to determine if repeated TENS applications to the acupoints before, during and after total knee replacement improved the post-operative pain management, in a manner similar to the use of pre-emptive and continuous opioid analgesia. Specifically, we attempted to delineate whether pre-emptive and repeated TENS applications could exert cumulative inhibitory effects on the post-operative pain intensity, improve the range of knee motion, reduce analgesic consumption, and shorten the length of hospital stay more than that of placebo stimulation.

Methods. In study 1, 20 young normal subjects, aged 20 to 39, were examined. They were randomly allocated to a TENS or placebo group. High-frequency (100 Hz, 200μs) TENS or placebo stimulation was applied to the acupuncture points (LI4) on each subject’s left hand for 30 min. Heat pain and vibration thresholds were measured using
the Medoc TSA-2001 and VSA-3000 respectively on the thenar eminence of each
subject's left hand. In study 2, 19 older normal subjects, aged 60 to 85, were
investigated. They were randomly allocated to a TENS or placebo group. Subjects
received 60 minutes of TENS or placebo stimulation applied to the four acupuncture
points (Extra36, Gb34, Sp9 and St35) around the knee joint twice daily over a 3-day
period. The heat pain thresholds were measured before and after TENS or placebo
stimulation. In study 3, 42 patients with osteoarthritic knee pain, aged 60 to 90, were
examined. They were randomly allocated to a TENS or placebo group. Sixty minutes of
TENS or placebo stimulation was applied to the same four acupuncture points around the
knee joint 2 times daily, 3 days before, 1 day during and 6 days after total knee
replacement. The post-operative pain intensity and range of knee flexion were measured
before, during and after treatment. The analgesic consumption at 6, 12 and 24 hours
after operation, and the length of hospital stay were recorded, the latter as the number of
days needed by the patients to reach the discharge criteria.

Results. The findings from study 1 showed a significant increase in heat pain
threshold after 30 min of TENS application to the LI4 acupoint in the young normal
subjects, when compared with that of placebo stimulation (p=0.002 to 0.004). In
contrast, no significant difference in the vibration threshold was found between the
TENS and placebo groups. In study 2, a significant increase in the heat pain threshold
obtained before treatment in session1 was found, when compared with that in session6 in
the TENS group (by 1.7°C, p=0.007), but not in the placebo group (by 0.7°C). In study
3, 3 main findings emerged. (1) Sixty minutes of TENS application in session1 was
found to produce a significant decrease of the knee pain intensity during and after TENS
when compared with that of placebo stimulation (p=0.000 to 0.003). The baseline VAS
score of TENS group dropped gradually from 100% to 83.3% (p=0.000) at 60 min
during, and further to 85.7% (p=0.001) at 20 min after TENS, in contrast to the
negligible changes shown during and after placebo stimulation. By the completion of
the treatment period consisted of 12 sessions after the surgery, there was a further
decrease to 31.5% before, 25.6% at 60 min during and 27.3% at 60 min after TENS
application. These scores were significantly less than those recorded in the placebo
group, which showed a decrease to 50.0% (p=0.003) before, 47.6% (p=0.000) at 60 min
during and 47.5% (p=0.000) at 60 min after placebo stimulation. (2) A significant
increase in knee flexion range was found between the TENS and placebo groups on each
of the 6 days after operation (p=0.000 to 0.012). (3) A final finding was that patients
receiving repeated TENS reached the hospital discharge criteria 2 days earlier than those receiving placebo stimulation, though the difference was not statistically significant.

Discussion. In contrast to placebo stimulation, 30 min of TENS to the LI4 acupoint increased the heat pain but not the vibration threshold in the young normal subjects. This result demonstrated that, like acupuncture, the effect of TENS on acupoint is to reduce pain but not tactile (specifically vibration) sensibility. Interestingly, repeated high-frequency TENS applications to the acupoints, for 60 min twice daily over a 3-day period, produced a cumulative antinociceptive effect on the heat pain threshold in the older normal subjects belonging to the TENS group. The important finding from our main study was that repeated TENS applications 2 times a day, 3 days before, 1 day during and 6 days after surgery, produced a reduction of the post-operative knee pain and an increase in the knee flexion range after total knee replacement significantly more than placebo stimulation. In addition, patients receiving repeated TENS applications reached the hospital discharge criteria 2 days earlier than those receiving placebo application. Taken together, these findings unequivocally demonstrated that TENS application to the acupoints before, during and after total knee replacement produced significant beneficial effects to the patients with osteoarthritic knee pain after surgery, in terms of improvement in their sensori-motor functions and the possible saving garnered from a tendency towards shortened hospital stay.
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I have learned most of the ideas, study designs and computer skills represented in this thesis during my more than three years at The Polytechnic University. I would like to express my gratitude to Professor Christina W.Y. Hui-Chan, my chief supervisor, for her earnest instructions, scientific advises, patient guiding, great encouragement and care. I also feel most indebted to Prof. Hui-Chan, who had put great efforts in editing the manuscript. Her good character, her dedication to work, her demand for the acme of perfection and logical thinking have been inspiring to me. These should propel me to strive for excellence in the future.

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LIST OF ABBREVIATIONS

OA       osteo-arthritis
RA       rheumatoid-arthritis
TKR      total knee replacement
PCA      patient-controlled analgesia
TENS     Transcutaneous Electrical Nerve Stimulation
VAS      visual analogue scale
ROM      range of motion
AMK      anatomic modular knee
PS       posterior-stabilized
LCS      low contact stress
ASA      American Society of Anesthesiology
CPM      continuous passive motion
MPQ      McQill Pain Questionnaire
IASP     International Association for the Study of Pain
MEAP     met-enkephalin-arg-phe
DynA     dynorphin A
SG       substantial gelatinosa
DNIC     diffuse noxious inhibitory control
PAG      periaqueductal grey matter
RVM      rostral ventral medulla
SPA      stimulus-produced analgesia
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CHAPTER 1

GENERAL INTRODUCTION
1. LITERATURE REVIEW

1.1 Total Knee Replacement

1.1.1 Introduction

Total knee replacement is a surgical procedure to replace a damaged or diseased knee joint with an artificial joint (prosthesis). It is one of the most successful operations practiced in the field of orthopedic surgery (Laskin 1991). On average, over 50,000 knee replacements are performed in the United States each year in 1980s (Laskin 1991). However, the number of such an operation needed and performed has more than tripled in just a few years in the 1990s. It has been estimated that in 1993, 179,000 total knee replacements were performed in the United States (Graves 1995, Katz et al. 1996). In Hong Kong, about 60 - 80 total knee replacements were done in Queen Mary Hospital every year during 1980s. In 1999, this number increased to about 100. Total knee replacement surgery has become a mainstay in the treatment of patients with advanced arthritis of the knee.

1.1.2 History and Development

The knee is the major joint most commonly affected by arthritis. Before the advent of total knee replacement, conservative measures such as debridement, osteotomy and arthrodesis were the basis of medical management. Unfortunately, many patients were rendered non-ambulatory by the end-stage of an arthritic knee (Bourne 1997). The need for a total knee replacement was obvious. The development of total knee replacement was parallel to that of total hip replacement. Prior to 1971, examples of pioneer total knee replacements included
mold arthroplasty of the femoral condyles, interposition implants and metal-on-
metal hinge arthroplasties (Landy and Walker 1988). The polycentric total knee
replacement was the first successful arthroplasty (Stein 1988). Up to now, more
studies on total knee replacement have focused on fixation (cemented vs
cementless), metal backing of the tibial and patellar components (Bourne 1997),
and functional recovery. Recently, major advances have been achieved in aseptic
technique, anesthesia, inert metals and fixation.

1.1.3 Indications and Contraindications

Pain, functional limitation and evidence of intra-articular disease on
radiographs are the primary indications for total knee replacement. The most
common joint disease that needs total knee replacement is osteoarthritis (Mancuso
et al. 1996). The prevalence of knee pain as a result of osteoarthritis is 6.8% in
men and 11% in women (Anderson and Felson 1988, Felson 1990, Lawrence et
al. 1990). One study by Mancuso et al. (1996) investigated the indications for
total knee arthroplasty in orthopedic surgeons in New York with a response rate
of 46%. The majority of orthopedists believed that patients should at least have
severe pain daily, pain at rest for several days/weeks, pain on transfer (e.g.,
standing up from a sitting position) for several days/weeks, inability to walk more
than 3 blocks, and/or having difficulty climbing stairs, before prescribing total
knee arthroplasty. Most surgeons considered the abnormality of joint space on
radiographs being one indicator. This surgery is also indicated for patients with
rheumatoid arthritis, when medical treatments have not been effective. Patients
with post-traumatic arthritis secondary to intra-articular fracture may also need total knee replacement (Laskin 1991).

Patients with neurological disease of the knee, severe bone loss, poor knee musculature and active sepsis are not suitable candidates for total knee replacement. Psychological disorders, such as depression, dementia, or lack of co-operation were not considered for total knee arthroplasty by most surgeons (Mancuso et al. 1996).

1.1.4 Surgical Techniques

Midline skin and capsular incision was the preferred procedure used to expose all the structure of the knee. The patella was inverted, and a lateral patella ligament release was done. The synovial membrane was resected as completely as possible. The medial and lateral soft tissue balance was confirmed in order to reach the knee in 90 degrees of flexion. For the femur, the posterior portion of the medial and lateral condyles was cut first, and used as a level guide for the prosthetic joint line. The anterior part of the femoral condyles was then resected. For the tibia, the articular surface of the medial and lateral tibial condyles was also removed. It was cut along the line at 7° tibiofemoral valgus to the longitudinal axis. The cut surface was covered by the prosthetic components, femoral component and tibial tray (Fig. 1.1). Before inserting the prosthesis, an entrance hole in the intramedullary was made ready for the intramedullary reference rod in the tibia. Suction was applied to the hole to prevent embolization of the marrow contents into the vascular channels during the insertion of the rod. For the patella, the patellar osteophytes were removed. The articular surface was
resected to a flat base and the patella button (component) was fixed on this base (Fig. 1.1). All components were inserted with cement. Akihide et al. (1997) suggested that, in order to prevent erosive changes of the patella resulting in prolonged pain even after surgery, the patella was replaced as part of total knee arthroplasty. With the advent of modern condylar components, resurfacing of the patella became a standard part of total knee arthroplasty (Bourne 1997).

In the treatment of bilateral knee arthritis, the surgeon will decide whether the surgery should be performed at one stage or all the procedures simultaneously. Several studies preferred the simultaneous approach (McLaughlin and Fisher 1985, Morrey et al. 1987, Ritter and Meding 1987, Soudry et al. 1985, Stein et al. 1988). This is because the morbidity with the simultaneous approach has been reported to be less than the staged procedure (Jankiewicz et al. 1994, McLaughlin and Fisher 1985). The chief advantage of simultaneous total knee replacement was to reduce the total medical cost, with saving ranging from 18% to 58% (Morrey et al. 1987, Ritter and Meding 1987). The length of hospital stay was shortened in patients receiving the simultaneous procedure when compared with the staged procedure (Jankiewicz et al. 1994, McLaughlin and Fisher 1985, Morrey et al. 1987, Ritter and Meding 1987).

Nerve injury is one of the complications after total knee replacement. The peroneal nerve is commonly involved. Since the rate of occurrence is very low, from 0.7% to 3.5% (Lu 1999), nerve injury will only rarely limit the effectiveness of TENS analgesia.

1.1.5 Fixation
The most frequent cause of failure in early total knee replacement designs was prosthetic loosening (Duffy et al. 1998). Fixation appeared very important to the success of total knee replacement. An in vitro study by Bert and McShane (1998) showed that implant stability was enhanced with the addition of cemented fixation around the tibia stem. In clinical studies, Stuart and Rand (1988) reviewed 44 cemented total knee replacements in patients with rheumatoid arthritis at a follow-up of 5 years. The 24 knees had excellent results, 14 had good results, and 6 had fair results. They concluded that cemented total knee replacement provides an excellent result for patients with rheumatoid arthritis. Stern et al. (1990) had 55 excellent and 13 good results at an average of 6.2 years after replacement in patients with gonarthrosis. The long-term stability of cemented total knee replacement has been investigated. Duffy et al. (1998) reported that cemented total knee replacement is a reliable procedure with excellent results at an average of 12.6 years follow-up, an estimated survival of 99% at 10 years, and an estimated survival of 95% at 15 years. Ranawat et al. (1993) reported 94.6% clinical survival at 15 years using a cemented posterior stabilized total knee arthroplasty, and Colizza et al. (1995) showed a survival of 96.4% for metal-backed posterior stabilized total knee arthroplasties at 11 years. There was no significant difference in pain and knee function scores between cement and cementless fixations (Duffy et al. 1998). The cementless fixation needed significantly more revisions because of loosening, when compared with cemented total knee replacements (Duffy et al. 1998).
1.1.6 Types of Prosthesis

The Anatomic Modular Knee (AMK) system of Depuy is indicated for patients older than 60 who are not very active. The femoral component has left and right sides. The tibial tray size may differ from that of the femoral component. The posterior-stabilized (PS) femoral component and a polyethylene line are always used. All the components are cemented.

New Jersey Low Contact Stress (LCS) system of Depuy is indicated for younger or more active patients. There is a symmetrical femoral component. The LCS rotating patellar component mimics normal anatomy. It has metal-backing and a polyethylene part that rotates over it. This rotating platform design allows for axial rotation, thus reducing the stress on the polyethylene and the tibia component (Buechel 1994).

1.1.7 Pharmacological Approach for Post-operative Pain after TKR

Three major pharmacological approaches have been commonly used for managing post-operative pain after total knee replacement. These are epidural infusion, intravenous patient-controlled analgesia and peripheral nerve block. A brief review of the clinical studies will be presented below.

Epidural infusion analgesic has been used for the post-operative pain after total knee replacement. It was reported to produce a 44% reduction of pain scores (VAS) 1 hour after the start of analgesic (Hommeril et al. 1994). Turner et al. (1996) demonstrated a significantly lower pain score with epidural ropivacaine infusion, when compared with no analgesic infusion during the first 10 hours after operation. Moiniche et al. (1994) reported that epidural analgesia, significantly
lowered pain scores within 48 hours after epidural infusion when compared with traditional intramuscular opioid injection. Ropivacaine and bupivacaine could be used in epidural infusion. Ropivacaine produced significantly less frequent and intense motor block over the 24 hours period than bupivacaine (p=0.015) (Muldoon et al. 1998).

Patient-controlled analgesia (PCA) is recommended to be a potentially superior form of post-operative pain control in patients receiving total knee replacement (Albert et al. 1991, Beattie et al. 1997). The 51% of patients receiving PCA protocol were reported to be pain-free and comfortable during the first 48 hours after total joint surgery, with the averaged total amount of morphine sulfate consumption being 51.4 mg (±27.8) (Albert et al. 1991). PCA has demonstrated a significantly better pain control at 2, 6 and 24 hours after total knee replacement when compared with placebo administration (Beattie et al. 1997). It has also shown a decreased length of hospital stay (Scalley 1988).

However, one conflicting study reported that PCA morphine (0.125kg/mg) provided no analgesic advantage over intramuscular treatment, from 6-24 hours after total knee replacement (McSwiney et al. 1997). The side effects of PCA, for example, nausea, still pose problems. Albert et al. (1991) reported that 35.1% of the patients discontinued PCA because of nausea (25%), intravenous infiltration (12.5%), failure to relieve pain (12.5%) and other complications.

The third approach, peripheral nerve block, followed by a continuous low-dose infusion of bupivacaine into the femoral nerve sheath after total knee replacement, was investigated (Edwards and Wright 1992). The study group showed significantly lower pain scores at 4 and 24 h post-operation (p<0.01), and
required less opioid medication (p<0.01) than the conventional intra-muscularly route after total knee replacement. Peripheral nerve block was reported to produce successful immediate analgesia for total knee replacement, i.e. the first 8 hours (Allen et al. 1998, Mansour and Bennetts 1996). Even morphine usage was decreased by approximately 50% in the peripheral nerve block group, which lasted till the second postoperative day (p<0.02) (Allen et al. 1998). However, Hirst et al. (1996) were unable to confirm improvement in the analgesia being provided by continuous infusion versus single injection femoral nerve block for total knee replacement, in terms of pain scores or morphine requirements.

When comparing epidural and patient-controlled intravenous morphine following knee replacement surgery, epidural morphine was found to provide more consistent analgesia following joint replacement surgery than patient-controlled morphine (Hendolin et al. 1996, Weller et al. 1991). Singelyn and co-investigators (1998) assessed the influence of three analgesic techniques on postoperative knee rehabilitation after total knee replacement. They reported that peripheral nerve block and epidural infusion analgesia provided better pain relief and rehabilitation outcomes, such as faster ambulation, better knee flexion and shorter hospital stay than PCA. However, there was a higher incidence of side effects with the epidural technique (Weller et al. 1991).

McBeath et al. (1995) investigated the correlation between patient-controlled analgesia and continuous epidural analgesia after total knee or total hip replacement on the length of hospital stay. They showed that both pharmacological approaches did not affect the length of hospital stay (p=0.054). They also found that the length of hospital stay did not correlate with age, weight,
height, type of surgery, or the American Society of Anesthesiology (ASA) classification.

Intra-articular morphine and/or bupivacaine injection has been used to control post-operative knee pain after joint replacement. This technique produced a brief reduction (the first 4 hours after operation) in pain scores in the morphine and bupivacaine treatment groups, when compared with placebo (saline) injection (Mauerhan et al. 1997). However, this technique has not been commonly used in the clinic.

1.1.8 Post-operative Rehabilitation

A post-operative rehabilitation program is organized for patients after total knee replacement in order to achieve independent function as soon as possible. Post-operative rehabilitation for total knee replacement has become important due to the demands for decreasing length of hospital stay and lowering hospital cost. Usually, the rehabilitation program after a total knee replacement operation is progressive on a daily basis. At day 1 or 2 after surgery, a bulky dressing covers the lower limb to reduce bleeding and control swelling. Either of the two rehabilitation modalities, for example, TENS or cold pack, could be applied to the patients for pain management. Patients are encouraged to do static exercises. From day 2 or 3 to day 6, an elastic stocking replaces the bulky dressing and progressive resistive as well as active exercises are preferred. Progressive resistance exercises to the muscles are an accepted approach to increase muscle strength (Spielholz 1990). In many facilities, continuous passive motion (CPM) has become a routine and is directly performed after operation (Ecker and Lotke
One week after the operation, patients are generally trained in muscle strengthening, walking and climbing up and down the stairs.

A number of studies have investigated the effects of rehabilitation approaches, such as cold pack and TENS for managing post-operative pain, range of knee motion and patients' function after total knee replacement.

Cold therapy is commonly used to control pain and edema after acute tissue injury. The positive effect of ice has been proven in previous studies. It was found to decrease enzymatic function and produce vasoconstriction (Levy and Marmar 1993). Vasoconstriction results in a reduction in blood flow, and contributes to a decrease in local inflammatory response and edema production. The mechanism of ice is at least partly due to its action on the peripheral nerves, which primarily slows down or blocks the transmission of pain signals. Recent studies showed that the cold compression device (or dressing) applied to the patients after total knee replacement reduced blood loss (Levy and Marmar 1993, Webb et al. 1998), and lowered opiate requirements (Levy and Marmar 1993, Webb et al. 1998). But this therapy did not influence the swelling and range of motion (Webb et al. 1998).

There are relatively few studies examining the effect of TENS on post-operative knee pain. One of the controlled studies showed that 15-20 min of the high-frequency TENS (100Hz, 160μs) produced a 50% reduction in the post-operative knee pain intensity as measured by the Visual Analogue Scale (VAS), while placebo TENS decreased the VAS score by 19% the first day after surgery (Arvidsson and Eriksson 1986). Angulo and Colwell (1990) investigated the analgesic effect of TENS using different stimulation intensities. High-frequency
TENS at sensory threshold produced a mean decrease of 50% in pain intensity as measured by the VAS, compared to a 38% decrease by TENS at sub-threshold intensity. However, a study by Walker et al. (1991) demonstrated that TENS (100µs, 70Hz) at sensory threshold, continuously applied for 3 post-operative days plus CPM, did not produce significant differences in the analgesic intake when compared with either placebo stimulation plus CPM or CPM only.

Taking together, these studies showed that high-frequency (100Hz), low-intensity (sensory threshold) TENS application after knee surgery reduced post-operative pain intensity, but not analgesic consumption. The duration of stimulation varied from a short period of time to 2-3 post-operative days.

1.1.9 Outcome Measurements for TKR

The patients receiving total knee replacement would expect reduced pain and improved knee function. Outcome measures for total knee replacement thus included pain intensity and knee function. The results have been shown to be predictable and reproducible.

A visual analogue scale was used to measure pain level in one study on patients receiving total knee arthroplasty (Hungerford and Krackow 1985). They reported decreased pain levels after comparing the pre-operative and post-operative measures in 71 OA patients and 36 RA patients. Murray et al. (1983) showed that 16 OA and 5 RA patients had decreased knee pain, when measured up to 24 months post-operatively. Kelley (1991) investigated 29 patients with either OA and RA with joint replacement, and found that they experienced a significant decrease in pain (p<0.05) at 6 weeks and 6 months after total hip or
knee joint arthroplasty. Heck et al. (1998) reported a decrease in the knee pain scores by 50% (p<0.0001) when compared with baseline measures. Crutchfield and his colleagues (1996) found that the mean scores as measured by the McGill Pain Questionnaire (MPQ) subscales declined during the post-operative period.

Range of motion (ROM) has been an important measure of outcome and is an important part of the knee scoring systems. Most studies reported that the final ROM averaged between 100° and 110° of knee flexion (Akagi et al. 1997, Duffy et al. 1998, Heck et al. 1998, Kumar et al. 1996), when pre-operative flexion was less than 90° (Anouchi et al. 1996). Anouchi et al. (1996) also concluded that those with poor pre-operative ROM would gain motion. Those in the mid-range stayed in the mid-range.

Muscle strength or muscle endurance was also measured. They served as indicators of the outcome of total knee replacement after one year, for comparison with those of the control normal subjects (Walsh et al. 1998). The strength of knee extensors and flexors, measured by the isokinetic peak torque, reached 71% and 72% respectively of those of age-matched control subjects at an angular velocity of 90°/s, and 73% and 85% at an angular velocity of 120°/s. The endurance of knee extensors and flexors of the subjects with total knee replacement, evaluated by the knee total work at angular velocities of 90°/s and 120°/s, achieved 73% and 76% respectively of the values obtained for the control subjects. Another study showed a significant and progressive increase by 30-53% in the strength of the operated flexor muscle, and a significant increase by 14-18% in the operated extensor muscle measured with isokinetic test (Lorentzen et al. 1999).
However, proprioceptive sensitivity was found to be reduced after unconstrained knee replacement in both the operated and the contralateral legs when compared with healthy controls, especially with the knee joint at approximately 60° (Fruchs et al. 1999). These investigators proposed that post-operative and persisting pain, functional deficits and instability of the knee joint probably contributed to the loss of proprioceptive sensitivity.

The final goal of total knee replacement is to achieve functional recovery and independent daily living. Most clinical studies have shown encouraging results. Heck et al. (1998) investigated 291 patients (330 total knee replacements). After two years, 88% of patients were satisfied with their knee replacement, and 88% patients had an improvement in their composite physical score. Stiffness scores also decreased by 39.3% (p<0.0001). Other studies showed that knee range of motion had improved from the baseline value by 33% to 43% after six months to two years (Duffy et al. 1998, Heck et al. 1998). Walsh et al. (1998) reported that patients with total knee replacement achieved over 80% of the normal and fast walking speeds of their age- and gender-matched counterparts after one year. However, it took the patients with total knee replacement more time to ascend and descend a flight of 10 stairs one-year after operation, when compared to the normal subjects.

Why did patients not recover their full functions several years after successful total knee replacement? It could be attributed to several factors, such as mechanical failure or loosening of the prosthesis (Sculco 1991), and decreasing proprioceptive sensitivity (Fruchs et al. 1999). Severe post-operative pain, or even persistent pain may also be a major contributing factor. Ritter (1997)
pointed out that 46.7% of patients have occasional pain and 7.1% have moderate or more pain 2 years after total knee replacement.

From the above review, it could be seen that the following outcome measures: (1) pain intensity assessed by the Visual Analogue Scale (VAS), (2) range of motion (ROM), (3) knee muscle strength and endurance, (4) knee function: e.g. walking and climbing, (5) analgesic consumption and (6) hospital stay, have been generally used in clinical studies due to the high reliability and validity of these measurements. They provided certain objective evidence to prove that total knee replacement surgery has become an important and successful approach to reduce the persistent pain and improve the functional activity in the arthritic patients. The cost benefit as measured by a shortened length of hospital stay has also demonstrated a socio-economical spin-off.

Pain after total knee replacement is one of the major complaints that affect the functional recovery of the knee. Management of post-operative pain has employed both pharmacological approaches like pre-emptive analgesia, and non-pharmacological methods, e.g. TENS. The relevant literature will now be represented.

1.2 Post-operative Pain: Definition, Measurement and Management

1.2.1 What Is Pain, Acute Pain and Post-operative Pain?

There are difficulties in trying to define pain, because the perception of and the response to pain are the results of a complex interaction of many factors (Sofer 1998). Some studies have described the pain as a sensation (e.g. Hervey 1984), while others have defined it in terms of tissue damage (e.g. Fields 1987).
McCaffery (1983) thought that pain was the subjective perception. The International Association for the Study of Pain, Subcommittee on Taxonomy offers the following definition of pain: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (IASP 1986, p.217). This definition recognizes the complex interaction between the subjective perception and the objective sensory aspects of pain. Actually, a highly intra-and inter-individual variability in the response of pain has been demonstrated (Filos and Lehmann 1999). Essentially, pain is multidimensional, consisting of sensory, affective, evaluative, cognitive and behavioral elements (Waterfield and Sim 1996).

Pain is beneficial because it is a signal of actual or potential tissue damage and initiates a response that removes the individual from harm. The task of detecting, conveying and interpreting pain stimuli depends on the peripheral and central nervous system. The sensory characteristics of pain, and the link between pain and tissue damage have been more clearly explained (Wall 1995). The chain of events results in the perception of pain at different anatomical levels of the nociceptive pathway, for example, the peripheral, spinal segmental, supraspinal and cortical levels. At the peripheral level, a receptor that responds to some kind of noxious stimulus, e.g. mechanical or thermal, is termed a nociceptor. A nociceptor is the termination of A-δ (from high threshold mechaoreceptors) or unmyelinated C afferent fibers (from polymodal nociceptors) that transmit noxious information to the dorsal horns in the spinal cord (Treede et al. 1992, Woolf and Chong 1993). A-δ fibers mediate the phasic pain, which is sharp, pricking in nature; while C fibers are implicated in tonic pain perception, which is
often described as dull or aching in nature. These fibers are finely myelinated and unmyelinated respectively, and conduct at speeds comparatively slower than the large diameter myelinated A-β fibers (Wall and Melzack 1994).

The cell bodies of A-δ and C fibers lie in the dorsal root ganglia of the spinal cord. They bifurcate into ascending and descending branches that may travel to higher central nervous system, before they synapse with the second order neurons at the spinal level. The incoming fibers synapse mainly in laminae I, II, III and V (Christensen and Perl 1970, Fitzgerald and Wall 1980, McMahon and Wall 1984).

There are two main ascending excitatory pathways concerned with nociceptive transmission. The spinothalamic tract, which is fast conducting, with discrete somatic organization resulting in rapid transmission of nociceptive information regarding the site, intensity and duration of stimulus, projects to the posterior ventral nuclei of the thalamus (Bovsher 1957, Mehler 1962). The spinoreticular tract, which is slow conducting, with a lack of somatic organization resulting in poor localization, dull aching and burning sensations, projects to the medial and interlaminar nuclei of the thalamus (Mehler 1962, Bowsher 1976).

From the thalamus, the impulses are delivered to various areas of the cerebral cortex. At the cortical level, the parietal lobe is involved in the localization and interpretation of the pain. The temporal lobe processes the pain memory. The frontal lobe provides a cognitive function to assess the significance of the pain and the emotional responses to it. The limbic system is involved in the affective and automatic response to pain (Snell 1992).
Acute pain has a sudden onset. It is most commonly caused by an accident or trauma resulting in localized tissue damage (Robert 1992, Lockwood 1996). Both the period of time over which the pain occurs (Levi and Maihafer 1987), and the characteristics of pain have been used for defining acute pain in various studies. The definition of acute pain covers several orders of magnitude of and duration less than 3 months (Mersky 1986), including pain due to a brief noxious stimulus as well as pain that accompanies the healing process (Treede 1995). Acute pain includes phase 1 pain, which is characteristic of the initial response of the nociceptive system to a noxious stimulus (Treede 1995), by sensitizing the nociceptors via the action of proteolytic and inflammatory agents that are released into the wound tissue (Richardson and Bresland 1998). Phase 2 pain creates the short-term plasticity of the nociceptive system and a consequence of prolonged noxious stimulation leading to tissue damage and peripheral inflammation (Cervero and Laird 1991). This is known as secondary hyper-analgesia. Secondary hyper-analgesia is due to the plastic changes in the central nervous system following the processing of painful stimuli, but not alterations in the nociceptor activity (Treede et al. 1992, Woolf 1991a, b).

When the body is damaged by the noxious stimulus, the body's protective mechanism is activated and the symptoms reflect the underlying pathology (Walsh 1997). Acute pain is accompanied by dilation of the pupils of the eyes, increased sweating, pulse and respiration rate. There is growing evidence that acute pain is one of the major components of a wide range of neural, endocrine, metabolic, immunological and inflammatory changes that constitute the stress
response to acute surgical injury and critical illness (Richardson and Bresland 1998).

Post-operative pain is a particular type of acute pain caused by operations for trauma and other medical conditions, and may diminish as healing occurs (Bonica 1985). It can take several days (Treede 1995). Surgical pain begins when an incision is made and tissue damage occurs. It is one of the common complications after surgery and affects the functional recovery of the patients. As early as 1973, Marks and Sacher reported that 73% of patients with post-operative pain experienced moderate to severe pain regardless of the analgesics prescribed. A recent study revealed a similar incidence of post-operative pain in the present decade. Seventy-seven percent of 500 randomly interviewed US patients reported having experienced pain after operation, with 81% of them experiencing moderate to severe pain (Warfield and Kahn 1995).

Post-operative pain can have harmful physiological and psychological effects. Roberge and McEwen (1998) defined three phases in the response to post-operative pain. The first phase involves the initial transmission of electrical impulses and the patient’s awareness of pain. The second phase involves the release of chemicals from the nerves and damaged tissues. During the third phase, an invasion of phagocytes and fibroblasts occurs, which coincides with the formation of reparative scar tissue. Post-operative pain is not only associated directly with the tissue damaging stimuli during surgery, cleaning and repackaging (Clifford et al. 1993). It may also arise from the production of pain-producing substances (e.g. substance P, potassium, lactic acid, bradykinin and hydrogen ions) generated at the site of the incision to decrease the pain threshold.
of nociceptors, thereby sensitizing the damaged nerve endings to produce pain (Sinatra 1993). The prolonged noxious stimulation leading to tissue damage and peripheral inflammation may result in persistent post-operative pain (Cervero and Laird 1991, Dubner 1991, Wall 1988, Woolf 1991b). This is central sensitization that may induce long lasting central neuronal alterations, to amplify and prolong pain during and beyond the stage of actual tissue damage (Dubner and Ruda 1992).

1.2.2 Relevant Pain Measurement in Human Studies

In any course of treatment, objective and subjective measurement are required to assess a patient’s response to the treatment. As Tanabe (1995) pointed out, it is only through promotion of pain assessment that pain management will become a priority. Quantitative measurement of pain severity would have profound therapeutic implications (Russell and Ronald 1996). Any measurement equipment and scales should be valid, sensitive and reliable in a particular framework and clinical context. The measure chosen should have meaning for both the therapist and the patient, and it should be easy to administer and complete (Waterfield and Sim 1996).

In clinical studies, the intensity of acute post-operative pain is usually measured using either a visual rating scale for the amount of pain or pain threshold in response to a given stimulus. Demand analgesic used to supplement other basic pain relief techniques has been suggested as a convenient measure of the effectiveness of the basic techniques used. Other clinical data such as the
frequency of post-operative complications, length of hospitalization, pulmonary function and range of joint motion have also been used.

1.2.2.1 Visual Analogue Scale (VAS)

The Visual Analogue Scale (VAS) (Huskisson 1976) is now the most widely used method of measuring pain intensity because of the ease and simplicity of its administration. The VAS measures the intensity or magnitude of pain along a continuous scale. There are 2 types of VAS, absolute and comparative. The absolute scale measures the severity of the pain at a particular point in time, while the comparative scale gives a measure of pain relief over time (Cole et al. 1994).

The VAS is usually a 10cm line with "no pain" written at the left end and "pain as bad as it could be" at the other. The patient is asked to rate his or her pain by making a mark at an appropriate point on the VAS line. A vertical or horizontal VAS can be used, but the horizontal scale is generally preferred (Dixon and Bired 1981, Sриwatanakul et al. 1983). The patient's score is derived by measuring the distance in millimeters between his/her mark and the left end of the scale.

![Diagram of VAS scale]

Make a mark on the line at the point which you think represents the level of your pain

Several researchers have discussed which point on the scale represents moderate pain intensity. Their suggestions vary from >30 mm (Seymour et al.
1996) to >60 mm (Stubhaug et al. 1995) and >75 mm (Curtis et al. 1994).

Recently, Collins et al. (1997) investigated 1,080 patients recording their initial pain intensities using the VAS. Of the patients reporting moderate pain, 85% scored over 30 mm, with a mean score of 49 mm. For those reporting severe pain, 85% scored over 54 mm with a mean score of 75 mm.

The VAS is not only being used for measuring pain intensity, it has also been used for measuring pain relief (Rhind et al. 1980), pain affect (Jensen and Karoly 1992), and other variables such as mood (Bond and Lader 1974) and functional capacity (Huskiisson et al. 1976).

The test-retest reliability of VAS has been extensively studied, and reported to be high when repeatedly used in the same individuals (Bowsher 1994, Carlsson 1983, Elton et al. 1979, Jensen and McFarland 1993, Revillet al. 1976, Waterfield and Sim 1996). As the VAS directly measures the intensity of pain, it has high content validity (Jensen and McFarland 1993, Cole 1994). The VAS and the Numeric Rating Scale have a correlation ranging from $r=0.77$ to 0.91 (Downie et al. 1978). The correlation between the VAS and the finger dynamometer measuring mechanical pain was $r=0.87$ ($p=0.001$) (Wilkie et al. 1990). VAS is one of most sensitive measures of pain intensity and of change in the pain sensation (McDowell and Newell 1987, Waterfield and Sim 1996). It was sensitive enough to detect a change of less than 20% in the perception of experimental thermal heat pain and clinical pain during TENS treatment (Marchand et al. 1991a,b). Price et al. (1994) reported that VAS and stimulus temperature have a high correlation, $r=0.98$. More patients preferred a VAS to a 4-point Vertical Rating Scale (VRS) (Joyce et al. 1975). Previous research

VAS is an unidimensional measurement (Waterfield and Sim 1996), and is difficult to use with subjects having poor understanding. Some investigators found that the failure rate for using VAS can be reduced greatly if the measure is explained carefully to the patients (Joyce et al. 1975, Scott and Huskisson 1976, Wilkie et al. 1990).

1.2.2.2 Thermal Pain Threshold

Thermal pain threshold is a controlled, repeatable, objective assessment with minimal temporal effects (Gracely 1989). Two thermal pain parameters including heat and cold pain thresholds are generally measured. The advantage of thermal testing is that it tests primary small-diameter afferent fibers, specifically the A-δ and C fibers that mediate the sensations of cold and heat because of modality specificity (Morin and Bushnell 1998).

There are two major methods for measuring the thermal pain threshold: method of limit and forced-choice. In the “method of limit”, stimulus intensity is gradually increased or decreased. The subjects are required to stop the stimulus by pressing a switch when they first perceive the pain. The forced-choice procedure requires the subject to determine the presence of a discrete stimulus in either one of two intervals of time or at one of two locations. The method of limit is considered simple and quick (Yarnitsky et al. 1995).
Thermal testing started about 50 years ago with the application of radiant heat at a distance to the skin (Hardy et al. 1950). It has developed in more recent years to “contact” stimulators based on the Peltier principle (Procacci et al. 1979, Yarnisky et al. 1995). The size and pressure on the tested area of the Peltier thermode may influence the result of the threshold recorded (Yarnitsky et al. 1992, 1995). The rate of temperature rise should also be considered. Some studies have shown that a fast rate of temperature rise should result in a lower threshold than a slow rise (Morin and Bushnell 1998, Yarnitsky and Ochoa 1990, Yarnitsky et al. 1992). This is because slower rate of temperature rise can cause a longer reaction time in the processing and perception of the pain by the peripheral and central nervous systems, and in making a stop to the stimulus.

Pain threshold is constantly related to physiological factors among the population or groups (Dar 1995). One study showed no significant difference in heat pain threshold between the upper and lower limbs, or between left and right sides of the body (Taylor et al. 1993). Furthermore, pain threshold cannot substitute the use of the VAS to assess the pain intensity. In fact, the correlation between pain threshold and measures of pain intensity is poor. It should be noted that pain threshold is a specific magnitude of stimulus intensity, and a measure that depends on the intensity of stimuli is always an approximation (Gracely 1994). In contrast, the VAS gives a discrete number along an analogue scale representing the pain intensity that patient perceived.

1.2.3 Pharmacological Management of Post-operative Pain

1.2.3.1 Patient-controlled Analgesia
In recent years, new methods and routes of administration, including patient-controlled analgesia (PCA) and epidural infusion, are increasingly being used to manage post-operative pain. Since these procedures have the advantage of providing sustained analgesia, a lower peak plasma concentration of the drug will occur, thereby minimizing the side-effects (Tempest 1992). Such continuous methods also provide more pain reduction than the traditional intramuscular procedure, when patients often experience pain before asking for pain medication (Warwick 1992). Better quality post-operative pain control facilitates earlier ambulation and quicker recovery of respiratory functions. It also may contribute to reduce some complications after operation (Lynch et al. 1998), thereby lowering morbidity and mortality rates and the length of hospital stay (Dubois 1991).

In 1968, Sechzer first used a nurse-observer to administer small intravenous doses of analgesics to patients on demand. Subsequently, Forrest and his colleagues (1970) described an experimental device that automatically administered intravenous analgesics when activated by pressing a button on a handgrip. In 1980s, PCA has been developed as a sophisticated, programmed drug delivery system administered bedside (Owen et al. 1986), and is now being used in the clinic. A pre-set dose of opioid can be delivered on a pre-determined time when the patient feels the need for it by pressing a button. Most people are able to control the self-administration of intravenous opioid safely to achieve effective pain relief (Joshi and White 1998).

The quantity of analgesic available to the patient is limited by certain parameters, such as the present demand dose size (increment) and the lockout
interval (minimum time between doses). The former may be an important factor for the success of PCA. Too small a demand dose may result in a failure to achieve adequate analgesia. Too large a demand dose may produce side-effects that also result in failure of the technique (Owen et al. 1989). The optimal demand dose can be defined as “the minimum dose to produce appreciable analgesia consistently without causing either subjective or objective side-effects” (Owen et al. 1989). The most appropriate size of demand dose for morphine was investigated. Originally, as little 0.1 mg was used per demand (Sechzer 1968). More recently, Rosen (1986) described the dose in the range of 2-4 mg as being satisfactory. White (1986) and Owen et al. (1989) suggested that 1 mg was appropriate. Two studies showed that when the lockout interval was 5 or 6 minutes, a PCA morphine dose of 1 mg produced more superior analgesia than 0.5 mg, and equal analgesia with fewer side-effects when compared with 2 mg (Bennett 1986, Owen et al. 1989).

The lockout interval is the minimum time between two demand doses. It is to prevent the patient from administering a second dose of analgesic when the previous dose is still acting. The lockout interval is based on the time of onset of the analgesic effect. If the lockout interval is too long, adequate analgesia cannot be obtained, as the serum opioid concentration falls below the minimal effective analgesic concentration before the next demand dose is being administered (Joshi and White 1998). The lockout interval depends on the size of the demand dose. Although the lockout intervals for morphine in a number of studies ranged from 2 to 20 minutes, there have been few studies investigating this aspect of PCA.
therapy. In a more recently study, Joshi and White (1998) suggested the lockout interval for a 1 mg demand dose of morphine to be 6 minutes.

Some researches had set out to compare PCA with intra-muscular injection therapy in the management of post-operative pain after orthopedic surgery (Notcutt and Morgan 1990, Raj et al. 1987, Scalley et al. 1988, Wermeling et al. 1992). They concluded that PCA provided more superior analgesia. Patients who received PCA analgesia reported less analgesic dosage and walked farther on the first post-operative day (Clifford and Beverly 1995).

PCA produces time-efficient analgesic effects (Clifford and Beverly 1995). Sarah (1998) showed that patients who received intra-muscular injection required 10 minutes to more than one hour to experience effective pain relief, whereas those receiving PCA experienced analgesic effect immediately or in less than 10 minutes.

If the patients are unable to follow the demand regimen, or do not want to participate, or if there is a lack of training of the healthcare personnel involved, PCA is not indicated. However, previous drug abuse is not an absolute contraindication, but these patients may require an increase in dosage to compensate for possible tolerance effects (Dubois 1991).

PCA is not only a drug delivery route, but PCA morphine consumption has also been used as one of the objective pain measurements in recent clinical pain studies. The dose of opioids required at different times is taken as an indicator of the severity of the post-operative pain. The plasma concentration of morphine has also been used to assess the efficacy of TENS (McCallum et al. 1988).
1.2.3.2 Epidural Infusion

Continuous epidural analgesia is rapidly becoming a primary method of post-operative pain management (Dubois 1991). This technique is believed to block sensory nerve pathways to prevent and reduce the pain (Sofear 1998). Continuous administration avoids the peaks and valleys in cerebrospinal fluid levels of the drug, providing more efficient analgesia while reducing the severity of side-effects (Downing et al. 1988, Planner et al. 1988). One study showed that the drug in the serum levels at 24 hours is low, with 90% of 20 subjects studied being less than 6.5 ng/ml (Walmsley et al. 1989).

The site of the epidural catheter placement may influence the adequacy of pain relief. It is normally placed at the L4-L5 level for lower limb orthopedic operations. Placing within the dermatomal distribution of the pain probably achieves the best effect with the smallest amount of drug (Raj 1996). Infusion analgesics involving bupivacaine and fentanyl are commonly used. The rate of epidural infusion used can be set from 6 to 10 ml/hr, according to the levels of pain perceived by the patients. The epidural infusion rate could be used as an indicator of pain change. Much smaller doses of analgesic are required by epidural infusion in comparison with other methods, including the intravenous route (Eisenach et al. 1988, Shenton 1993).

Risks and side-effects do exist in epidural analgesia. The small fraction of the drug that crosses the epidural tends to remain in the cerebrospinal fluid. The drug travels to the ventricle through passive flow of the cerebrospinal fluid which creates the possibility of increased side-effects of central origin, such as nausea,
vomiting and respiratory depression (Dubois 1991, Richardson and Bresland 1998). Some degree of motor block can affect the ability of the patient to move (Sofear 1998). Patients having an epidural infusion should have their respiration rate and blood pressure volume closely monitored, to prevent the possible vasodilatory effects of a local anesthetic on the sympathetic nerve system (Sofear 1998).

1.2.3.3 Pre-emptive Analgesia for Post-operative Pain

In recent years, a novel pharmacological approach using continuous pre-emptive administration of opioids has offered the possibility of reducing post-operative pain after major surgery. This approach is based on the concept that the development of central sensitization during and after surgery can be decreased or even prevented.

Peripheral tissue injury provokes two kinds of modifications in the response of the nervous system. One is peripheral sensitization, that is, the alterations in primary afferent nociceptor activity. The other is central sensitization triggered by nociceptive afferent inputs (Wall and Woolf 1984, Woolf and Wall 1986a,b). It is a nociceptive activity-dependent increase in the excitability of neurons in the central nervous system (Cerver et al. 1988, Clifford et al. 1993, Cook et al. 1987, Hylden et al. 1989, Simone et al. 1991, Treede et al. 1992, Woolf and King 1990).

Peripheral sensitization may alter the high threshold nociceptor sensitivity in thermal receptors and mechanoreceptors in the immediate environment of tissue injury (LaMotte et al. 1991, Wassef 1998). In the presence of tissue injury,
the release of substances such as norepinephrine, bradykinin, 5-HT and prostaglandins from the peripheral nerve endings (Handwerker and Reeh 1992), result in inflammation with sensitization of various classes of afferent fibers (Treede et al. 1992). The peripheral injury may also result in an expansion of the receptive fields of the nociceptors, along with a decrease in the threshold of the dorsal horn neurons (Dubner 1991, Dubner and Ruda 1992). This could further result in sensitization of the secondary nociceptive neurons in the spinal cord (Woolf 1991a,b). This expansion response may be prolonged, depending on the type of afferent and the body parts activated by the noxious stimulus (Woolf 1991a,b). Richardson and Bresland (1998) found that the activation of unmyelinated C-fiber triggered secondary hyper-algesia. Similar studies in the decerebrated rat showed that nerve impulses in the C-fibers induced a prolonged, widespread increase of reflex (Woolf and Wall 1986a) and inter-neuron excitability (Cook et al. 1987). This triggered central hyper-excitability is particularly strong and prolonged if the stimulation is applied to deep tissues such as muscles or joint (Woolf and Wall 1986b, Wall and Woolf 1984). Central sensitization and peripheral sensitization can form a closed-loop nociceptive pathway. It may be still self-sustaining, even when stimuli from the injured tissue begin to subside (Woolf and Chong 1993). Similar alterations are proposed to occur in surgical patients, thereby amplifying and prolonging post-operative pain, giving rise to possible persistent post-operative pain (Dubner 1991, Wall 1988, Woolf and Chong 1993, Woolf and Thompson 1991).

The events described above provide a conceptual framework for a pre-emptive and continuous method that could reduce the peripheral and central
neuronal changes induced by tissue damage, so that a reduction or elimination of post-operative pain is possible.

In order to prevent the establishment of central sensitization that amplifies the peripheral nociceptive inputs and contributes to heightened post-operative pain, the potential peripheral triggers for the induction of central sensitization needs to be reduced in a timely fashion (Clifford et al. 1993). The important concept of "timing" of analgesic administration has been suggested to be of major importance in the treatment of post-operative pain (Clifford et al. 1993, Wall 1988, Woolf 1983, Woolf 1989, Woolf and Thomson 1991). It has encouraged animal and clinical studies to test whether pre-operative opioid can preempt post-operative pain. More specifically, rat studies showed that pre-operative administration of opiates was more effective than post-operative administration in reducing the excitability generated in the rat dorsal horn neurons by neurophysiological recordings (Coderre et al. 1987, 1990, Dickenson 1987, Woolf, 1989, Woolf and Wall 1986a,b). In clinical studies on human, non-steroid drugs (NSAIDS), local anesthetics and opioids have been investigated (Badner et al. 1996, Collis et al. 1995, Fletcher et al. 1995, Joel et al. 1994, Mansfield et al. 1994, Negre et al. 1994, O'Hanlon et al. 1996, Parke et al. 1995, Wong et al. 1997). These opioids, either alone or in combination, were applied to the patients 30 to 90 min before surgery, either continuously or intermittently. Some studies have shown positive results in reducing post-operative pain or medication intake (Negre et al. 1994, Parke et al. 1995, Wong et al. 1997). Others produced results that were mixtures of weak positive or negative findings (Dahl et al. 1994, Dahl and Kehlet 1993, Hendolin et al. 1996, McQuary 1994). In this connection, a
surgical incision causing tissue injury in human is likely to be different from chemical irritation, inflammation, or nerve injury models in animal studies. The prolonged and extensive post-operative pain perceived by human is multidimensional in nature, with mixed cutaneous, muscular, and pain behavior components (Wassef 1998). In contrast, the animal studies generally exhibit a well-localized injury, or the effect of selective afferent fiber stimulation.

Continuous pre-emptive administration of analgesics appears to offer a greater possibility of reducing pain after major surgery. Such a continuous method is thought to prevent the prolonged noxious stimulation generated by the inflammatory reaction in tissue damaged during surgery, possibly including even the secondary hyper-analgesia after operation (central sensitization). However, using pre- and intra-operative analgesic administration alone have been reported to be insufficient for many patients.

A range of pharmacological approaches has been developed for post-operative pain control. Those described in this section are a sample of the most widely used in the clinic. These approaches have produced better analgesic effects for most of the patients after operation. However, the high rate of incidence of side effects has contributed to a failure to produce pain relief. It is very important and necessary to introduce other non-pharmacological therapies, such as electrotherapy, as an adjunctive approach.

1.3 Transcutaneous Electrical Nerve Stimulation (TENS)
1.3.1 History of TENS

As far back as ancient Egypt, the use of electricity as a therapeutic approach has been reported. For example, *Malapterurus electricus* was used for the treatment of painful conditions (Walsh 1997). With the development of the battery and induction coil in the 1800s, electrical current was further applied as a treatment modality (Walsh 1997). Over the past hundred years, various electrical machines for pain-relief have been developed. The "gate control theory" of pain, which provides a neuro-physiological basis for analgesia through low intensity electrical stimulation, was proposed by Melzack and Wall in 1965. This theory contributed to the development of transcutaneous electrical nerve stimulation (TENS). Wall and Sweet (1967) provided clinical evidence to support the "gate control theory" when they reported the success of low intensity, high frequency TENS in reducing chronic neurological pain. In the same year, TENS was first used to evaluate patients for dorsal column electrode implantation by Shealy and others (1967). Over the next 25 years, non-invasive and non-addictive TENS has been widely used with relatively few complications for acute and chronic pain management. Its influence on the autonomic nervous system and ability to induce changes to the neurohumoral mechanisms have also been delineated (Lockwood 1996).

1.3.2 Technical Aspects of TENS Devices

TENS induces electrical stimulation in the neuromuscular system by passing electricity through the skin from electrodes placed on the surface. Control of the pulse width, current amplitude, wave form, frequency and intensity as well
as electrode design and placement may be important for successful TENS application.

For most TENS devices, the pulse width usually ranges from 50-200 microseconds. The amplitude usually ranges from 0 to 50 mA with an electrode impedance of 1 kilo-ohm. Both amplitude and pulse width determine the strength of the stimulus (Manneimer and Lampe 1984). Increasing the amplitude and/or the pulse width can increase the strength of the stimulus. Most TENS devices offer electrical pulses with various wave forms. The rectangular wave is the most common (Woolf and Thompson 1994). The biphasic symmetrical pulse is preferable (Anderson 1979), because it can make each electrode acting as a cathode during alternating the phases of the pulse (Walsh 1997). This can reduce the incidence of chemical irritation to the skin when compared with a monophasic pulse (Anderson 1979).

Frequency is a time-dependent parameter. It refers to the number of pulses delivered per second and is measured in Hertz (Hz). The optimal frequency for TENS may vary according to the nature of pain. Some studies suggest that frequencies from 100 Hz to 150 Hz are more efficient for pain control than frequencies from 2 to 4 Hz (Lockwood 1996, Woolf and Thompson 1994). This is termed high-frequency conventional TENS stimulation (100-150 Hz), in contrast to low-frequency acupuncture-like TENS stimulation (2-4 Hz).

Intensity is determined by the response of the patient. For clinical purpose, Sluka et al. (1998) categorized TENS into high or low intensity. With low-intensity TENS, the stimulation amplitude is increased until the patient feels a comfortable tingling, buzzing, pricking (perceived with high frequency),
tapping, or vibratory (perceived with low frequency) sensation with some small muscle contraction. With high-intensity TENS, the stimulation intensity is increased to produce an overt muscle contraction. Some authors suggested that the intensity should be increased to the maximally tolerable level but not too noxious stimulation (e.g. Sluka et al. 1998). In physiotherapeutic clinics, an intensity of two or three times the sensory threshold is commonly used, and has been proven effective in relieving OA pain (e.g. Cheing and Hui-Chan 1999). It should be noted that increasing the pulse duration, frequency and intensity of TENS was found to increase the amount of inhibitory effects on the activity of dorsal horn neurons in rats (Garrison and Foreman 1994).

Another important factor for successful TENS application is the electrode design, including its material and size as well as electrode location and proper contact with skin. A good electrode material should have a good conductivity and a low interface impedance with no irritation or toxicity to the patients (Walsh 1997). It should also reduce skin irritation problems and increase stimulation comfort (Szeto 1988). The most commonly used electrode is silicon rubber with carbon particles. Recently, disposable and reusable self-adhesive electrodes have become more commonly used at a more reasonable cost (Woolf and Thompson 1994). Adhesive gels are used to keep a good contact of the surface of electrode to the skin. Such a gel can reduce the incidence of current density hot spots (Walsh 1997). Gels can also be replaced and refreshed.

Electrode size is important to determine the area and amount of stimulation delivered to the tissues (Walsh 1997). It is inversely related with the current density (Mannheimer and Lampe 1984). The larger the electrode size, the
less the current density. This is because a larger electrode is likely to distribute the current more widely (Oösterwijk 1994). Electrode size should be at least 4 cm² to prevent skin irritation and chemical burn. Small electrodes are usually applied to precisely targeting points, e.g. a motor or an acupuncture point (Walsh 1996), whereas larger electrodes are more suitable for stimulating large muscle groups.

The shape of an electrode is another important consideration. Electrodes with angular edges tend to concentrate the electrical field at corners, resulting in current density hot spots. This problem is minimized by having electrodes with round corners (Walsh 1996).

The optimal electrode site varies with the condition to be treated. Generally, there are four broad categories of anatomical sites for TENS application in previous studies. These are: (1) painful areas (Moore and Blacker 1983, Taylor 1983), (2) peripheral nerve sites (Loeser et al. 1975, Moore and Blacker 1983, Taylor 1983), (3) spinal nerve roots (Wadsworth and Chanmugana 1983) and (4) three other specific types of points: acupuncture points (Cheing and Hui-Chan 1996, 1999, Moore and Blacker 1983, Wadsworth and Chanmugana 1983), trigger points (Moore and Blacker 1983) and motor points (Moore and Blacker 1983, Wadsworth and Chanmugana 1983). The three types of specific points are more preferred because they may be more sensitive to electrical currents (Walsh 1996). Several clinical studies have proven the success of TENS application on these points (Chen et al. 1998, Cheing and Hui-Chan 1996, 1999, Fox and Melzack 1976, Laitinen 1976, Moore and Black 1983, Wadsworth and Chanmugana 1983). Moreover, placement of the electrodes should be more than
1 cm apart at the edges to avoid short-circuiting (Woolf and Thompson 1994). It may be placed unilaterally or bilaterally, depending on the site of the pain and its origin (Walsh 1996). The number of electrodes used will be depended on the number of channels used, i.e. single channel with two electrodes, and dual channels with four electrodes (Wadsworth and Chanmugana 1983).

1.3.3 Modes of TENS

1.3.3.1 Conventional TENS

Conventional TENS is characterized by high frequency, typically around 100 Hz, and low intensity. The pulse duration is usually short (50-80 μs). The sensation experienced is often tingling, buzzing or pricking. This mode of TENS is one of the most commonly used treatment supplements to analgesics for pain management. According to the gate control theory (Melzack and Wall 1965), these parameters are thought to stimulate the large diameter afferent, thereby inhibiting the transmission of nociceptive signals via small diameter fiber and reducing pain. Johnson et al. (1991) conducted a long-term clinical study of patients using high frequency TENS and proved the inhibitory effect of TENS. The study showed that 30% of patients experienced immediate analgesia, 75% within ½ hour, and 95% with in 1 hour. The analgesia effect of conventional TENS tends to be relatively short, lasting for a few hours post-treatment (Walsh 1996). Recently, some studies reported an important and interesting finding that the inhibitory effect of TENS could cumulate over time, when TENS was repeated daily application over two (Liu and Hui-Chan 1994, Marchand et al. 1993) to four weeks (Cheing and Hui-Chan 1996).
1.3.3.2 Acupuncture-like TENS

Acupuncture-like TENS uses low frequency (1-4Hz) and high intensity stimulation with long pulse duration (200μs). The intensity is high enough to produce muscle contraction. Acupuncture-like TENS was developed by Eriksson and Sjölund (1976) in an attempt to encompass the mechanisms of both acupuncture and gate control theory to improve TENS efficacy. TENS in this mode was presumed to be stimulating primarily the nociceptive fibers and motor fibers (Walsh 1996). Other studies indicated that several opioids may contribute to the pain relieving effect produced by acupuncture-like TENS (Sluka et al. 1998). Endorphins were thought to be involved (Chen and Han 1992, Dymond 1976, Han and Wang 1992, LeBars et al. 1981). Furthermore, Han et al. (1991) suggested that TENS could trigger the release of endogenous opioids other than endorphins at central nervous system sites relevant to pain control. They found that conventional low-frequency (2 Hz) TENS, applied at the Hegu and Zusanli acupoints, resulted in a marked increase (367%) in met-enkephalin-arg-phe (ir-MEAP) from the preproenkephalin (Han et al. 1991). Additionally, an increase in beta-endorphin in the blood and cerebrospinal fluid has been demonstrated after TENS at either high or low frequency in normal subjects (Hughes et al. 1984, Salar et al. 1981). Further study by Sluka (1999) found that low-frequency TENS produced anti-hyperalgesia through μ-opioid receptors in the spinal cord.

Based on the central location for pain modulation, acupuncture-like TENS can be applied at a distant site, to the acupuncture points related to the body part where pain is experienced. This is especially important to the patients when
electrical paraesthesia cannot be achieved in the painful area (Johnson et al. 1992a).

1.3.3.3 Burst, Train TENS

This mode of TENS combines high and low frequency TENS. A baseline low frequency current is delivered which contains a high frequency train (Walsh 1996). Usually, the frequency of the current is 1-4 Hz with an internal frequency of the trains around 100 Hz. This burst train mode produces a more comfortable muscle contraction when compared with acupuncture-like TENS (Walsh 1996). This mode of TENS analgesia is thought to be based on similar pain control mechanism as that of conventional and acupuncture-like TENS. As mentioned before, Han et al. (1991) reported that low-frequency (2 Hz) TENS resulted in a marked increase (367%) in met-enkephalin-arg-phe (ir-MEAP), whereas high frequency (100 Hz) TENS produced a 49% increase in dynorphin A (ir-Dyn A) in the lumbar cerebrospinal fluid. An increase in the plasma concentration of met-enkephalin was also observed during burst TENS treatment (Johnson et al. 1992a).

1.3.3.4 Brief, Intense TENS

Mannheimer and Lampe (1984) described brief, intense TENS when continuous TENS was administered using high frequency (100-150 Hz), long duration (150–250 μs) pulse at the highest tolerable intensity. The analgesic effect produced by brief, intense TENS was proposed to be primarily due to a peripheral blockade of nociceptive transmission in small diameter peripheral
afferent (Mannheimer and Lampe 1984). Although there are relatively few reports in the literature demonstrating the clinical use of intense TENS, some investigators recommended this mode for acute pain control (Johnson et al. 1992a, Mannheimer and Lampe 1984).

The efficacy of the above four modes of TENS analgesia has been investigated (Johnson 1992b). The gradual onset time of the analgesic effects (>30 min) produced by 30 min of brief intense and acupuncture-like TENS was longer than that of 30 min of conventional TENS. A rapid decrease (< 10 minutes) of cold pain threshold generated by both the conventional and brief intense TENS modes was noted when compared with acupuncture-like TENS (>30 min). From the parameters of TENS used in this study, high-frequency with long duration pulses applied to the acupuncture point appeared to produce a more superior analgesic effect. Variations in the analgesia effects of these stimulation modes may be attributed in part to different analgesic mechanisms as reviewed below.

1.3.4 Possible Analgesic Mechanisms Evoked by TENS

1.3.4.1 Physiological Blocking Effects

Several studies have reported that the application of high frequency electrical currents over a peripheral nerve could reduce the conduction velocity of a nerve (Campbell and Taub 1973, Ignelzi and Nyquist 1976, 1979, Walmsley et al 1986). When peripheral conduction in the large diameter fibers is slowed down, the volume of nociceptive traffic can be accordingly reduced, and this will reduce the perception of pain (Walsh 1997).
1.3.4.2 Gate Control Theory

In 1965, Melzack and Wall proposed the gate control theory to explain the mechanism that cutaneous stimuli can modulate pain transmission. A constant and dynamic interaction was thought to take place between the large-diameter (A-β) fiber inputs and the smaller-diameter (A-δ and C) fiber inputs at the segmental level of the spinal cord. The larger fibers transmit input from pressure or touch stimuli, whereas the smaller fibers carry input from specific or diffuse pain. The substantial gelatinosa (SG) in the spinal cord act as a gating site that produces pre-synaptic inhibition on both types of afferent fibers. Activity in the large fibers increases pre-synaptic inhibition of the small fibers carrying nociceptive information, whereas activity in the small fibers facilitates the transmission of pain signals. Activation of the SG cells can excite the T cells to convey noxious stimuli to the higher nervous system centers. The T cells can also be influenced in an excitatory or inhibitory manner by the descending mechanisms. Levin and Hui-Chan (1993) showed that both acupuncture-like and conventional TENS excited similar afferent nerves, predominantly in the A-α,β range. According to the gate control theory, these large diameter fibers are thought to inhibit activities in the small nociceptive fibers (Melzack and Wall 1965). TENS at the intensities applied in humans activates large A-β afferent fibers, resulting in tactile sensations, therefore activates the substantial gelationosa in the spinal cord that produces pre-synaptic inhibition of the small A-δ and C fibers carrying the input of pain sensation.
1.3.4.3 Diffuse Noxious Inhibitory Control

In the sensory pathway, some dorsal horn neurons are strongly inhibited when a noxious stimulus is applied to any part of the body far away from their excitatory receptive fields. This phenomenon is termed "Diffuse Noxious Inhibitory Control" (DNIC) (LeBars et al. 1979a,b). The noxious stimulus could be mechanical, thermal, chemical or electrical (Villanueva and LeBars 1995). The stronger the stimulus, the more powerful the inhibitory effects (Villanueva and LeBars 1995). The inhibitory neurons are all convergent dorsal horn neurons receiving both A-δ and C afferent inputs (LeBars et al. 1981). Application of TENS to the rat has been demonstrated to produce a 60–100% inhibition in the C fibers innervating the dorsal horn convergent neurons (LeBars et al. 1979a, b). Recent studies confirmed that the spinoreticular tracts are involved in the pain modulation by DNIC and that the brainstem is an important link (Villanueva et al. 1986, Willer et al. 1990, Woolf 1989). Ascending excitatory signals may activate diffuse noxious inhibitory controls (DNIC), thereby inhibiting spinal and trigeminal convergent neurons and reduce pain (Garrison and Foreman 1994, Villanueva and LeBars 1995). Note that the longer-lasting post-stimulus inhibitory effects can persist for several minutes (LeBars et al. 1981).

1.3.4.4 Counterirritation

Counterirritation is a term used to describe the sensation that intense electrical, thermal, or mechanical stimulation is applied to reduce pain. It is believed that the intense sensory stimulation produced by counterirritation is modulated through a descending control system (Walsh 1997). The descending
control system involves different parts of central nervous system, such as the periaqueductal grey matter (PAG) which has more opioid receptors, the rostral ventral medulla (RVM), the nucleus raphe magnus and its adjacent reticular nuclei and the spinal dorsal horns. The projecting neurons are links between the PAG and various sub-regions of the RVM. Signals descending from the PAG and RVM project to the spinal dorsal horn to inhibit the nociceptive neurons there. Counterirritation through descending pain inhibitory pathway for pain control does appear to differ from the gate control theory (Basbaum and Field 1978, 1984, Walsh 1997). In fact, its inhibitory action at the spinal cord was thought to be exerted via direct post-synaptic rather than pre-synaptic inhibition (Basbaum and Field 1978, 1984). The so-called endogenous pain inhibitory system first proposed by Basbaum and Field (1984) will now be presented below.

1.3.4.5 Endogenous Pain Inhibitory System

Studies have demonstrated the presence of endogenous analgesia. For example, electrical stimulation of certain central nervous system sites has been found to produce profound analgesia. This stimulus-produced analgesia (SPA) has been presumed to be associated with behavioral consequences similar to those observed during morphine administration (Liebeskind and Paul 1976). Further studies in humans have demonstrated effective relief from clinical pain with SPA (Akil et al. 1978, Hosobuchi et al. 1977). This finding is in agreement with the discovery of endogenous opioids analgesia.

Up to now, endogenous morphine-like peptides have been identified and isolated in different locations within the central nervous system (Basbaum and
Field 1984, Hughes 1975, Liebeskind et al. 1976, Matsukura et al. 1978). They are released at both the brainstem and spinal levels (Walsh 1997). Biological opioid receptors, such as μ-, δ- and κ-receptors, have also been confirmed to be located in various central nervous system sites (Kane and Taub 1975).

To investigate the role of opioids in TENS analgesia, several studies measured the level of endogenous opioids in blood plasma and cerebrospinal fluid before and after the application of TENS (Johnson et al. 1992a, O’Brien et al. 1984, Salar et al. 1981). Further studies showed that TENS applied at different frequencies induced the release of different opioid peptides. Met-enkephalin-Arg-Phe was released by low frequency TENS, whereas dynorphin A was induced by high frequency TENS application (Han et al. 1991, Han and Wang 1992). Met-enkephalin was also observed during the burst type of TENS stimulation (Johnson et al. 1992a). These peptides were thought to bind to specific receptors to produce pain reduction. Findings from rat studies suggested that electroacupuncture analgesia produced by stimulation at 2 Hz was mediated by μ- and δ-receptors, that at 100 Hz by κ-receptor, and that at 2-15 Hz by the combined action of these three receptors in the spinal cord (Chen and Han 1992). Sluka and co-investigators (1999) reported that low-frequency TENS produced anti-hyperalgesia through μ-opioid receptors, and high-frequency TENS produced anti-hyperalgesia through δ-opioid receptors in the spinal cord in an arthritic rat model. However, not all analgesic effects in the central nervous system are opioid-mediated (Lewis 1980). Activation of different analgesia-producing systems involving complex environmental, attention and recognition factors are difficult to interpret.
Non-opioid mechanisms have also been shown to be involved, e.g. in electro-acupuncture induced analgesia. Briefly, electro-acupuncture had been shown to elevate the level of serotonin 1-tryptophan 5-hydroxy tryptamine, and 5-hydroxy tryptamine neural activity in the brain, which enhanced analgesic effect (Paul and Pastermack 1988, Xia et al. 1986). The release of catecholamines and acetylcholine has also been reported during acupuncture analgesia (Shiryo 1985).

The theories mentioned above provide some basic insight behind the analgesia mechanisms underlying pain management. With regard to the analgesic efficacy of a given modality, it should best be determined, where possible, by its effects on both experimental and clinical pain.

1.3.5 TENS and Experimental Pain: Thermal Pain

Thermal induced pain is the most commonly used type of experimental pain. Pertovaara (1980) used a “thermostimulator” to apply thermal stimuli either proximal or distal to the TENS electrodes attached to the extensor surface of the forearm. The thermal pain threshold was found to be significantly increased in 5 out of 6 subjects (p<0.02), when 45 mA of TENS was applied for 20 min at a site distal to the thermal stimuli. Interestingly, there was no significant increase in pain threshold when 45 mA of TENS was applied at a proximal site, or when less intense (35 mA) of TENS was applied at a distal site. The author suggested that peripheral electronic blockade or fatigue of pain mediating fibers was responsible for elevating the pain threshold.

One encouraging result was shown in a later study (Marchard et al. 1991a). In this study, thermal stimulus was applied to the subjects’ cheeks using
a contact thermode. A branch of the trigeminal nerve was the target of the electrical stimulation with 125µs pulses at 100Hz for 25 minutes. Both during and after TENS, the thermal pain threshold was significantly increased (p=0.002).

Eriksson et al. (1985) designed a study to investigate whether TENS analgesia was due to central changes in humans by measuring the thermal pain threshold. Both heat and cold pain thresholds on the thenar region of the hand were measured respectively, when both conventional (80 Hz) and acupuncture-like (2 Hz) TENS were applied over the ipsilateral and contralateral median nerve for 15 minutes. Both heat and cold pain thresholds were increased after both conventional and acupuncture-like TENS. In addition, similar effects were seen for both contralateral and ipsilateral TENS applications, therefore providing evidence that TENS-induced analgesia may be mediated by a relatively diffuse central as opposed to very localized peripheral mechanism.

Contrary to the findings reported above, 15 min of conventional TENS (100Hz, 200µs) did not change the heat pain threshold in 6 healthy subjects and 34 patients with acute teeth pain (Ekblom and Hansson 1987). Among possible explanations, an altered response in patients with acute teeth pain and the small sample size of the healthy subjects (n=6) could explain the negative results.

The studies investigating TENS analgesia by measuring thermal pain threshold suggested that the site, intensity and duration of TENS stimulation, sample size and population could be important variables for methodological considerations in the present study.

1.3.6 TENS and Clinical Acute Post-operative Pain
Post-operative pain is acute, localized and usually lasts at least 72 hours (Hall-Lord et al. 1999). Routine post-operative pain management involves administrating opioids that may have some unwanted side-effects, such as nausea, sedation and respiratory depression. Therefore, a simple and non-invasive approach with less side-effects should be considered. In most clinics, TENS is offered as an adjunct to routine pain medication. The relief of post-operative pain was thought to be one of the most successful applications of TENS, using different outcome measures to assess the post-operative pain intensity. However, there have also been some negative reports of TENS on post-operative pain.

Hymes and colleagues (1974) first reported the use of TENS in the management of acute post-operative pain. The surgical pain threshold was significantly elevated after TENS application to a proximal nerve. Other studies on the use of TENS in post-operative pain management followed in the early 1990s (e.g., Daniel and Clifford 1990). In these studies, stimulation started immediately when the patients returned to the recovery room and continued for up to 72 hours after surgery. TENS at sensory threshold sensation, delivered with 100-160μs pulses at 70-100Hz for a period ranging from 20 to 180 min, was shown to increase the pain threshold up to 50% immediately when compared with placebo stimulation.

In some studies, subjective post-operative pain intensity was the outcome measure. Most studies reported significantly lower pain scores (Bayindir et al. 1991, Hargreaves and Lander 1989, Ho et al. 1987, Sim 1991, Warfield et al. 1985). Different modes of TENS including conventional, acupuncture-like and burst types showed immediate analgesia (79% of burst TENS patients were
completely free of pain at rest) when compared with placebo stimulation (80% of placebo patients had severe pain at rest).

The effect of TENS on the amount of analgesic consumption has been also investigated. Some studies reported no significant difference between TENS and control groups in the amount of opiate requirement after surgery (Forster et al. 1994, Hargreaves and Lander 1989, McCallum et al. 1988, Sim 1991). But others showed that the patients receiving TENS were administrated fewer doses of analgesics than the control patients (Issenman et al. 1985, Schomburg and Carter-Baker 1983, Wang et al. 1997). Laitinen & Nuutinen (1991) found no significant difference in the amount of total opiate required in the 60 patients receiving abdominal surgery among four groups: control, indomethacin, 2 Hz TENS plus indomethacin, 100 Hz TENS plus indomethacin. In this study, TENS was continuously applied for 16 hours after operation. In contrast, Wang et al. (1997) reported that the total morphine requirement after abdominal surgery was decreased by 20%, 31% and 54% with sham-, low- and high-intensity TENS respectively. The total amount of morphine required in the high-intensity TENS group was decreased by 65%, 55% and 46% when compared with the PCA-only, sham- and low-intensity TENS while treatment stimulation was continuously administered for 2 days. Comparing the treatment protocols used in these two studies, the duration of TENS application was an important variable for the effect of TENS in reducing post-operative pain.

In summary, the analgesic effects produced by different modes, duration and intensity of TENS stimulation have been investigated. Most studies reported that TENS produced immediate analgesia. However, some negative results have
been noted. In the studies hitherto, TENS was usually applied to the patients 1 to 3 days after surgery, and was reported to be effective only for mild and moderate post-operative pain, but not for severe pain. It should be noted that no studies to-date have investigated the effect of repeated TENS application before, during and after total knee replacement.

2. **Rationale and Objectives of the Studies**

There have been conflicting reports on the inhibitory effects of TENS on both the acute heat pain and vibration threshold. For example, Marchand et al. (1991a) found that heat pain threshold increased significantly (from 46.7 to 47.9°C) \((p=0.002)\) during and 15 min after 30 min of conventional TENS (100Hz, 125μs), as compared with placebo stimulation in 7 healthy subjects (5 men and 2 women). On the other hand, Ekbloem and Hansson (1987) found that 15 min of conventional TENS (100Hz, 200μs) did not change the heat pain threshold in 6 normal subjects and in 34 patients with acute teeth pain. Such a controversy could have arisen from different experimental protocols such as the duration, location and parameters of TENS being used, different sample sizes and populations in the different studies. Alternately, TENS could exert different effects on pain (mediated by small diameter fibers) and vibration sensation (mediated by large diameter fibers). The first objective of our study therefore set out to delineate the influence and specificity of TENS on pain sensation as measured by heat pain threshold, when compared with the tactile sensation as measured by vibration threshold in the same subjects.
Research studies in humans from our research group have shown that repeated TENS application for 60 min daily over a 2-week period produced cumulative antinociceptive effects on the experimental electrical pain elicited in young normal subjects (Liu and Hui-Chan 1994). Furthermore, a 48.8% decrease of chronic low back pain was found when the same TENS protocol was applied to the patients with chronic low back pain, in contrast to those receiving placebo stimulation (Cheing and Hui-Chan 1996). One of our recent studies further showed a reduction of chronic knee pain intensity to 68.4% as measured by VAS, when compared with the baseline value after two weeks of TENS (Cheing and Hui-Chan 1998). It was further decreased to 54.1% after 4 weeks. These studies demonstrated similar cumulative antinociceptive effects of repeated TENS applications on various pain conditions. The cumulative analgesic effect of repeated TENS application could be explained by an increase the release of endogenous opioids (Luo et al. 1996), or plastic changes in the nervous system (Romita et al. 1997). The second objective of the present thesis was to determine if TENS application for 60 min twice daily over a 3-day period, for a total of 6 treatment sessions, produced a cumulative pain relief in older normal subjects, when compared with placebo stimulation.

Furthermore, we wonder if the cumulative inhibitory effect of repeated TENS applied to the acupoints 3 days before, 1 day during and 6 days after knee surgery could reduce the post-operative pain. As reviewed before, there is a growing body of evidence that post-operative pain may produce harmful physiological and psychological effects (Dransner 1992), partly due to central sensitization that may induce long lasting central neuronal alterations. Melzack et
al. (1987) showed that elderly patients often have more continuous pain following surgery than younger people do. Further evidence demonstrated that the older patients who had undergone knee replacement surgery were more likely to report intense pain when compared with other orthopedic and abdominal surgeries (e.g. Hall-Lord et al. 1999). If the post-operative pain on the first two days after surgery was not well controlled, severe, persistent pain may delay the recovery process after surgical intervention (Melzack 1990). In fact, un-treated post-operative pain may be a significant confounding factor for increasing the length of hospital stay and subsequent higher costs of medical care (Wisner 1990, Mangano et al. 1991, Christensen and Kehlet 1993, Duggleby and Lander 1994). Seers (1987) found that over 86% of reported pain was not controlled for a considerable time. The inhibitory effect of TENS on post-operative pain has been studied in cardiac (Bayindir et al. 1991, Forster et al., 1994), abdominal (Hargreaves and Lander 1989, Schomberg and Carter-Baker 1983, Sim 1991) and spinal surgeries (Issenman et al. 1985). Some studies reported significantly lower pain scores (Bayindir et al. 1991, Hargreaves and Lander 1989), or fewer doses of analgesics taken than control patients (Wang et al. 1997). However, some negative results were also found (e.g., Forster et al. 1994). In the studies hitherto, TENS was usually applied during the first 2 or 3 days after surgery. The pain intensity was measured only by the finish of the treatment period. However, post-operative pain may be prolonged for several days or even weeks due e.g. to the sensitization of the central nervous system after operation (Section1.2.3.3). Therefore, if TENS was just applied for 2 or 3 days, the period of treatment may be not long enough for the more lasting post-operative pain control. It should be noted that
no study to-date has investigated the possible pre-emptive and cumulative inhibitory effect of TENS, when it was repeatedly applied before, during and after total knee replacement. As reviewed under the section entitled “Pre-emptive analgesia for post-operative pain”, continuous administration of drugs before, during and after surgery in both experimental animal studies (Dickenson 1987, Woolf and Wall 1986a,b) and most of the clinical studies (Clifford et al. 1993, Lascelles et al. 1997) has shown positive results. A question therefore arises: Could pre-emptive and continued transcutaneous electrical nerve stimulation (TENS) applied to the patients before, during and after surgery improve post-operative pain management in a manner similar to the use of pre-emptive analgesia? Therefore, the objectives of our studies are as follows:

Objective 1: To determine if the inhibitory effect of TENS applied to the acupuncture point, was specific to pain as measured by the heat pain threshold, when compared with tactile sensibility as measured by the vibration threshold.

Objective 2: To examine whether repeated TENS applications to the acupoints, twice a day over a 3-day period, produced cumulative analgesic effect on the acute experimental pain as measured by heat pain threshold, when compared with placebo stimulation in older normal subjects.

Objective 3: To determine if repeated TENS applications to the acupoints before, during and after total knee replacement improved the post-operative pain management, in a manner similar to the use of pre-emptive and continuous opioid analgesia. Specifically, we set out
to delineate whether pre-emptive and repeated TENS applications reduced the post-operative pain intensity, improved the range of knee motion, decreased the analgesic consumption, and shortened the length of hospital stay when compared with placebo stimulation.

Chapter 2 presents the instrumentation used in this study and the results of the pilot studies. Chapter 3 explores the effect of TENS on heat pain threshold and vibration threshold when compared with placebo stimulation. Chapter 4 compares the effects between repeated TENS and placebo stimulation for 6 sessions on heat pain threshold in older normal subjects. Chapter 5 delineates the effects on post-operative pain intensity, range of knee motion, analgesic consumption and length of hospital stay as compared with placebo stimulation, when repeated TENS was applied before, during and after total knee replacement. Chapter 6 summarizes and concludes our findings.
Fig. 1.1  The different parts of the prosthesis used in total knee replacement
CHAPTER 2

METHODOLOGY AND PILOT STUDIES
2.1 Summary

Visual analogue scale (VAS), range of knee motion (ROM) and analgesic consumption have been used to examine the effectiveness of total knee replacement surgery or management of post-operative pain in clinical studies. These measurements provided certain objective evidence that total knee replacement surgery has become an important and successful approach to reduce the persistent pain, and improve the functional activity in the patients with osteoarthritis and rheumatoarthritis. Its cost benefit was reflected by a shortened length of hospital stay (Heck et al. 1998). These outcome measurements were therefore adopted in the present thesis.

Now, the antinociceptive effectiveness of TENS applied twice daily for e.g. 3 days, had not yet been delineated. Our objective was to determine the effectiveness of such a stimulation protocol, by first using thermal pain threshold, before applying such a protocol to the patients receiving total knee replacement surgery. Therefore, we set out to systematically define the sensitivity simultaneously with repeatability of heat pain threshold, to ensure that the heat pain measurements employed in our studies produced repeatable and sensitive data, so that the effectiveness of the presented TENS protocol could be determined.

The repeatability study was conducted in 8 young normal subjects on the hands, knees, feet and left back, using the Method of Limits. These subjects attended 3 separate testing sessions to have their heat pain threshold measured, with the same measurement repeated twice at one and two weeks following the first one. In the study on the sensitivity of heat pain threshold, 10 young normal
subjects performed subjective psychophysical estimates involving warm and hot cutaneous stimuli. Ten levels of temperature ranging from 32 to 50°C were applied for 10 seconds to the left knee in a random order. Subjects gave continuous ratings of perceived temperature and pain intensity using the visual analogue scale (VAS). Intra-class correlation coefficient (ICC) and linear regression were used for data analysis in repeatability and sensitivity respectively. Our results showed that the ICC values of heat pain thresholds of various tested sites ranged from 0.87 to 0.95. A linear correlation was found between subjective thermal sensation and heat stimulus intensity, with a high value of r=0.93 and a slope of 5.04. We concluded that the heat pain threshold measurement, using the Medoc TSA-2001, was not only highly repeatable, but also highly sensitive. Therefore, it could be used to determine the extent of cumulative TENS analgesic effect before and after total knee replacement surgery.

Vibration threshold measurement has been used to assess the sensory functions of large diameter afferent fibers (Gerr and Letz 1988). To ensure that the vibration threshold measurement produced repeatable data to define possible TENS analgesia effect on vibration threshold, a repeatability study was conducted on 10 young normal subjects in both hands across 3 sessions separated by 3 days, using the Medoc VSA-3000 device with both the up- and down-methods. Intra-class correlation coefficient (ICC) from the SPSS statistics package (version 8) was used to analyze the vibration threshold values obtained from the 3 separate sessions. Our results showed that ICC values of vibration threshold with the up- and down-methods on both of their hands ranged from 0.95 to 0.96. We concluded that the vibration threshold measurement, using the Medoc VSA-3000,
was highly repeatable. Therefore, it could be used to define possible TENS analgesic effect on vibration threshold.
2.2 Introduction

The patients receiving total knee replacement would expect reduced pain and improved knee function. Outcome measures such as visual analogue scale, analgesic consumption and range of knee motion for total knee replacement assess pain intensity and knee function. Their results have been shown to be predictable and reproducible as presented below.

Hungerford and Krackow (1985) used a visual analogue scale to measure pain intensity in patients receiving total knee arthroplasty. They reported decreased pain intensity after comparing the pre-operative and post-operative measures in 71 patients with osteoarthritis (OA) and 36 patients with rheumatoid arthritis (RA). Murray et al. (1983) showed that 16 patients with OA and 5 patients with RA had decreased knee pain, when measured up to 24 months post-operatively. Kelley (1991) investigated 29 patients with either OA and RA receiving joint replacement and found that they experienced a significant decrease in pain ($p<0.05$), at 6 weeks and 6 months after total hip or knee joint arthroplasty. Heck et al. (1998) reported a decrease in the knee pain scores by 50% ($p<0.0001$) when compared with the baseline measures.

In recent years, new methods and routes of administration, including patient-controlled analgesia (PCA) and epidural infusion, are increasingly being used to manage post-operative pain. Since these procedures have the advantage of providing sustained analgesia due to a lower peak plasma concentration of the drug, their usage minimized the side-effects (Tempest 1992). PCA is not only a drug delivery route; PCA morphine consumption has also been used as one of the objective pain measurements in recent clinical pain studies. The dose of opioids
required at different times has been taken as an indicator of the severity of the post-operative pain. Wang and co-investigators (1997) repeatedly applied transcutaneous electrical stimulation to the patients for 30 min every 2 hours on the first day after abdominal surgery. The intensity of stimulation was set in the standard dense-and-disperse mode, with the frequency alternating at 2 Hz and 100 Hz every 3s. The post-operative morphine consumption measured between 8-16 hours and the total amount given in 24 hours were respectively 15±15mg and 52±46mg in the placebo group, which were significantly more than 5±4mg and 21±11mg in the stimulation group (p<0.05).

Continuous epidural analgesia is rapidly becoming a primary method of post-operative pain management (Dubois 1991). This technique is believed to block sensory nerve pathways to prevent and reduce the pain (Sofear 1998). Continuous administration avoids the peaks and valleys of the drug in cerebrospinal fluid levels, providing more efficient analgesia while reducing the severity of side effects (Downing et al. 1988, Planner et al. 1988). The rate of epidural infusion has been used as one of the indicators to assess pain relief. One study showed that the drug in the serum levels at 24 hours was low, with 90% of 20 subjects studied being less than 6.5 ng/ml (Walmsley et al. 1989).

Range of motion (ROM) has been an important measure of outcome and is an important part of the knee scoring systems. Most studies reported that the final range of knee flexion averaged between 100° and 110° (Akagi et al. 1997, Duffy et al. 1998, Heck et al. 1998, Kumar et al. 1996), when pre-operative flexion range was less than 90° (Anouchi et al. 1996). Anouchi et al. (1996) also
concluded that those with poor pre-operative range of knee flexion would gain more motion. Those in the mid-range stayed in the mid-range.

From the above review, it could be seen that the following outcome measures: pain intensity assessed by the visual analogue scale (VAS), knee function assessed by the range of motion (ROM), and the analgesic consumption after operation of the knee surgery or the management of post-operative pain have been used in clinical studies to examine the treatment effectiveness. They provided certain objective evidences to prove that total knee replacement surgery has become an important and successful approach, to reduce the persistent pain and improve the functional activity in the patients with knee osteoarthritis. Furthermore, the cost benefit was reflected by a shortened length of hospital stay (e.g. Heck et al. 1998). These measurements were therefore adopted in the present thesis.

Now, the antinociceptive effectiveness of TENS applied twice daily for e.g. 3 days had not yet been delineated. Our objective was to determine the effectiveness of such a stimulation protocol by first using thermal pain threshold, before applying such a stimulation protocol to patients receiving total knee replacement surgery. Since thermal pain threshold is a controlled, repeatable, objective assessment with minimal temporal effects (Gracely 1989), it has often been used to assess subjective pain intensity in research studies on pain mechanisms and management. The advantage of thermal testing is that it tests primary small-diameter afferent fibers, specifically the A-δ and C fibers that mediate the sensation of cold and heat pain because of modality specificity (Morin and Bushnell 1998). Previous investigators had demonstrated a high
repeatability of heat pain threshold measurement (e.g. Yarnitsky et al. 1995). However, few studies had been performed to investigate the sensitivity of thermal threshold measurement. We therefore set out to systematically define the sensitivity simultaneously with repeatability of heat pain threshold, to ensure that the heat pain measurements employed in our studies produced repeatable and sensitive data in order to determine the effectiveness proposed TENS protocol before studying its antinociceptive effectiveness in patients receiving total knee replacement surgery.

Vibration threshold measurement has been used to assess the sensory functions of large diameter afferent fibers (Gerr and Letz 1988). To ensure that the vibration threshold measurement produced repeatable data to define possible TENS analgesic effect on vibration threshold, the repeatability of this measurement was also conducted as part of the pilot study.

2.3 Methods

2.3.1 Recording of Heat Pain Threshold

Heat pain threshold was measured using the Medoc TSA-2001 device (Fig. 2.1). It was determined using the Method of Limits by applying increasingly warm and hot stimuli to subjects' hands, knees and feet on both sides, and the left side of the back between the spinous process of lumbar 3rd and 4th vertebrae. Temperature stimuli were produced using a feedback-controlled thermode, size 46 x30 mm², attached to the tested area (Fig. 2.2). The best contact between the probe and the same tested body surface was achieved as much as possible, in
order to keep constant contact pressure on the same stimulus location. The temperature applied ranged from 32 to 50°C. The rate of temperature rise was held at a constant 1.5°C/sec, whereas the drop rate was fixed at 10°C/sec, in order to have enough time for cooling down. Subjects sat face away from the screen of the computer, and received no visual or auditory cues denoting the stimulus onset.

The procedures for heat pain threshold measurement were first explained to the subjects; a demonstration was then given. Subjects received training for 3 times before the experiment started. The same experimenter followed a standardized protocol to record all the threshold data. During testing, a thermal probe was placed firmly on the target area. The subjects were asked to press the switch when they first perceived the pain. To determine the heat pain threshold, subjects received 4 successive stimuli starting with an adaptation temperature of 32°C, at a temperature rise rate of 1.5°C/s. A minimum interval of 30s elapsed between successive stimuli, in order to avoid possible sensitization or suppression of cutaneous receptors (Yarnitsky and Ochoa 1990). The mean temperature value in °C of 4 successive tests was recorded as the heat pain threshold. The repeatability and sensitivity of heat pain threshold measurements will be presented and discussed more in details in Section 2.4.

2.3.2 Recording of Subjective Sensation of Knee Pain

The test-retest reliability of VAS has been extensively studied, and reported to be high when repeatedly used in the same individuals (Bowsher 1994, Carlsson 1983, Elton et al. 1979, Jensen and McFarland 1993, Revillet al. 1976, Waterfield and Sim 1996). As the VAS directly measures the intensity of pain, it
has high content validity (Jensen and McFarland 1993, Cole 1994). The VAS and the numeric rating scale have a high correlation, with the correlation coefficient ranging from $r=0.77$ to 0.91 (Downie et al. 1978). The correlation between the VAS and the finger dynamometer measuring mechanical pain was $r=0.87$ ($p=0.001$) (Wilkie et al. 1990). VAS was sensitive enough to detect a change of less than 20% in the perception of experimental thermal heat pain and clinical pain during TENS treatment (Marchand et al. 1991a,b). Price et al. (1994) reported that VAS and stimulus temperature had a high correlation, $r=0.98$.

The intensity of chronic knee pain or post-operative knee pain was measured using a visual analogue scale consisting of a 10cm wooden ruler and a metal cursor (Fig.2.3). At the left end of this ruler, "no pain" was indicated, and at the other extreme, "pain as bad as it could be". The subjects were asked to rate their pain by moving the metal cursor along the VAS horizontal line to an appropriate point that represented the level of their pain intensities. The distance of the pointer from the left end marked with "no pain" was recorded for analysis. Patients were instructed to return the VAS cursor to the left end of the scale after each estimate, to prevent possible bias due to comparison with sequential stimuli. Subject was asked to move the metal cursor 3 times. The average of these 3 values was estimated and recorded as the VAS score.

2.3.3 Recording of Range of Knee Motion

The reliability of goniometric measurements and visual estimates of knee range of motion has been reported and demonstrated to have a high correlation, with the correlation coefficient ranging from $r=0.82$ to 0.94 (Watkins et al. 1991).
A transparent metal universal goniometer (Medical Co.) was used to measure the knee range (Fig. 2.4). For all the measurements, the axis of the goniometer was placed on the lateral epicondyle of the femur. The stationary arm was placed parallel to the midline of the femur on a line from the lateral epicondyle to the greater trochanter. The movable arm was placed parallel to the lateral midline of the fibula towards the lateral malleolus (Gilliam and Barstow 1997). The range of knee flexion was taken with the subject actively moving the knee to the maximally flexed position, and then extending his/her knee as much as he/she could in prone lying. The range between these two positions was recorded with the goniometer. The range of knee flexion was measured 3 times. The average of these data was calculated and recorded as the value of range of knee flexion.

2.3.4 Recording of Post-operative Analgesic Consumption

A PCA device (Grasby 3300 PCA pump, Grasby Medical LTD) was connected to the patient’s intravenous catheter to administer the general anesthetic (Fig.2.5). The PCA device was programmed to deliver the morphine at 1 mg bolus doses on demand, with a minimum lockout interval of 5 min. As reviewed in Chapter 1, when the lockout interval was 5 or 6 minutes, a PCA morphine dose of 1 mg produced more superior analgesia than 0.5 mg, but equal analgesia with fewer side-effects when compared with 2 mg (Bennett 1986, Owen et al. 1989).

When the patients were administered epidural anesthesia (Syringe Pump, Model STC-525, Tumeuo Co.), the catheter was kept in the disc space between L4 and L5. Marcain (0.0625%) and fentanyl (3.3 μg/ml) were delivered to the patients at a rate ranging from 5 to 15 ml/hr (Fig.2.6).
The PCA morphine consumption and epidural fentanyl infusion rate at 6, 12 and 24 hours were recorded for analysis.

2.3.5 Recording of “Length of Hospital Stay”

Our initial plan was to record the number of days when patients stayed in the hospital. In practice, there were many factors affecting the length of hospital stay in Hong Kong. For example, the patients must wait to be transferred to another rehabilitation center when beds were ready for them, even though they had already met the criteria for discharge. There were altogether 5 such criteria. The patient was able to (1) walk unaided on the ground for 15 min, (2) climb 2 or 3 flight of stairs, (3) flex their knees up to 90° with no flexion contracture, (4) have their muscle strength graded 4, and (5) be independent in self-care activities. Therefore, the days when patients reached the criteria of discharge as judged by the physician on duty, even when they were not discharged, were recorded and regarded as the length of hospital stay.

2.4 Pilot Studies

2.4.1 Repeatability and Sensitivity of Heat Pain Threshold Measurements

2.4.1.1 Introduction

Heat pain threshold is often used to quantify subjective pain intensity in research studies on pain mechanisms and management. This measurement provides a valuable tool to examine possible modulation of experimental pain
perception by clinical pain (Gracely 1989). It is necessary that this measurement provide results that are repeatable and valid enough to determine the effectiveness of the proposed TENS protocol before extending it to the patients receiving total knee replacement surgery. Previous investigators had demonstrated a high repeatability of heat pain threshold measurement (e.g. Yarnitsky et al. 1995). Few studies have investigated the sensitivity of heat pain threshold measurement. To what extent could heat pain threshold ratings represent different levels of a heat stimulus? We therefore set out to systematically define the sensitivity simultaneously with repeatability of heat pain threshold, using the Medoc TSA-2001 device.

2.4.1.2 Methods

The study on heat pain threshold repeatability was performed on 8 young normal subjects (age: 26.8±6.7 yr., female: n=3, male: n=5, weight: 59.9±9.0 kg, height: 164.4±7.9 cm.). In the study on sensitivity, 10 young normal subjects, (age: 27.0±7.2 yr., female: n=4, male: n=6, weight: 60.1±9.4 kg, height: 165.1±8.2 cm) were examined. All the subjects had no pain syndrome, neurological or neuromuscular disorders. They were given a detailed explanation of the experimental procedures verbally and through an “Informed Consent Form” which they signed.

In the study on repeatability, 8 subjects attended 3 separate testing sessions to have their heat pain thresholds measured. The same measurement was repeated twice at one and two weeks following the first one. During each session, non-painful and painful training employing the Method of limits was
administered at the thenar eminence of each subject 3 times before testing. Heat pain threshold was determined using the Medoc TSA-2001 device, by applying increasingly warm and hot stimuli to subjects’ hands, knees and feet on both side, and to the left side of their back between the spinous process of the lumbar 3rd and 4th vertebrae. At each site, 4 measurements were obtained for each heat pain threshold and the mean value was computed. The tests were repeated 1 and 2 weeks following the first one in each subject.

In the study on sensitivity, 10 young normal subjects performed subjective psychophysical estimates involving warm and hot cutaneous stimuli. Ten levels of heat stimulus were applied varying from 32°C to 50°C for 10 seconds, at 2°C increments to the left knee in a random order, with appropriated time intervals in between for cooling down. Subjects were asked to estimate the intensity of each stimulus by moving a cursor along a 100 mm horizontal line on a computer screen. They were instructed to return the VAS cursor to the left extreme of the scale after each estimate, to prevent possible biases due to comparison of sequential stimuli.

Intra-class correlation coefficient (ICC) and linear regression were used respectively for analysis of the data on repeatability and sensitivity.

2.4.1.3 Results

Table 2.1 showed the results of intra-class correlation coefficient (ICC) of the heat pain threshold measurements recorded in the hands, knees and feet on both sides and the left side of back at L3 and L4. Note that these ICC values ranged from 0.87 to 0.95, thus showing no significant difference in the data.
obtained from the different body parts over 3 different occasions. In other words, the heat pain threshold measurement, using the Medoc TSA-2001, was repeatable in the 8 normal young subjects tested.

A linear correlation was found between subjective thermal sensation and heat pain stimulus intensity, with a high value of $r=0.93$ and a slope of 5.04 in the 10 young normal subjects (Fig.2.7).

2.4.1.4 Discussion

The high repeatability of our heat pain threshold measurements concurred with that reported by Yarnitsky et al. (1995). Using the same paradigm as ours, these investigators found a high repeatability of the heat pain threshold in the thenar eminence ($r=5.85$) and foot ($r=4.47$) of 106 normal subjects (female: $n=65$, male: $n=41$), aged from 20 to 79 and separated into 3 different age groups: 20-39 yr. ($n=46$), 40-59 yr. ($n=47$), 60-79 yr. ($n=13$). Compared with the finding by Yarnitsky et al. (1995) in 46 young normal subjects aged from 20 to 39, our study showed a higher heat pain threshold in the hand (46.5 vs. their 45.1°C) and foot (48.6 vs. their 45.1°C). What could have caused the difference in the findings between the two studies? Fillingim (1998) demonstrated that the heat pain threshold in male was significantly higher than female with both slow and fast rate of temperature rise ($p<0.05$). The higher percentage of males, 62.2% (3/8), in our study as opposed to the 34.7% (17/46) in the study by Yarnitsky et al. (1995), may thus be one factor for the relatively higher heat pain threshold found by us.

Our study showed that the heat pain threshold of the low back (45.9°C) was lower than other areas such as the hand (46.5°C), knee (48.2°C) and foot
(48.6°C). Because a large portion of the somato-sensory cortex is devoted to the hand when compared with the very small part to the low back, pain sensation should be more readily perceived by the subjects in their hands (and even feet) when compared with the low back. However, our study showed that the heat pain threshold of the hand and foot was higher than the low back. The reason for this is not clear, and needs to be addressed in further studies.

Our finding also showed that there was a linear correlation between subjective thermal sensation and heat stimulus intensity at a temperature rise rate of 1.5°C/sec, with a high value of $r=0.93$ and a slope of 5.04. This result was in agreement with that of Morin and Bushnell (1998), who found a linear correlation between these two factors with a temperature rise rate of 5°C/sec. These investigators further demonstrated that the stimulus-response functions were steeper for noxious (47 to 48°C) than for innocuous temperature (41 to 43°C) in the heat range. The slope of the stimulus-response was 69.7 for noxious temperature, and 10.5 for innocuous temperature. The rate of temperature rise appeared to be one variable between the two studies. There were some findings showing that different rate of temperature rise could be coded by different afferent pathways. For example, some studies indicated that the information about heat pain threshold was transmitted by C fibers, when the rate of temperature rise was less than 2.0°C/s (Torebjörk et al. 1984, Yarnitsky et al. 1991, Yarnitsky and Ochoa 1990). But, according to DePace and Newton (1996), the heat pain caused by intense thermal stimulation could activate A-δ mechano-thermal receptors. Details besides, under our present experimental paradigm, heat pain information
processing by the nervous system appeared to be a linear function of the stimulus intensity in young normal subjects.

From the pilot study reported above, we concluded that the experimental set-up for measuring the heat pain threshold in this study was highly repeatable and sensitive. Therefore, it could be used to assess the extent of cumulative TENS analgesic effect before and after total knee replacement surgery.

2.4.2 Repeatability of Vibration Threshold Measurement

2.4.2.1 Introduction

Vibration threshold measurement has been used as a tool to assess the sensory functions of large diameter afferent fibers (Gerr and Letz 1988). Previous studies showed the high repeatability of vibration threshold measurement, using the Vibration II, in the normal subjects and patients who had diabetics and were at risk for peripheral neuropathy (Gerr and Letz 1988, 1990). However, the repeatability of the vibration threshold assessment using the Medoc VSA-3000 device, a new instrument, has not been examined. We therefore set out to delineate the repeatability of vibration threshold measurement, using the Medoc VSA-3000 device, to define the existence of any TENS analgesic effect on vibration threshold before and after TENS.

2.4.2.2 Methods

The study on vibration threshold repeatability was performed on 10 normal young subjects (age: 26.6±5.9 yr., weight: 58.0±9.6 kg, height: 163.6±7.5
cm). All the subjects had no pain syndrome, neurological or neuromuscular disorders. They were given a detailed explanation of the experimental procedures verbally and through an "Informed Consent Form" which they signed.

A Medoc VSA-3000 device (Fig. 2.8) was used to measure the vibration threshold in both hands across 3 sessions separated by 3 days with both up- and down-methods. In the up-method, the subjects were asked to press the switch when they first perceived the vibratory sensation, as the vibratory stimuli gradually increased. In contrast, the subjects were asked to press the switch when they did not feel any vibratory sensation as the vibration stimuli gradually decreased in the down-method. The vibration frequency was fixed at 100 Hz, with amplitude ranging from 0.1 to 25.0 mm at 0.1 mm increments.

A training session for the vibration threshold measurement was administered to the thenar eminence of both hands three times before testing. In order to keep the same tested area in each session, a circle was drawn with permanent ink on the thenar eminence where the vibrator was to be applied. Four stimuli were given to the subjects each session in an ascending and descending order. The mean amplitude threshold value of 4 trials (mm) was computed for the vibration threshold. The vibration threshold was repeatedly measured in each subject across 3 sessions separated by 3 days.

Intra-class correlation coefficients (ICC) from the SPSS statistics package (version 8.0) were used to analyze the vibration threshold values obtained from the three separate sessions.

2.4.2.3 Results
Table 2.2 that showed the ICC values of the vibration threshold recorded in both hands in 10 young normal subjects ranged from 0.95 to 0.96, using the up- and down-methods. In other words, this assessment had been demonstrated to give repeatable measurements of the vibration thresholds, using the Medoc VSA-3000, with both the up- and down-methods in 10 young, normal subjects.

2.4.2.4 Discussion

Gerr and his investigators (1988, 1990) examined the repeatability of vibration threshold measurements, using the Vibration II (Sensortek, Inc.Clifton, N) with the Method of Limit in 22 normal subjects (12 males and 10 females), and in 22 patients (11 males and 11 females) who had diabetics for 14.5 years (1-40 yr.), and were at risk for peripheral neuropathy. The vibration frequency of Vibration II device was set at 120 Hz. Their findings showed that the correlation between the vibration threshold measured on two testing sessions was $r=0.81$ in the normal subjects, and $r=0.81$ in the patients. In our study, we found the intra-class correlation coefficient values of the vibration threshold recorded in both hands of 10 young normal subjects ranged from 0.95 to 0.96, using the Medoc VSA-3000, with the Method of Limits in both ascending and descending orders. Comparing to the findings of Gerr et al. (1990), the intra-class correlation coefficient values in our study were relatively higher, ranging from 0.95 to 0.96. This could be due to the different instruments or the different vibration frequency being used for measuring the vibration threshold in the two studies: 100 Hz in our study versus 120 Hz in the study by Gerr et al. (1990). The reason why the vibration frequency was chosen to be 100 Hz in our study was that vibration at
this frequency is known to activate the Pacinian corpuscle (PC) receptors which are most sensitive to high frequency vibration (Sherrick et al. 1990, Vallbo and Johansson 1984). The higher repeatability of our data could also be due to the fact that we had ensured that the same site was stimulated across the 3 sessions, by marking the stimulation site in our study with permanent ink. We had also made sure that the contact between the vibrator and the body area was firm, because it was known to increase the accuracy of the vibration threshold measurement. In conclusion, vibration threshold measurement using the Medoc VSA-3000 was highly repeatable. Therefore, it could be used to define the existence of any TENS analgesic effect on vibration threshold which we did in the study presented in next Chapter.  

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1 *Note: Part of this chapter was presented in an international conference and published as an abstract*

Fig. 2.1  Heat pain threshold was measured with the Medoc TSA-2001 device. A temperature control unit was used to initiate each heating cycle. The thermode could sense the temperature change and send the feedback to the control unit.

Fig. 2.2  Thermal stimuli were produced using a feedback controlled Peltier thermode, size 46x30mm², attached to the tested areas.
Fig. 2.3  Visual Analogue Scale (VAS). The subject's score was calculated by measuring the distance (mm) between the mark he/she made and the left end of the scale. Subjects were instructed to return the VAS cursor to the left end of the scale after each estimate, to prevent possible bias due to comparison with sequential stimuli.

Fig. 2.4  Recording of range of knee motion using the metal goniometer (Medical Co.)
Fig. 2.5 The patient-controlled analgesia (PCA) device was connected to the patient’s IV catheter. Patients can press the switch by themselves to have the opioid when they perceived severe pain.

Fig. 2.6 The epidural anesthesia device was connected to the lumbar space between L4 and L5. The rate of infusion was shown as marked in the device.
Fig. 2.7 Relationship between subjective sensation and heat stimulus intensity, denoted by a linear regression line drawn through the pooled data obtained from 10 subjects. X-axis, the different levels of heat stimulus intensity in °C, and y-axis, the ratings of subjective perception expressed as percentages of their maximum value for each subject. Each data point represents the mean of 10 trials. The correlation coefficient of the linear regression line ($r$) had a high value of $r=0.93$ with a slope of 5.04.
Fig. 2.8  The Medoc VSA-3000, a computerized device for the quantitative assessment of vibration threshold.
Table 2.1 Repeatability of heat pain threshold measurements in 8 young normal subjects across 3 sessions with one week apart

<table>
<thead>
<tr>
<th>Site</th>
<th>ICC $^a$</th>
<th>Heat Pain Threshold Measurements ($^\circ$C) $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(3,3)</td>
<td>Week 1</td>
</tr>
<tr>
<td>Hand: right</td>
<td>0.87</td>
<td>46.5±0.6</td>
</tr>
<tr>
<td>left</td>
<td>0.92</td>
<td>46.5±0.8</td>
</tr>
<tr>
<td>Knee: right</td>
<td>0.93</td>
<td>48.2±0.8</td>
</tr>
<tr>
<td>left</td>
<td>0.89</td>
<td>47.9±1.1</td>
</tr>
<tr>
<td>Foot: right</td>
<td>0.95</td>
<td>48.6±1.2</td>
</tr>
<tr>
<td>left</td>
<td>0.93</td>
<td>48.0±1.2</td>
</tr>
<tr>
<td>Back (L3,4)</td>
<td>0.90</td>
<td>45.9±2.6</td>
</tr>
</tbody>
</table>

$^a$ Intra-class correlation coefficient of heat pain threshold measured in 8 healthy subjects 3 times, with one week apart in different parts of the body.

$^b$ Values are mean ± S.D. of 4 trials


<table>
<thead>
<tr>
<th>Site</th>
<th>ICC&lt;sup&gt;a&lt;/sup&gt; (3,3)</th>
<th>Vibration Threshold Measurements (mm)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 3</td>
</tr>
<tr>
<td>Left hand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up</td>
<td>0.95</td>
<td>0.26±0.09</td>
</tr>
<tr>
<td>Down</td>
<td>0.96</td>
<td>0.58±0.14</td>
</tr>
<tr>
<td>Right hand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up</td>
<td>0.96</td>
<td>0.29±0.11</td>
</tr>
<tr>
<td>Down</td>
<td>0.95</td>
<td>0.56±0.13</td>
</tr>
</tbody>
</table>

<sup>a</sup> Intra-class correlation coefficient of vibration threshold measured in 10 healthy subjects 3 times with 3 days apart in both hands, using the up- and down-methods.

<sup>b</sup> Values are mean ± S.D. of 4 trials.
CHAPTER 3

TENS ON ACUPOINTS INDUCED PROLONGED INHIBITION OF HEAT PAIN BUT NOT VIBRATION SENSITIVITY IN YOUNG NORMAL SUBJECTS
3.1 Summary

There have been conflicting reports on the inhibitory effects of TENS on both the acute heat pain and vibration thresholds. Such a controversy could have arisen from different experimental protocols such as the duration, location and parameters of TENS being used in the different studies, or the frequency of vibratory stimulation used to measure the vibration threshold. Alternately, TENS could exert different effects on pain (mediated by small diameter fibers) and tactile sensation (mediated by large diameter fibers). This study set out to determine if the inhibitory effect of TENS applied to the same acupuncture point is specific to pain as measured by the heat pain threshold, when compared with tactile sensibility as measured by the vibration threshold.

Twenty young normal subjects, aged from 20 to 39 (mean = 30.2 ± S.D. 2.79), participated in the study. They were randomly allocated to a TENS or placebo group. Thirty minutes of conventional TENS (200μs pulses at 100 Hz and 2-3 times sensory threshold) or placebo stimulation was applied to the acupuncture point (LI4) on each subject’s left hand. Heat pain and vibration thresholds were measured using the Medoc TSA-2001 and the VSA-3000 respectively on the thenar eminence of each subject’s left hand. These assessments were done at 10 min intervals, namely 30, 20 and 10 min before and 0, 10, 20, 30, 40 and 50 min after 30 min of TENS or placebo stimulation. Repeated measures ANOVA was used to analyze the data obtained at the different time intervals (3 before and 6 after each TENS or placebo stimulation) between the two groups.
Our findings showed a significant increase in the heat pain threshold, by 0.8°C and 1.5°C respectively at 0 min (p=0.002) and 20 min (p=0.004) after 30 min of TENS, when compared with placebo stimulation to the LI4 acupoint on the left hand. In contrast, no significant difference in vibration threshold was found between TENS and placebo groups.

To sum, in contrast to placebo stimulation, 30 min of TENS to the LI4 acupoints increased the heat pain threshold but not the vibration threshold in young normal subjects. This result demonstrated that, like acupuncture, the effect of TENS on the acupoints is to reduce pain but not tactile (specifically vibration) sensibility. If so, TENS on acupoints will be preferable to needle acupuncture, by virtue of its non-invasive nature.
3.2 Introduction

High frequency TENS has been widely used in the clinic for reduction of the pain. To more precisely assess the inhibitory analgesic effect of TENS, many investigators have studied the effect of TENS on the experimental pain induced by electricity or heat. Although positive results showing the inhibitory effect of TENS on electrically induced pain have been reported (e.g. Liu and Hui-Chan 1994), studies on thermal pain have demonstrated conflicting results. To elaborate, Pertovaara (1980) used a “thermostimulator” to apply thermal stimuli either proximal or distal to the TENS electrodes attached to the extensor surface of the forearm. The thermal pain threshold was found to be significantly increased in 5 out of 6 subjects (p<0.02), when 45 mA of TENS was applied for 20 min at a site distal to the thermal stimuli. Interestingly, there was no significant increase in pain threshold when 45 mA of TENS was applied at a proximal site, or when less intense (35 mA) TENS was applied at a distal site. Eriksson et al. (1985) designed a study to investigate whether TENS analgesia was due to central changes in humans by measuring the thermal pain threshold. Heat and cold pain thresholds of the thenar region of the hand were measured respectively, when both conventional (80 Hz) and acupuncture-like (2 Hz) TENS were applied over the ipsilateral and contralateral median nerve for 15 minutes. Both heat and cold pain thresholds were increased after conventional and acupuncture-like TENS. In addition, similar effects were seen for both contralateral and ipsilateral TENS applications, thereby providing evidence that TENS-induced analgesia may be mediated by a relatively diffuse central as opposed to very localized peripheral mechanism. Although the above two studies
showed the inhibitory effect of TENS at certain intensities and frequencies on the experimental pain induced by heat or cold, these two studies had not controlled for possible placebo effects.

An encouraging result was shown in a later controlled study by Marchard et al. (1991a). In this study, thermal stimulus was applied to the subjects' cheeks using a contact thermode. A branch of the trigeminal nerve on the cheek was the target of the transcutaneous electrical nerve stimulation (TENS) applied with 125μs pulses at 100 Hz or placebo stimulation for 25 minutes. Both during and after TENS, the thermal pain threshold was significantly increased (p=0.002), whereas placebo stimulation did not alter thermal perception. Contrary to these findings, Ekblom and Hansson (1987) showed that 15 min of conventional TENS (100Hz, 200μs) did not change the heat pain threshold in 6 healthy subjects and in 34 patients with acute tooth pain. Among possible explanations, an altered response in patients with acute tooth pain, the small sample size of the healthy subjects (n=6) and less stimulation duration (15 vs. 25 min) could explain the negative results. Taken together, the studies investigating TENS analgesia by measuring thermal pain threshold suggested that the site, intensity and duration of TENS stimulation, sample size and population could be important variables for methodological considerations in the present study.

Besides the inhibitory effect of TENS on pain sensation, there has been increasing focus on the effect of TENS on other sensations, such as vibratory sensation. Several earlier findings indicated that TENS did not alter vibrotactile threshold (Ferrington et al. 1977, Pertovaara and Hämäläinen 1982). However, some studies have reported an elevated vibration threshold after TENS
application in normal subjects and patients with pain (Pertovaara and Hämäläinen 1982, Zoppi et al. 1981). Therefore, there is an ongoing debate whether the inhibitory effect of TENS is specific to pain modality alone. A search of the literature reviewed a lack of study to explore the effect of TENS on pain together with vibratory sensation in the same subjects. The present study was therefore undertaken to determine whether the inhibitory effect of TENS applied to an acupuncture point is specific to pain as measured by the heat pain threshold, and not to tactile sensibility as measured by the vibration threshold.

3.3 Methods

3.3.1 Subjects and Testing Procedures

Twenty young normal subjects, aged 20 to 39, with no history of neurological or neuromuscular disorders or pain syndrome, participated in the study. Their age, height and weight were recorded as shown in Table 3.1. All the subjects were given a detailed explanation of the experimental procedure verbally and through an “Informed Consent Form” which they signed. They were randomly allocated to one of two groups, TENS or placebo. Heat pain and vibration thresholds were measured respectively in each subject. All the experiments were conducted at room temperature (20-22°C) in a sound-attenuated laboratory. Subjects were seated at a table with their left hand on the table. The left thenar eminence and the area around acupuncture point L14 were cleaned with alcohol. The heat pain thresholds and the vibration thresholds of their left thenar eminence were then measured respectively at 10 min intervals: 30, 20 and
10 minutes before and 0, 10, 20, 30, 40 and 50 minutes after TENS or placebo stimulation had been applied to each subject’s left thenar eminence and acupuncture point LI4. All subjects were told that the stimulation might or might not be perceived as a tingling sensation, depending on the particular apparatus.

3.3.2 TENS and Placebo Stimulation

A portable TENS unit (ATAODYMAXIMAIII, Staodyn, Inc., Longmount, CO) with a two-channel adjustable stimulator, was used in this study. Two carbon electrodes (3.5 cm x 3.5cm) were applied to the thenar eminence of the left hand and the acupuncture point LI4 (Fig. 3.3). The stimulation consisted of biphasic square pulses, with 200μs duration, delivered at constant current output with a frequency of 100 Hz. The stimulus intensity was adjusted to produce a strong tingling but comfortable sensation in each subject (about 2 to 3 times the sensory threshold intensity).

For placebo stimulation, a placebo TENS machine looking identical to the real TENS units but with the internal circuit disconnected by the manufacturer was used. The apparatus was switched on and the investigator turned the intensity knob up. This was carried out so that the subject could see and believe that the apparatus was working.

3.3.3 Recording

3.3.3.1 Heat pain threshold measurement
Heat pain threshold was measured using the Medoc TSA-2001 device (Fig. 3.1). The repeatability of this measure in the 8 normal young subjects has been determined and demonstrated in Chapter 2 to be high, with an intra-class correlation coefficient of r=0.87 to 0.95 in the different body parts (Table 2.1). The heat pain threshold measurement was also found to be highly sensitive. There was a linear correlation between subjective thermal sensation and heat stimulus intensity, with r=0.93 and a slope of 5.04. As presented in Chapter 2, the procedures for heat pain threshold measurement were first explained to the subjects, then a demonstration was given. Subjects received training on the right hand for 3 times before the experiment started. The same experimenter followed a standardized protocol to record all the threshold data. During testing, a thermal probe was placed firmly on the thenar eminence of each subject’s left hand (Fig. 3.1). To determine the heat pain threshold, subjects received 4 successive stimuli starting from an adaptation temperature of 32°C, at a temperature rise rate of 1.5°C/s. A minimal interval of 30s elapsed between successive stimuli, in order to avoid possible sensitization or suppression of the thermal receptors (Yarnitsky and Ochoa 1990). Subjects were asked to press a switch when they first perceived the pain sensation. The mean temperature value in °C of 4 successive tests was recorded as the heat pain threshold.

3.3.3.2 Vibration threshold measurement

Vibration threshold was measured using the Medoc VSA-3000 device (Fig. 3.2). The vibration frequency was fixed at 100 Hz, with amplitude ranging from 0.1 to 25.0 mm at 0.1 mm increments. The reason why the vibration
frequency was chosen to be 100 Hz was that vibration at this frequency is known to activate the Pacinian corpuscle (PC) receptors, which are most sensitive to high frequency vibration (Sherrick et al. 1990, Vallbo and Johansson 1984).

A training session for the vibration threshold measurement was administered to the thenar eminence of both hands 3 times before testing. In order to keep the same tested area in each session, a circle was drawn with permanent ink on the thenar eminence where the vibrator was to be applied. Four stimuli were given to the subjects each session in an ascending (up-method) and descending order (down-method). In the up-method, the subjects were asked to press the switch when they first perceived the vibratory sensation as the vibration stimuli gradually increased. In contrast, the subjects were asked to press the switch when they did not feel any vibratory sensation as the vibration stimuli gradually decreased in the down-method. The mean amplitude threshold value of 4 trials (mm) was computed for the vibration threshold.

The repeatability of vibration threshold measurement with both up- and down-methods in the 10 young normal subjects has been determined and demonstrated to be high in Chapter 2, with an intra-class correlation coefficient of r=0.95 to 0.96 in both hands (Table 2.2). In other words, our experimental paradigm had been demonstrated to give repeatable measurements of the vibration thresholds with both the up- and down-methods.

3.3.4 Statistical Analysis

Differences in heat pain and vibration thresholds between TENS and placebo stimulation both before and after each treatment were calculated. Each
data point was normalized with respect to the control value obtained before TENS or placebo stimulation. Repeated measured ANOVA from the SPSS statistic package (version 9.0) was used to analyze the differences in the measurements of the heat pain and vibration thresholds between TENS and placebo stimulation at 7 levels of time. One level of time was the average estimate of 3 ensemble averages obtained before TENS or placebo stimulation. The other 6 levels of time were the 6 ensemble averages obtained after TENS or placebo stimulation at the 6 time intervals. The significant level was set at p=0.05.

3.4 Results

3.4.1 Relevant Demographic Data

Table 3.1 presented the relevant demographic data of the 20 young normal subjects. For the TENS group (n=10), the age was 30.6 ± S.D. 4.2 yr., the height was 160.3±11.2 cm and the weight was 55.5±8.7 kg, the gender: male was 6, female was 4. For the placebo group (n=10), the age was 29.8±3.4 yr., the height was 157.9±10.1 cm and the weight was 59.1±9.8 kg, the gender: male was 5, female was 5. There were no significant differences in age, height and weight between the TENS and placebo groups when an independent samples t-test (SPSS statistic package, version 9.0) was used. In other words, these variables were similar between TENS and placebo groups.

3.4.2 Effect of 30 min of TENS on Heat Pain Threshold
Table 3.2 showed the mean values and standard deviation of the heat pain thresholds at 30, 20 and 10 min before and 0, 10, 20, 30, 40 and 50 min after TENS or placebo stimulation in 20 young normal subjects.

Repeated measures ANOVA was used to analyze the differences in heat pain threshold between TENS and placebo stimulation at the 7 levels of time. Significant differences were found when comparing the measurements among the 7 levels of time in each group (p=0.000) as well as the combined group-time effect (p=0.001). In other words, an interaction was found between the two main factors of group and time. Due to the probability of an interaction effect, a contrast test was done to further compare the measurements obtained among the 7 levels of times within each group. An independent samples t-test was then used to further compare the measurements between the two groups, with the alpha adjustment set at p=0.007 (0.05/7).

Fig. 3.4 showed that, in the TENS group, a significant increase in heat pain threshold was found at 0 min (p=0.001), 10 min (p=0.002), 20 min (p=0.003) and 30 min (p=0.007) after 30 min of TENS stimulation when compared with the mean control value, computed as the average of the 3 trial ensembles recorded before TENS stimulation. The average real increase in heat pain threshold was 1.3°C (from 45.8 to 47.1°C) at 0 min, 2.0°C (from 45.8 to 47.8°C) at 10 min, 2.0°C (from 45.8 to 47.8°C) at 20 min and 1.6°C (from 45.8 to 47.4°C) at 30 min (Table 3.2). No significant differences were found at the other time intervals. These findings showed the analgesic effect of TENS to last for 30 min after 30 min of stimulation.
In the placebo group, repeated measures ANOVA (contrast, first) method showed no significant difference in the heat pain threshold obtained before and after placebo stimulation (Table 3.2).

As mentioned, an independent samples t-test was then used to compare the changes in heat pain threshold between the TENS and the placebo groups. The heat pain threshold in the TENS group was significantly more increased at 0 min (p=0.002) and 20 min (p=0.004) after 30 min of TENS stimulation (Fig. 3.4). The real increase in heat pain threshold between TENS and placebo groups was 0.8°C (from 46.3 to 47.1°C) at 0 min and 1.5°C (from 46.3 to 47.8°C) at 20 min (Table 3.2). There was no significant difference between the two groups at any other time intervals.

3.4.3 Effect of 30 min of TENS on Vibration Threshold

The mean value and standard deviation of the vibration thresholds recorded at different time intervals in both TENS and placebo groups were shown in Table 3.3.

Repeated measures ANOVA was used to analyze the differences in vibration thresholds between TENS and placebo groups at 7 levels of time. One measurement is the average of the 3 trial ensembles recorded before stimulation; the others were recorded at the 6 time intervals after stimulation. No significant differences were found when comparing the measurements recorded at the 7 different levels of time in each group (p=.836, p=.946), as well as the combined group-time effect (p=.974, p=.996) with the up- and down-method respectively.
Table 3.3 further showed that no significant difference was found at each
time level between TENS and placebo groups at 30, 20, 10 min before TENS or
placebo stimulation and at 10 min intervals for up to 50 min after TENS or
placebo stimulation.

3.5 Discussion

3.5.1 TENS Application to Acupuncture Points

In contrast to placebo stimulation, our findings indicated that the heat pain
threshold was significantly elevated after 20 min of TENS application to acupoint
(LI4) (Table 3.2). The real increase in heat pain threshold was 0.81°C at 0 min
and 1.54°C at 20 min after TENS when compared with placebo stimulation
(p<0.007, Table 3.2). Although this effect had not be compared with that TENS
applied to non-acupoints in our study, pain threshold has been found to be
significantly increased by administering high-frequency TENS to the LI4 point in
rats by Han et al. (1986). This point was thought to be one of the most effective
pain-relieving acupuncture points (Han et al. 1991, Johnson et al. 1996, Mao
1998). Furthermore, in a human study, 68% of the patients receiving TENS to
acupoints, as opposed to only 32% of the patients receiving TENS to the non-
acupoints, reported post-operative pain reduction (Chen et al. 1998).

High-frequency TENS applied to the acupuncture points is based either on
traditional Chinese acupuncture practice, or a theoretical understanding of the
mechanisms of the action of TENS. Acupuncture can activate the body's pain
modulation system and increase the release of endogenous opioids in the central
nervous system (Mao 1998). TENS appears to exert its beneficial effects through several modes of action. To elaborate, it has been found to activate large A-\(\alpha,\beta\) afferent fibers (Levin and Hui-Chan 1993). According to the gate control theory of Melzack and Wall (1965), activation of the large diameter fibers could produce pre-synaptic inhibition of the small A-\(\delta\) and C fibers carrying pain sensation. Moreover, TENS could also activate extra-segmental mechanisms consistent with acupuncture analgesia (Eriksson et al. 1979), and/or the release of endogenous opioids (Han et al 1991) to be discussed in more details later. Finally, possible placebo effects produced by TENS could also contribute to the antinociceptive effect on pain threshold (Johnson et al. 1991).

Marchand et al. (1991a) found a significant increase in the heat pain threshold of the cheek, by 1.2 °C (from 46.7 to 47.9°C) after 25 min of high frequency TENS (100Hz, 125\(\mu\)s), applied to the subject’s cheek around an area innervated by the maxillary branch of the trigeminal nerve. Our study showed a significant elevation of the heat pain threshold, by 1.54°C after 30 min of TENS applied to the acupoint LI4 when compared with placebo stimulation. The somewhat greater (1.54 – 1.2 = 0.34°C, or 28%) increase in the heat pain threshold after TENS stimulation in our study, as compared with that by Marchand et al., could be due to variables such as the different sites of pain and duration of TENS stimulation (30 min vs. 25 min), but it could also be partly ascribed to the different sites of TENS application, e.g. acupoints on the hand versus nerve root on the cheek. If so, we suggest that TENS could be applied to the acupoints to produce similar if not better analgesic effect.
3.5.2 Effect of 30 min of TENS Stimulation on Heat Pain Threshold

Our result showed a significant increase of the heat pain threshold after 30 min of TENS application. The heat pain threshold peaked at 10 min post-stimulation when compared with placebo stimulation to the same site, i.e. LI4 acupoint on the left hand (Fig.3.4). The time course of TENS analgesia demonstrated a gradual onset (=30 min from stimulation onset, Fig. 3.4) and offset (=50 min from stimulation onset) on the heat pain threshold. Our results confirmed those of both animal and human studies showing TENS analgesia to display a typical time course of gradual onset and offset as presented below.

In rats, Han and his co-investigators found that the onset of 30 min of TENS–induced analgesia was slow, with the maximum analgesic effect (56-95% above the baseline) achieved in approximately 20-30 minutes during TENS stimulation (Han et al. 1989). The pain threshold remained elevated throughout the stimulation period. It returned to the baseline value 45 minutes after the termination of stimulation. In human studies, Cheing and Hui-Chan (1999) demonstrated that 60 min of TENS application to acupoints around the knee joint in humans produced similar progressive and prolonged analgesic effects on osteoarthritic knee pain during and after the stimulation. It reduced the pre-stimulation VAS score from 100% to 72.1% ± 25.9% during, and to 63.1% ± 31.2% (p<0.001) after TENS, in contrast to the negligible changes obtained during, and after placebo stimulation (p=0.786). In other words, TENS analgesia had a gradual onset (time to peak maximal inhibitory effect=60min) and offset (more than 60 min post-stimulation).
Such gradual onset and offset of TENS analgesic action is consistent with the results of some investigators demonstrating the possible involvement of endogenous opioids. For example, Han and his co-worker (1991) found that 30 min of acupuncture-like TENS markedly increased (367%) the release of met-enkephalin-arg-phe (p<0.05); whereas conventional TENS produced a 49% increase in the release of dynorphin A in the cerebrospinal fluid of 37 normal subjects. The gradual onset and offset of TENS analgesia can be explained by the time delay in releasing the endogenous opioids to their subsequent action. A prolonged after-discharge in the dorsal horn neurons may also contribute to the gradual offset (Dubuisson 1989). In addition to these mechanisms, a continuous synaptic activation and possible plastic changes in the central inhibitory mechanism could be involved in the persistent antinociceptive effect of TENS (Romita et al. 1987).

Since the 1970s, the analgesic effect of needle acupuncture has been reported to demonstrate a gradual onset and offset on pain. For example, Andersson and Holmgren (1975) examined the effects of needle acupuncture manually, applied at 2/sec to the hands (LI4) and cheeks in 34 dental students, by measuring the electrical tooth pain threshold value in μA before, during and after stimulation. They found that the electrical tooth pain threshold was gradually increased, and reached a peak only at 60-75 min during stimulation. Furthermore, it was gradually decreased to the baseline at 35 min after stimulation. Our result demonstrated that, like acupuncture, the effect of TENS applied to the acupoints was to reduce pain with a gradual onset and offset. This being the case, TENS on
acupoints will be preferable to needle acupuncture, by virtue of its non-invasive nature.

3.5.3 Selective Inhibitory Effect of TENS on Heat Pain Threshold but not Vibration Threshold

In contrast to placebo stimulation, our findings indicated that the heat pain threshold was significantly elevated after 20 min of TENS application to acupoint (LI4) (Table 3.2). The real increase in heat pain threshold was 0.81°C at 0 min and 1.54°C at 20 min after TENS when compared with placebo stimulation (p<0.007, Table 3.2). In contrast to the antinociceptive response to the heat pain, neither TENS nor placebo stimulation produced any inhibitory effect on the vibration threshold (Table 3.3).

Why did TENS applied to the same acupoints in the same subjects produce inhibitory effects specific to the heat pain threshold but not to the vibration threshold? Different afferent pathways are known to mediate heat pain and vibration sensation. Previous studies have shown that the activities of C nociceptors in monkeys and in humans are highly correlated with the psychophysical measurements of heat pain threshold and magnitude (Torebjörk et al. 1984). Further studies indicated that heat pain threshold was signaled by small C fiber activity with low rates of temperature rise (<2.0°C/s) (Yarnitsky and Ochoa 1990). In contrast, sensation of vibration at a frequency of 100 Hz is mediated by the Pacinian corpuscles that are most sensitive to high frequency vibration (Lamore and Keemink 1988, Ribot-Ciscar et al. 1989, Vallbo and Johansson 1984, Horch 1991). These receptors are mediated by the large A-β
fibers. In other words, the pathway and termination of pain and vibration sensitive afferent fibers in the spinal cord are different. In accordance with the gate control theory (Melzack and Wall 1965), the analgesic effect produced by 30 min of TENS on the heat pain threshold could be presumed to inhibit to some extent the transmission mediated by small unmyelinated C fibers through activating the large A-β fibers. Furthermore, the ascending excitatory pathways mediating pain sensation and vibration sensation are different. The spinothalamus and spinoreticular are two major tracts that convey nociceptive information to the higher centers in the central nervous system. In contrast, two different ascending tracts, the spinocervical tract and dorsal lemniscal column, play an important role in the ascending transmission of vibrotactile sensation (Rowe and Tarvin 1988, Truex et al. 1965). The terminations of the fibers mediating these two different sensations are different in the higher centers such as the thalamus. It is believed that the lateral and medial portions of the dorsal nucleus of the thalamus are related to pain and vibration respectively. TENS analgesia may also be explained by an increase in the release of an endogenous opioid thought to bind to specific opioid receptors to reduce the pain. For example, Han and co-workers (1991, 1992) found Met-enkephalin-Arg-Phe and dynorphin to be markedly increased after low and high frequency TENS application in both normal human and in rats. Consequently, the inhibitory effects of TENS on the different ascending pathways could differ too. Vibrotactile adaptation is presumed to result from a possible increase in ionic concentrations, such as ionic potassium, and to affect the responsiveness of the central neurons (Rowe and Tarvin 1988). In accordance with these physiological, anatomical and neuro-chemical results by the other
investigators, our present findings also showed that the inhibitory effect of TENS is specific to pain, but not to vibration.

3.6 Conclusion

In contrast to placebo stimulation, 30 min of TENS to acupoints increased heat pain threshold but not vibration threshold, an effect that had a slow onset and that outlasted the stimulation by 20 min when compared with placebo stimulation. This result demonstrated that, like acupuncture, the inhibitory effect of TENS is specific to pain, but not to other sensory (vibration) sensibility. If so, TENS on acupoints will be preferable to needle acupuncture by virtue of its non-invasive nature. ²

² Note: Part of this chapter was presented in an international conference and published as an abstract

Fig. 3.1  Heat pain threshold was measured with the Medoc TSA-2001 device. The thermal probe was placed on the thenar eminence of each subject's left hand.

Fig. 3.2  The Medoc VSA-3000, a computerized device for the quantitative assessment of vibration threshold.
Fig. 3.3  Two electrodes (3.5 cm x 3.5 cm) connected to the TENS unit were attached to the thenar eminence of the left hand and acupuncture point LI4.
Fig. 3.4 Effect of TENS on heat pain threshold in young normal subjects. Note that within the TENS group, the heat pain threshold was found to be significantly increased at 0 min (*p=.001), 10 min (**p=.002), 20 min (**p=.003) and 30 min (**p=.007) after the termination of 30 min of TENS. In contrast, between groups, the heat pain threshold was found to be significantly more increased in the TENS group than in the placebo group at 0 min (#p=.002) and 20 min (##p=.004) after stimulation.
Table 3.1 Relevant demographic data of the 20 young normal subjects

<table>
<thead>
<tr>
<th></th>
<th>Group 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Group 2&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Group 1&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Group 2&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
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<tr>
<td></td>
<td>(n=10)</td>
<td>(n=10)</td>
<td>(n=10)</td>
<td>(n=10)</td>
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<tr>
<td>Treatment</td>
<td>TENS</td>
<td>Placebo</td>
<td>TENS</td>
<td>Placebo</td>
</tr>
<tr>
<td>Threshold</td>
<td>Heat pain</td>
<td>Heat pain</td>
<td>Vibration</td>
<td>Vibration</td>
</tr>
<tr>
<td>Age</td>
<td>30.6±4.2</td>
<td>29.8±3.4</td>
<td>30.6±4.2</td>
<td>29.8±3.4</td>
</tr>
<tr>
<td>Height</td>
<td>160.3±11.2</td>
<td>157.9±10.1</td>
<td>160.3±11.2</td>
<td>157.9±10.1</td>
</tr>
<tr>
<td>Weight</td>
<td>55.5±8.7</td>
<td>59.1±9.8</td>
<td>55.5±8.7</td>
<td>59.1±9.8</td>
</tr>
<tr>
<td>Gender</td>
<td>Male: 6 Female: 4</td>
<td>Male: 5 Female: 5</td>
<td>Male: 6 Female: 4</td>
<td>Male: 5 Female: 5</td>
</tr>
</tbody>
</table>

Values are means ± S.D.

<sup>a</sup> Heat pain threshold measured in TENS and placebo groups

<sup>b</sup> Vibration threshold measured in TENS and placebo groups

N.B. When the independent samples t-test was used to analyze the age, height and weight between TENS and placebo groups, no significant differences were found.
Table 3.2 Comparison of heat pain threshold (°C) between TENS and placebo groups

<table>
<thead>
<tr>
<th></th>
<th>TENS group^a</th>
<th>Placebo group^a</th>
<th>p value^b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=10)</td>
<td>(n=10)</td>
<td></td>
</tr>
<tr>
<td>Before: 30 min</td>
<td>45.6±2.7</td>
<td>46.1±0.6</td>
<td></td>
</tr>
<tr>
<td>20 min</td>
<td>45.8±2.5</td>
<td>46.8±0.9</td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td>45.8±2.6</td>
<td>46.0±0.9</td>
<td></td>
</tr>
<tr>
<td>means^c</td>
<td>45.8±2.6</td>
<td>46.3±0.8</td>
<td>0.165</td>
</tr>
<tr>
<td>After: 0 min</td>
<td>47.1±2.6</td>
<td>46.3±0.9</td>
<td>0.002*</td>
</tr>
<tr>
<td>10 min</td>
<td>47.8±1.8</td>
<td>46.3±0.5</td>
<td>0.012</td>
</tr>
<tr>
<td>20 min</td>
<td>47.8±1.6</td>
<td>46.3±0.6</td>
<td>0.004*</td>
</tr>
<tr>
<td>30 min</td>
<td>47.4±2.4</td>
<td>46.2±0.9</td>
<td>0.008</td>
</tr>
<tr>
<td>40 min</td>
<td>46.9±2.4</td>
<td>46.5±0.5</td>
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</tr>
<tr>
<td>50 min</td>
<td>46.5±2.4</td>
<td>46.3±0.7</td>
<td>0.202</td>
</tr>
</tbody>
</table>

^a Values are means ± S.D. of the heat pain thresholds

^b Because of an interaction being found between the two main factors of group and time, an independent samples t-test was used to compare the measurements between the two groups at the different time intervals, with the alpha adjustment set at p=0.007 (0.05/7). * indicated the p values when the heat pain threshold was compared between TENS and placebo stimulation. * denotes significant difference in the heat pain threshold between the two groups.

^c The average of the 3 trial ensembles recorded before TENS and placebo stimulation.
Table 3.3 Comparison of vibration thresholds (mm) between TENS and placebo groups with the up- and down-methods

<table>
<thead>
<tr>
<th></th>
<th>TENS group (n=10)</th>
<th>Placebo group (n=10)</th>
<th>p value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Up-method</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>0.30±0.16</td>
<td>0.29±0.16</td>
<td></td>
</tr>
<tr>
<td>20 min</td>
<td>0.32±0.16</td>
<td>0.29±0.14</td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td>0.32±0.17</td>
<td>0.28±0.14</td>
<td></td>
</tr>
<tr>
<td>means&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.31±0.16</td>
<td>0.29±0.15</td>
<td>0.857</td>
</tr>
<tr>
<td>After:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 min</td>
<td>0.34±0.17</td>
<td>0.29±0.15</td>
<td>0.732</td>
</tr>
<tr>
<td>10 min</td>
<td>0.35±0.18</td>
<td>0.29±0.16</td>
<td>0.656</td>
</tr>
<tr>
<td>20 min</td>
<td>0.34±0.16</td>
<td>0.28±0.12</td>
<td>0.748</td>
</tr>
<tr>
<td>30 min</td>
<td>0.35±0.18</td>
<td>0.29±0.13</td>
<td>0.391</td>
</tr>
<tr>
<td>40 min</td>
<td>0.33±0.15</td>
<td>0.28±0.14</td>
<td>0.630</td>
</tr>
<tr>
<td>50 min</td>
<td>0.33±0.14</td>
<td>0.29±0.15</td>
<td>0.654</td>
</tr>
<tr>
<td><strong>Down-method</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before:</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>0.59±0.13</td>
<td>0.57±0.11</td>
<td></td>
</tr>
<tr>
<td>20 min</td>
<td>0.60±0.13</td>
<td>0.57±0.13</td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td>0.60±0.13</td>
<td>0.56±0.12</td>
<td></td>
</tr>
<tr>
<td>means&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.60±0.13</td>
<td>0.57±0.12</td>
<td>0.435</td>
</tr>
<tr>
<td>After:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 min</td>
<td>0.60±0.15</td>
<td>0.57±0.14</td>
<td>0.644</td>
</tr>
<tr>
<td>10 min</td>
<td>0.61±0.17</td>
<td>0.58±0.15</td>
<td>0.892</td>
</tr>
<tr>
<td>20 min</td>
<td>0.60±0.16</td>
<td>0.57±0.13</td>
<td>0.727</td>
</tr>
<tr>
<td>30 min</td>
<td>0.61±0.14</td>
<td>0.57±0.14</td>
<td>0.517</td>
</tr>
<tr>
<td>40 min</td>
<td>0.58±0.11</td>
<td>0.57±0.12</td>
<td>0.793</td>
</tr>
<tr>
<td>50 min</td>
<td>0.58±0.12</td>
<td>0.56±0.11</td>
<td>0.867</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values are means ± S.D. of the vibration thresholds

<sup>b</sup> indicated the p values when the vibration threshold was compared between TENS and placebo stimulation at 7 different time intervals

<sup>c</sup> The average of the 3 trial ensembles recorded before TENS and placebo stimulation.
CHAPTER 4

ANTINOCICEPTIVE EFFECT OF 6 SESSIONS OF TENS ON HEAT PAIN THRESHOLD IN OLDER NORMAL SUBJECTS
4.1 Summary

Recent studies showed that TENS produced cumulative analgesic effects on the intensity of different types of pain. Briefly, Liu and Hui-Chan (1994) demonstrated that 60 min of daily TENS, repeatedly 5 times a week for 2 weeks, led to a decrease of 30% in the electrically induced pain in young normal subjects. Cheing and Hui-Chan (1996) found that the same TENS protocol produced a decrease of 48.8% pain in patients with chronic low back pain. They further demonstrated that 2 weeks of TENS resulted in a decrease of 32.6% of knee OA pain, and that 4 weeks of TENS led to a further decrease of pain (45.9%) in older patients with chronic knee OA pain (Cheing and Hui-Chan 1998). The treatment protocol used in the above studies involved the application of TENS or placebo stimulation for 60 min each day over a 2- to 4-week period. In the present study, we set out to determine if TENS application for 60 min twice daily, over a shorter (3-day) period, could have produced cumulative analgesic effects on the heat pain threshold, when compared with that of placebo stimulation in the older normal subjects.

Nineteen older normal subjects, aged 60 to 85, participated in this study. All the subjects were randomly allocated into a TENS or placebo group. Sixty minutes of TENS (200\mu s in pulses at 100 Hz with 2 – 3 times sensory threshold intensity) or placebo stimulation was applied to four acupoints (Extra 36, St35, Sp9 and Gb34) around the knee joint twice daily over a 3-day period (=6 sessions in total). Heat pain threshold was measured at 30, 20 and 10 min before, 20, 40 and 60 min during, and 10, 20, 30, 40, 50 and 60 min after 60 min of TENS or placebo stimulation in session. It was also measured before and after TENS or
placebo stimulation in the other 5 sessions, from session₁ to session₅. For analyzing the effect of a single session, repeated measures ANOVA was used to analyze the difference in the heat pain threshold measured at 10 time intervals (1 time before, 3 times during and 6 times after TENS or placebo stimulation) in session₁. For analyzing the cumulative effect across sessions, repeated measures ANOVA was also used to analyze the difference in the pre-stimulation heat pain thresholds obtained in session₁ and session₅ between the TENS and placebo groups. In the analysis of means, p<0.05 with Bonferroni adjustment was considered significant.

Our findings showed that 60 min of TENS produced a significant increase in the heat pain threshold at 20 min (p=0.016), 30 min (p=0.007) and 40 min (p=0.005) after TENS, when compared with that after placebo stimulation in session₁. Furthermore, the inhibitory effects on the heat pain threshold in the older normal subjects manifested a gradual onset and offset. This analgesic pattern was similar to that produced by 30 min of TENS in the young normal subjects.

Repeated TENS application to the four acupoints around the knee joint, for 60 min twice daily for 3 days, did produce a cumulative antinociceptive effect on the heat pain threshold in the older normal subjects receiving TENS. By the finish of 6 treatment sessions, there was a significant increase in the pre-stimulation heat pain threshold, from 46.9°C in session₁ to 48.6 °C in session₅, or by 1.7°C in the TENS group (p=0.007). The existence of such a cumulative antinociceptive effect, as denoted by a significant rise in the heat pain threshold before TENS in session₅, when compared with that in session₅, suggested possible
plastic changes in the nervous system in the TENS group. Our results further showed that the difference in the heat pain threshold after treatment in session 6 between the TENS and placebo groups was almost but not yet significant (p=0.027, Table 4.3). This finding suggested that application of TENS twice daily for more than 6 sessions may bring about a real between-group difference.
4.2 Introduction

Recent studies showed that TENS produced cumulative analgesic effects on the intensity of different kinds of pain. Briefly, Liu and Hui-Chan (1994) demonstrated that 60 min of daily TENS, repeated 5 times a week for 2 weeks, led to a decrease of 30% in the electrically induced pain in young normal subjects. Cheing and Hui-Chan (1996) found that the same TENS protocol produced a decrease of 48.8% pain in patients with chronic low back pain. They further demonstrated that 2 weeks of TENS resulted in a decrease of 32.6% of knee OA pain, and that 4 weeks of TENS led to a further decrease of pain (45.9%) in the older patients with chronic knee OA pain (Cheing and Hui-Chan 1998). The treatment protocol used in these studies involved the applications of TENS or placebo stimulation for 60 min each day over a 2- to 4-week period. In the present study, we set out to determine if TENS application for 60 min twice daily, over a shorter (3-day) period, could have produced cumulative analgesic effects on the heat pain threshold in the older normal subjects, when compared with that of placebo stimulation.

4.3 Methods

4.3.1 Subjects

Nineteen older normal subjects, aged 65 to 90, with no history of neurological or neuromuscular disorders or pain syndrome, participated in the study. All the subjects were given a detailed explanation of the experimental
procedure verbally and through an “Informed Consent Form” which they signed. The age, height, weight and gender of subjects were recorded.

4.3.2 Treatment Procedures

The subjects were randomly assigned to one of two groups. Group 1 received TENS stimulation and Group 2 received placebo stimulation.

In the TENS group, 10 normal subjects were examined. Subjects received 60 min of TENS stimulation, twice a day over a 3-day period (= 6 sessions in total). TENS was provided using a conventional stimulation unit that produced symmetrical biphasic square pulses, with 200μs pulses delivered at a frequency of 100 Hz. The stimulus intensity was adjusted to produce a strong but comfortable sensation (2-3 times sensory threshold) for each subject. Four carbon electrodes (3.5 cm x 3.5cm) connected to 2 channels were placed on the 4 acupuncture points around the knee joints: Extra36, St.35, Gb.34 and Sp.9 (Louise 1980) (Fig.4.1).

In the placebo group, 9 normal subjects were studied and received 60 min of placebo stimulation twice a day over a 3-day period. Four electrodes connected to a placebo apparatus were placed on the same 4 acupoints around the knee joint. For placebo stimulation, a placebo TENS machine looking identical to the real TENS units, but with the internal circuit disconnected by the manufacture, was used. The apparatus was switched on and the investigator turned the intensity knob up. This was carried out so that the subject could see and believe that the apparatus was working.
All the subjects were told that they might or might not feel the stimulation depending on the technique of apparatus.

4.3.3 Recording

4.3.3.1 Heat Pain Threshold Measurement

Heat pain threshold in each subject’s knee was measured using the Medoc TSA-2001 device (Fig. 4.2). The repeatability of this measurement outcome in the young normal subjects has been demonstrated to be high in Chapter 2, with an intra-class correlation coefficient of $r=0.87$ to 0.95 in the different body parts (Table 2.1). As described in Chapter 2, the procedures for the heat pain threshold measurements were first explained to each subject, followed by a demonstration. To determine the heat pain threshold, each subject received 4 successive stimuli starting from an adaptation temperature of 32°C, at a temperature rise rate of 1.5°C/s. A minimal interval of 30 second was provided between successive stimuli, in order to avoid possible sensitization or suppression of the thermal receptors (Yamitsky and Ochoa 1990). Subjects were asked to press a switch when they first perceived the pain sensation. The mean temperature value in °C of 4 successive tests was recorded as the heat pain threshold.

For the first treatment session, the heat pain threshold was measured in the knee joint at 30, 20 and 10 min before, 20, 40 and 60 during, and 10, 20, 30, 40, 50 and 60 min after TENS or placebo stimulation. The heat pain threshold was then measured in the other 5 treatment sessions, from session2 to session6, before and after each TENS or placebo stimulation. The heat pain threshold values
obtained from each time interval were normalized with respect to the pre-stimulation baseline values.

4.3.4 Statistical Analysis

An independent t-test was used to compare the relevant demographic data: age, height, weight and gender between the TENS and placebo groups.

For analyzing the effect of a single treatment session, repeated measured ANOVA was used to analyze the differences in the normalized heat pain thresholds between the TENS and placebo stimulation at 10 time intervals in session1. One level of time was the average estimate of 3 ensemble averages obtained before TENS or placebo stimulation. Three levels of time were the 3 ensemble averages obtained during TENS or placebo stimulation at the 3 time intervals, and the other 6 levels of time were the 6 ensemble averages obtained after TENS or placebo stimulation at the 6 time intervals. For analyzing the cumulative effects across sessions, repeated measures ANOVA was also used to analyze the difference in the pre-stimulation normalized heat pain thresholds obtained in session, and session, between the TENS and placebo groups.

In the analysis of means, p<0.05 with Bonferroni adjustment was considered significant.

4.4 Results

4.4.1 Relevant Demographic Data
All 19 subjects completed the 6 treatment sessions, administered twice a day over a 3-day period. Table 4.1 presents the relevant demographic data of these subjects. The ages for the TENS and placebo groups were respectively 75.4±7.2 and 76.1±9.1 yr., the heights were 154.6±7.0 and 155.4±8.8 cm, and the weights were 60.5±7.8 and 60.7±9.4 kg, the genders (M; F) were 6; 3 and 5; 4. In other words, the age, height, weight and gender were similar between the two groups of subjects.

4.4.2 Influence of 60 min of TENS on Heat Pain Threshold

The means and standard deviation of the heat pain thresholds measured at 30, 20 and 10 min before, 20, 40 and 60 min during and 10, 20, 30, 40, 50 and 60 min after 60 min of TENS or placebo stimulation in session, were shown in Table 4.2.

Repeated measures ANOVA was used to analyze the differences in the heat pain thresholds between the TENS and placebo stimulation at 10 levels of time (1 level of time was the average estimate of 3 ensemble averages obtained before; 3 levels of time were the 3 ensemble averages obtained at 3 time intervals during; and the other 6 levels of time were the 6 ensemble averages obtained at 6 time intervals after TENS or placebo stimulation). No significant differences were found for the two main factors, when comparing the measurements recorded at the 10 levels of time in each group (p=0.104) or the group-time effect (p=0.348). In other words, no interaction was found between the two main factors of “group” and “time”.
In contrast to placebo stimulation which produced negligible effects, the heat pain threshold was found to be significantly increased at 20 min (p=0.016), 30 min (p=0.007) and 40 min (p=0.005) after TENS stimulation when compared with the average estimate of the 3 ensemble averages obtained prior to TENS (Fig. 4.3). In the TENS group, the real increase in heat pain threshold from before to after TENS was 1.5°C (from 46.4 to 47.9°C) at 20 min, 1.7°C (from 46.4 to 48.1°C) at 30 min, and 1.8°C (from 46.4 to 48.2°C) at 40 min. As shown in Table 4.2, the real increase in the heat pain threshold was also significantly different between the TENS and placebo groups, being 1.3°C (47.9 and 46.6°C respectively, p=0.016) at 20 min, 1.4°C (48.1 and 46.7°C, p=0.007) at 30 min, and 1.5°C (48.2 and 46.7°C, p=0.005) at 40 min after stimulation.

Figure 4.3 showed that the heat pain threshold gradually increased and peaked at 30 to 40 min after 60 min of TENS stimulation when compared with placebo stimulation. It then gradually decreased to the pre-stimulation baseline. In other words, 60 min of TENS produced an antinociceptive effect on the heat pain threshold with a gradual onset and offset.

4.4.3 Effects of 6 Sessions of Repeated TENS on Heat Pain Threshold

The mean values of the heat pain thresholds measured before and after TENS or placebo stimulation in session1, 3 and 6 were illustrated in Table 4.3.

Repeated measures ANOVA was used to analyze the differences in the normalized heat pain thresholds obtained before treatment in session1, and session6, between the TENS and placebo groups. Since an interaction of “group” and “session” was found (p=0.012), repeated measures ANOVA was used to analyze
the difference in the normalized heat pain thresholds obtained before session₁ and session₀ within the TENS or placebo group. An independent samples t-test was further used to compare the normalized heat pain thresholds between the 2 groups, with the alpha adjustment set at p= 0.025 (0.05/2).

For within-group comparison, the pre-stimulation heat pain threshold was significantly increased from session₁ to session₀, by 1.7°C (from 46.9 ± 3.1 to 48.6 ± 1.8°C, p=0.007) in the TENS group (Table 4.3, Fig.4.4). In contrast, no significant change in the heat pain threshold obtained before placebo stimulation in session₁ was found, when compared with that obtained in session₀, from 46.7 ± 2.3 to 47.4 ± 2.0°C or by 0.7°C (p=0.191) in the placebo group (Table 4.3).

For between-group comparison, no significant difference in the heat pain threshold obtained before treatment in session₀ was found between the TENS and placebo groups (p=0.178, Table 4.3). However, it should be noted that the difference in the heat pain threshold obtained after treatment in session₀ between the TENS and placebo groups was close to a significant level (p=0.027).

4.5 Discussion

4.5.1 Effects of 60 min of TENS on Heat Pain Threshold

Our result showed a significant increase in the heat pain threshold after 60 min of TENS but not placebo stimulation to the 4 acupoints around the knee joint in the older normal subjects. This increase in the heat pain threshold further demonstrated a gradual onset and offset. More specifically, the heat pain threshold gradually increased during 60 min of TENS, and was sustained for up to
40 min after 60 min of TENS stimulation before returning to the baseline. As reported in Chapter 3, we found that 30 min of TENS application to an acupoint in the hand of young normal subjects produced inhibitory effects on the heat pain threshold, with a gradual onset (≈30 min from stimulation onset, Fig. 3.2) and offset (≈30 min after stimulation). The inhibitory effect of 60 min of TENS application to the 4 acupuncture points around the knee thus demonstrated a similar gradual onset and offset in the older normal subjects. Furthermore, 60 min of TENS application to knee in the old normal subjects seemed to produce somewhat longer lasting inhibitory effect (offset=40 min after stimulation) in the heat pain threshold when compared with 30 min of TENS application to the hand in the young normal subjects (offset=30 min after stimulation). This finding was in agreement with previous studies regarding the time course of 30 min and 60 min of TENS analgesic effect on the different kinds of pain as detailed below.

A study by Chan and Tsang (1987) demonstrated that the antinociceptive effect of 30min of TENS on the flexion reflex peaked at the end of the 30 min of TENS stimulation in young normal subjects. In rat experiment, Wang et al. (1992) showed that 30 min of TENS exerted an antinociceptive effect on the tail flick test lasting for 30 min.

Liu and Hui-Chan (1994) showed that 60 min of conventional TENS to the low back (L4-S1) produced a significant inhibition of electrically induced pain in young normal subjects. Such an inhibition had a gradual onset (time to peak maximum inhibitory effect=60 min) and offset (more than 60 min post-stimulation). In agreement with these results, Cheing and Hui-Chan (1996) demonstrated that 60 min of conventional TENS applied to the low back (L4-S1)
produced a significant inhibition of chronic low back pain lasting for 60 min, after 60 min of TENS in patients with low back pain.

Indeed, 60 min of TENS appeared to produce analgesic effects longer than 30 min of TENS. What could be the underlying mechanisms? A gradual onset and offset of TENS analgesia can be explained by the cumulative time delay in releasing the endogenous opioids and their subsequent more prolonged action in the central nervous system when TENS was applied for 60 as opposed to 30 minutes (Chapter 3). If so, we suggested that 60 min of TENS could be applied to the patients in the clinic for more prolonged analgesic effect.

4.5.2 Cumulative Inhibitory Effect of Repeated TENS Applications on Heat Pain Threshold

Our results further demonstrated a significant elevation of the heat pain threshold measured before TENS treatment in session, to that measured in session, in the older normal subjects. In other words, a cumulative inhibitory effect of repeated TENS applications on the heat pain threshold was found in the TENS group (p=0.007, Table 4.3), but not in the placebo group (p=0.191). This finding could be explained by possible neural and/or neuro-chemical changes as a result of repeated TENS stimulation. Such repeated stimulation could have resulted in an increase in heat pain threshold through temporal activation and subsequent summation of afferent activity at spinal or higher levels (Price et al. 1977, Sluka et al. 1998). The latter has been found to trigger the release of endogenous opioids. For instance, Luo and co-workers (1996) found that biweekly electroacupuncture stimulation for 4 weeks in the arthritic rats increased
the methionine enkephalin in the cerebrospinal fluid, which peaked in the third week and was significantly higher than the normal level (p<0.05).

Our result further showed that the difference in the heat pain threshold after treatment in session, between the TENS and placebo groups was almost but not yet significant (p=0.027, Table 4.3). This finding suggested that applications of TENS twice daily for more than 6 sessions might bring about a real between-group difference. We therefore embarked on our main study to examine the effects of 12 sessions of TENS on post-surgical pain in patients with knee OA after total knee replacement (see Chapter 5).

4.6 Conclusion

Sixty minutes of TENS produced an increase in the heat pain threshold in the older normal subject. The gradual onset and offset of such an analgesic effect was similar to that produced by 30 min of TENS in the young normal subjects. Moreover, repeated high-frequency TENS applications to the acupoints around the knee joint, for 60 min twice daily over a 3-day period, produced a cumulative antinociceptive effect on the heat pain threshold in the older normal subjects receiving TENS, but not in the placebo group. The existence of such a cumulative antinociceptive effect, as denoted by a significant rise in the heat pain threshold before TENS in session, when compared with that in session, suggested possible plastic changes in the nervous system in the TENS group. However, although 6 sessions of TENS produced analgesic effects that tended to be greater than that of placebo stimulation, the between-group difference was not significant. This prompted us to use a longer period of stimulation for the main
study, launched to examine the effects of pre-emptive and continued daily TENS on post-surgical pain in the patients with knee osteoarthritis receiving total knee replacement. This will now be presented in details in the next Chapter (Chapter 5).³

³ Note: Part of this chapter will be submitted:

### Table 4.1 Relevant demographic data in older normal subjects

<table>
<thead>
<tr>
<th></th>
<th>TENS (n=10)</th>
<th>Placebo (n=9)</th>
<th>p value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
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<td>76.1±9.1</td>
<td>0.967</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>154.6±7.0</td>
<td>155.4±8.8</td>
<td>0.818</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.5±7.8</td>
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<td>0.852</td>
</tr>
<tr>
<td>Gender (M;F)</td>
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<td>5;4</td>
<td>0.210</td>
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</tbody>
</table>

Values are means ±S.D.

<sup>a</sup> denotes non-significant difference in the demographic data between TENS and placebo groups
Table 4.2 Summary of heat pain threshold in older normal subjects (°C)

<table>
<thead>
<tr>
<th></th>
<th>TENS group (n=10)⁴</th>
<th>Placebo group (n=9)⁴</th>
<th>p value⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30min</td>
<td>46.4 ± 2.1</td>
<td>46.0 ± 2.7</td>
<td></td>
</tr>
<tr>
<td>20min</td>
<td>46.5 ± 2.3</td>
<td>46.1 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td>46.3 ± 1.8</td>
<td>46.3 ± 2.8</td>
<td></td>
</tr>
<tr>
<td>means⁶</td>
<td>46.4 ± 2.1</td>
<td>46.2 ± 2.6</td>
<td>0.612</td>
</tr>
<tr>
<td>During:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20min</td>
<td>46.9 ± 2.2</td>
<td>46.0 ± 2.9</td>
<td>0.517</td>
</tr>
<tr>
<td>40min</td>
<td>46.6 ± 2.3</td>
<td>47.0 ± 1.8</td>
<td>0.119</td>
</tr>
<tr>
<td>60min</td>
<td>47.5 ± 2.0</td>
<td>46.7 ± 2.1</td>
<td>0.073</td>
</tr>
<tr>
<td>After:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10min</td>
<td>47.7 ± 2.2</td>
<td>46.3 ± 3.0</td>
<td>0.166</td>
</tr>
<tr>
<td>20min</td>
<td>47.9 ± 1.5</td>
<td>46.6 ± 2.9</td>
<td>0.016*</td>
</tr>
<tr>
<td>30min</td>
<td>48.1 ± 1.4</td>
<td>46.7 ± 2.6</td>
<td>0.007*</td>
</tr>
<tr>
<td>40min</td>
<td>48.2 ± 1.2</td>
<td>46.7 ± 2.6</td>
<td>0.005*</td>
</tr>
<tr>
<td>50min</td>
<td>47.1 ± 1.7</td>
<td>46.5 ± 2.5</td>
<td>0.231</td>
</tr>
<tr>
<td>60min</td>
<td>46.3 ± 2.0</td>
<td>46.3 ± 2.3</td>
<td>0.658</td>
</tr>
</tbody>
</table>

⁴ values are means ± S.D. of the heat pain threshold.
⁵ indicates the p values when the heat pain threshold were compared between the TENS and placebo groups at 10 levels of time intervals (1 level of time before, 3 levels of time during and 6 levels of time after TENS of placebo stimulation) using repeated measures ANOVA.
⁶ denotes significant differences in the heat pain threshold measured at 3 time intervals (20, 30 and 40 min after treatment) between the TENS and placebo groups.
⁷ average estimate of the 3 ensemble averages obtained before TENS or placebo stimulation.
Table 4.3 A Comparison of the heat pain threshold (°C) measured before and after TENS or placebo stimulation on each day for 3 days

<table>
<thead>
<tr>
<th>Session</th>
<th>Older normal subjects (n=19)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TENS (n=10)</td>
<td>Placebo (n=9)</td>
<td>p value^c</td>
</tr>
<tr>
<td>#1 – Day 1 Before</td>
<td>46.9±3.1 (100%)</td>
<td>46.7±2.3 (100%)</td>
<td>0.016*</td>
</tr>
<tr>
<td>After</td>
<td>48.5±1.0 (103.6%±3.9)</td>
<td>46.0±2.6 (98.8%±7.0%)</td>
<td>0.579</td>
</tr>
<tr>
<td>p value^a</td>
<td>0.011*</td>
<td>0.579</td>
<td></td>
</tr>
<tr>
<td>#3 – Day 2 Before</td>
<td>47.9±2.7 (102.2%±2.5%)</td>
<td>47.2±1.9 (101.2%±2.8%)</td>
<td>0.550</td>
</tr>
<tr>
<td>After</td>
<td>48.7±1.8 (103.9%±3.7%)</td>
<td>46.4±2.9 (99.5%±8.1%)</td>
<td>0.055</td>
</tr>
<tr>
<td>p value^a</td>
<td>0.130</td>
<td>0.478</td>
<td></td>
</tr>
<tr>
<td>#6 – Day 3 Before</td>
<td>48.6±1.8 (103.8%±3.9%)</td>
<td>47.4±2.00 (101.5%±3.2%)</td>
<td>0.178</td>
</tr>
<tr>
<td>After</td>
<td>49.4±1.3 (105.7%±5.9%)</td>
<td>47.7±1.7 (102.2%±2.8%)</td>
<td>0.027*</td>
</tr>
<tr>
<td>p value^a</td>
<td>0.051</td>
<td>0.222</td>
<td></td>
</tr>
<tr>
<td>&quot;session&quot;^b</td>
<td>0.007*</td>
<td>0.191</td>
<td></td>
</tr>
</tbody>
</table>

Values are means±S.D.
Values in ( ) are normalized with respect to the initial threshold (heat pain threshold / initial heat pain threshold x 100%).

^a indicates the p values when the heat pain threshold were compared before and after TENS or placebo stimulation using independent samples t-test.
^b indicated the p values when the heat pain threshold obtained prior to the treatment in session, were compared with those in session, within the TENS or placebo group.
^c indicates the p values when the heat pain threshold were compared before and after each treatment session between the TENS and placebo groups.
* indicates that p value reached a significant level.
* indicates that p value reached close to a significant level.
Fig. 4.1 Four electrodes connected to a portable TENS unit were placed on the four acupuncture points: Sp9: on the lower border of the medial condyle on the tibia, in the depression on the medial border of the tibia. Extra 36: the point in the depression medial to the patellar tip. St35: when the knee is flexed, the point is at the lower border of the patella, in the depression lateral to the patellar ligament. Gb34: in the depression anterior and inferior to the head of the fibula.
Fig. 4.2 Experimental set-up

The thermod was attached to the area above the knee joint for measuring the heat pain threshold, using the Medoc TSA-2001.

Four electrodes connected to a portable TENS unit were applied to the 4 acupuncture points (Extra36, St35, Gb34 and Sp9: Fig. 4.1) around the knee joint.
Fig. 4.3 In contrast to placebo stimulation which produced negligible effects, TENS significantly increased the heat pain threshold at 20 min ($p=0.016$), 30 min ($p=0.007$) and 40 min ($p=0.005$) after stimulation. The real increase in heat pain threshold was $1.5^\circ C$ (from $46.4^\circ C$ before TENS to $47.9^\circ C$) at 20 min, $1.7^\circ C$ (from 46.4 to 48.1$^\circ C$) at 30 min and $1.8^\circ C$ (from 46.4 to 48.2$^\circ C$) at 40 min after TENS application.

The real increase in the heat pain threshold was also significantly different between the TENS and placebo groups, being $1.3^\circ C$ (47.9 and 46.6$^\circ C$ respectively, $p=0.016$) at 20 min, $1.4^\circ C$ (48.1 and 46.7$^\circ C$, $p=0.007$) at 30 min, and $1.5^\circ C$ (48.2 and 46.7$^\circ C$, $p=0.005$) at 40 min after stimulation.
For within-group comparison, the heat pain threshold was found to be significantly increased after TENS stimulation in session 1 (p=0.011). There was also a significant increase in the pre-stimulation heat pain threshold from session 1 to session 6 (p=0.007).

For between-group comparison, no significant difference in the heat pain threshold was found between TENS and placebo groups across session 1, 3, and 6.
CHAPTER 5

INHIBITORY EFFECT OF REPEATED TENS ON POST-OPERATIVE PAIN IN OLDER PATIENTS AFTER TOTAL KNEE REPLACEMENT
5.1 Summary

Previous studies have demonstrated cumulative inhibitory effects of TENS on subjective chronic knee pain intensity. Briefly, Cheing and Hui-Chan (1996) found that the 60 min of TENS, repeated 5 times a week for 2 weeks, produced a cumulative decrease of 48.8% pain in patients with chronic low back pain. They further demonstrated that 2 weeks of the same TENS protocol resulted in a decrease of 32.6% of osteoarthritic (OA) knee pain, and that 4 weeks of TENS led to a further decrease (45.9%) of pain in older patients with chronic knee pain (Cheing and Hui-Chan 1998). It should be noted that no study to-date has investigated the possible cumulative analgesic effect of pre-emptive and repeated TENS application on post-operative pain in patients with knee OA. This study set out to delineate if TENS, repeated twice daily for 3 days before, 1 day during and 6 days after surgery, produced cumulative inhibitory effects, which could improve the management of post-operative pain. If so, it may reduce the analgesic consumption, and even shorten the length of hospital stays.

The study was performed in 42 patients, aged 50 to 85, undergoing total knee replacement surgery. All the patients were randomly allocated to a TENS or placebo group. Sixty minutes of TENS (200μs pulses at 100 Hz with 2-3 times sensory threshold) or placebo stimulation was applied to 4 acupuncture points (Extra 36, St35, Sp9 and Gb34) around the knee joint in each patient, 2 times each day, 3 days before, 1 day during, and 6 days after surgery (= 20 sessions in total). Four outcome measurements were recorded: (1) subjective post-operative knee pain intensity, (2) range of knee flexion, (3) analgesic consumption and (4) length of hospital stay, defined as the number of days needed by the patients to reach the
discharge criteria. Repeated measures ANOVA was used to analyze the
differences in the means of the following 2 values obtained before each of the 6
treatment sessions between the TENS and placebo groups: (1) post-operative pain
intensity measured by VAS and (2) range of knee flexion. Paired t-test was used
to analyze the difference in the doses of PCA morphine consumption and the rates
of epidural fentanyl infusion at 6, 12 and 24 hours after operation between the
TENS and placebo groups. Length of hospital stay was measured as the number
of days needed by the patients to reach the discharge criteria; and paired t-test was
used to compare the means between the TENS and placebo groups. Significant
levels in all statistical methods were set at \( p=0.05 \) with Bonferroni adjustment.

Our results showed that (1) 60 min of TENS application in session,
produced a significant decrease of the post-operative knee pain intensity during
and after TENS, when compared with that of placebo stimulation (\( p=0.000 \) to
0.003). The baseline VAS score of TENS group gradually dropped from 100% to
83.3% at 60 min during, to 85.7% and 94.3% at 20 and 60 min after TENS, in
contrast to the negligible changes shown during and after placebo stimulation. By
the completion of 12 treatment sessions, there was a further decrease to 31.5%
before, 25.6% at 60 min during and 27.3% at 60 min after TENS application.
These scores were significantly less than those recorded in the placebo group,
which showed a decrease to 50.0% before, 47.6% at 60 min during and 47.5% at
60 min after placebo stimulation (\( p=0.000 \) to 0.003). (2) Furthermore, a
significant increase in the range of knee flexion was found between the TENS and
placebo groups on each of the 6 days after operation (\( p=0.000 \) to 0.012). (3)
However, no statistical difference in the analgesic consumption – either in the
PCA morphine taken or in the rate of epidural fentanyl infusion, was found between the TENS and placebo groups. (4) A final finding was that the patients receiving repeated TENS tended to reach the hospital discharge criteria 2 days earlier than those receiving placebo stimulation.

It was concluded that TENS applied for 60 min, 2 times each day for 10 days (3 days before, 1 day during and 6 days after total knee replacement), reduced the post-operative knee pain and improved knee flexion significantly more than placebo stimulation. The existence of such a cumulative antinociceptive effect, as denoted by a significant decrease in the post-operative knee pain intensity obtained prior to treatment in session, after surgery, suggested possible plastic changes in the nervous system. It is noteworthy that the effects of real afferent TENS stimulation were significantly more than those of placebo stimulation. Furthermore, patients receiving repeated TENS application tended to reach the discharge criteria 2 days earlier on the average than those receiving placebo application. These findings unequivocally demonstrated that TENS application to the acupoints before, during and after total knee replacement produced significant beneficial effects to the patients with osteoarthritic knee pain after total knee replacement, in terms of a significant improvement in their sensori-motor functions and the possible saving garnered from a tendency towards shortened hospital stay.
5.2 Introduction

Total knee replacement is the surgery to replace a damaged or diseased knee joint with an artificial joint (Laskin 1991). The number of such an operation needed and performed has more than tripled over the past 10 years, reaching 179,000 each year in the United States (Graves 1995, Katz et al. 1996). One of complications after total knee replacement is post-operative pain. Post-operative pain is an acute pain caused by operations for traumatic or other injuries medical conditions. There is a growing body of evidence suggesting that post-operative pain may produce harmful physiological and psychological effects (Dransner 1992), partly due to a central sensitization process that may induce long lasting central neuronal alterations. Melzack et al. (1987) observed that older patients often had more continuous pain following surgery than younger people did. Further evidence demonstrated that older patients who had undergone knee replacement surgery were more likely to report intense pain, when compared with other orthopedic and abdominal surgeries (e.g. Hall-Lord et al. 1999). If the post-operative pain on the first two days after surgery was not well controlled, severe, persistent pain may delay the recovery process after surgical intervention (Melzack 1990). In fact, un-treated post-operative pain may be a significant confounding factor for increasing the length of hospital stay and subsequent higher costs of medical care (Christensen and Kehlet 1993, Duggleby and Lander 1994, Mangano et al. 1991, Wisner 1990). It should thus be considered as a major medical, economic and social concern (Filos and Lehmann 1999). Therefore, it is important to improve post-operative pain control.
TENS has been used as one of the additional approaches for post-operative pain management. The inhibitory effect of TENS on post-operative pain has been studied following cardiac (Bayiindir et al. 1991, Forster et al. 1994), abdominal (Hargreaves and Lander 1989, Schomburg and Carter-Baker 1983, Sim 1991, Wang et al. 1997) and spinal surgeries (Issenman et al. 1985). Some studies reported significantly lower pain scores (Bayiindir et al. 1991, Hargreaves and Lander 1989), or fewer dose of analgesics taken than the control patients (Wang et al. 1997). However, some negative results have also been found (e.g., Forster et al. 1994). In the studies hitherto, TENS was usually applied during the first 2 or 3 days after surgery. The pain intensity was measured only by the finish of the treatment period. Now, post-operative pain may be prolonged for several days or even weeks due to e.g. the sensitization of the central nervous system after operation (Section 1.2.3.3). Therefore, if TENS was just applied for 2 or 3 days, the period of treatment may not be long enough for more lasting post-operative pain control.

Recent research studies on daily TENS application over a 2- to 4-week period have shown that it produced a cumulative inhibitory effect on chronic clinical pain. Briefly, Cheing and Hui-Chan (1996) found that 60 min of TENS, repeated 5 time a week for 2 weeks, produced a decrease of 48.8% pain in patients with chronic low back pain. They further demonstrated that 2 weeks of the same TENS protocol resulted in a decrease of 32.6% of osteoarthritic (OA) knee pain, and that 4 weeks of TENS led to a further decrease (45.9%) of pain in older patients with chronic knee pain (Cheing and Hui-Chan 1998). In Chapter 4, we further showed that TENS applied twice a day for 3 days (=6 treatment sessions)
significantly increased the pre-stimulation heat pain threshold in the older normal subjects receiving TENS. However, no study to-date has investigated the possible cumulative inhibitory effect of TENS on post-operative knee pain, when TENS was repeatedly applied before, during and after total knee replacement.

As reviewed under the section entitled "Pre-emptive analgesia for post-operative pain", a novel pharmacological approach using continuous pre-emptive administration of opioids has offered the possibility of reducing post-operative pain after a major surgery. This method is based on the hypothesis that it will prevent the central sensitization resulting from the continuous transmission of sensory nociceptive stimuli after surgery. The underlying principle requires that an appropriate pharmacological intervention is applied before pain occurs, rather than in response to it. The timing of the drug administration is aimed to prevent the spinal cord from reaching a hyper-excitabile state that leads to excessive response to afferent pain nerve impulses (Wassef 1998). Therefore, pre-emptive analgesia has been proposed to produce the prolonged effects that outlasted the presence of drugs (Wall 1988). Since the inflammatory reaction to tissue injury during surgery may contribute to the post-operative pain, or even prolong the pain, continuous pre-emptive drug administration may be more effective in controlling post-operative pain. A review of the experimental animal and the clinical human studies on pre-emptive analgesia shows encouraging results. A question therefore arose: Could continuous Transcutaneous Electrical Nerve Stimulation (TENS) applied to the patients before, during and after surgery improve post-operative pain management in a manner similar to the use of pre-emptive analgesia by pharmacological intervention? In other words, will the
repeated application of TENS before, during and after surgery produce a cumulative inhibitory effect to reduce post-operative knee pain and improve range of motion of the knee joint? If so, it may reduce analgesic consumption, and even shorten the length of hospital stay.

5.3 Methods

5.3.1 Subjects

Forty-four patients, aged 65 to 90, admitted to the Queen Mary Hospital in Hong Kong to receive total knee replacement, were recruited according to the following inclusion criteria: male or female, receiving TKR of one or two knees, receiving no TENS for the previous 3 months, and not using a cardiac pacemaker. Subjects were not accepted if any of the following conditions existed: a previous tibial osteotomy, a history of septic osteoarthritis or osteomyelitis, a severe medical disability that limited the ability to walk, disabling disease involving other joints, inflammatory arthropathy and severe deformity of the lower extremities, and complications after surgery, e.g. infection, pulmonary and cardiac disorders. All the operation procedures were performed with a uniform technique under the same group of surgeons in the Department of Orthopedic, Queen Mary Hospital. (Please refer to Chapter 1 for more details of the surgical procedure for total knee replacement.) After surgery, each subject received a standard rehabilitation protocol for 2 weeks in the hospital administered by the same group of therapists. The age, gender, height and weight of each patient were recorded.
All patients were provided with an explanation of the purpose of the study and an opportunity to ask questions. They were given a detailed explanation of the experimental procedures verbally and through an "Informed Consent Form" which they signed. Subjects were assured that non-participation or withdrawal would not jeopardize their medical care. The study protocol, including the consent form, was approved by The Hong Kong Polytechnic University.

5.3.2 Treatment Procedures

The 44 patients were randomly allocated to one of two groups, TENS or placebo stimulation, with 22 per group. All patients were told that they might or might not feel the stimulation given.

TENS was applied with 200μs pulses at a frequency of 100 Hz. The intensity was adjusted for each subject to produce a strong but comfortable sensation, approximate 2 – 3 times sensory threshold intensity. For placebo stimulation, a placebo TENS machine looking identical to the real TENS unit but with the internal circuit disconnected by the manufacture was used. The apparatus was switched on and the investigator turned the intensity dial up. This was carried out so that the subject could see and believe that the apparatus was working.

Four sterile rubber electrodes (35 cm x 35 cm) connected to a TENS or placebo machine were placed on the four acupuncture points: Extra36, St35, Sp9 and Gb34, around each subject's operated knee joint after wound closure and before dressing the wound in the operation room by the same investigator. TENS or placebo stimulation was repeatedly applied to 4 acupoints of each patient's
knee joint for 60 min each session, 2 sessions daily, 3 days before, 1 day during and 6 days after total knee replacement surgery over a 10-day period (=20 sessions in total). If the patients received bilateral knee surgery, TENS or placebo was applied to the knee manifesting more severe pain before the operation.

5.3.3 Recording

5.3.3.1 Subjective Post-operative Knee Pain Intensity

Knee pain intensity was measured using a visual analogue scale (Fig. 2.3, Chapter 2). The patients were asked to rate their pain by moving the metal cursor along the VAS line to an appropriate point that represented the level of their pain intensities. The distance of the pointer from the left end marked with “no pain” was recorded for analysis. Patients were instructed to return the VAS cursor to the left end of the scale after each estimate, to prevent possible bias due to comparison with sequential stimuli.

The VAS scores of post-operative pain intensities were recorded on each day (from session\textsubscript{1} to session\textsubscript{12}) over a 6-day period after surgery. In each treatment session, the VAS scores were recorded at 30, 20 and 10 min before, 20, 40 and 60 min during and 20, 40 and 60 min after each TENS or placebo application. The VAS values obtained from each time interval were normalized with respect to the pre-stimulation baseline value.

5.3.3.2 Range of Knee Flexion
A transparent metal universal goniometer was used to measure the range of knee flexion (Fig. 2.5). The procedure of this measurement has been described in more details in Chapter 2. The range of knee flexion was measured and recorded daily, from session 1 to session 12, over the 6-day period after surgery. In each assessment session, the value of the range of knee flexion was recorded before and after TENS or placebo stimulation.

5.3.3.3 Analgesic Consumption

The analgesic approach to the patients for total knee replacement surgery was usually decided by the physical conditions of the patients. Patients might receive patient-controlled analgesia (PCA) morphine if they had general anesthesia (Fig. 2.5, Chapter 2), or epidural opioid infusion if they were given epidural anesthesia (Fig. 2.6, Chapter 2). Generally, on arrival in the ward, the PCA device was connected to the patient’s intravenous catheter. Alternately, an epidural catheter was placed in between L4,5. The PCA device was programmed to deliver morphine at 1 mg bolus doses on demand, with a minimum lockout interval of 5 min. Epidural fentanyl (3.3 μg/ml) was given when the patient had an epidural anesthesia. The epidural catheter was kept in the location at lumbar, 5. The rate of epidural fentanyl flow was adjusted, ranging from 5 to 15 ml/hour, according to the severity of post-operative pain as perceived by the patients. The PCA morphine consumption (mg) and the rate of epidural fentanyl infusion (ml/hour) at 6, 12 and 24 hours after total knee replacement were recorded in each patient.
5.3.3.4 “Length of Hospital Stay”

Our initial plan was to record the numbers of days when patients stayed in the hospital. In reality, there were many factors affecting the length of hospital stay. For example, the patients must wait to be transferred to another rehabilitation center when there were beds for them, even though they had already met the criteria for discharge. There were altogether 5 such criteria. The patient was able to (1) walk unaided on the ground for 15 min, (2) climb 2 or 3 flight of stairs, (3) flex their knees up to 90° with no flexion contracture, (4) have their muscle strength graded 4, and (5) be independent in self-care activities. Therefore, the numbers of days needed by the patients to reach the criteria for discharge as judged by the physician on duty, even they were not discharged, were recorded and termed here as the “length of hospital stay”.

5.3.4 Statistical Analysis

Four outcome measurements were recorded at the times indicated: (1) Subjective post-operative knee pain was measured at 30, 20 and 10 min before, 20, 40 and 60 min during and 20, 40 and 60 min after each TENS or placebo stimulation over a 6-day period after operation. (2) Range of knee flexion was evaluated with a transparent metal universal goniometer before and after each TENS or placebo stimulation over a 6-day period after operation. (3) Analgesic consumption including the patient-controlled analgesia morphine and the rates of epidural fentanyl infusion was recorded at 6, 12 and 24 hours after operation, and (4) the length of hospital stay was measured in terms of the days needed by the patients to reach the criteria for discharge. The data analysis included: (i) the
use of repeated measures ANOVA to analyze the difference of post-operative knee pain intensity, as measured by the VAS scores normalized with respect to the baseline value, between the TENS and placebo groups at the 9 time intervals in each treatment session. Three levels of time were the average of 3 ensembles averages obtained at 3 time intervals before TENS or placebo stimulation. Another 3 levels of time were the 3 ensembles averages obtained at the 3 time intervals separately during and after TENS or placebo stimulation. The same statistic method was also used to analyze the difference in the normalized VAS scores obtained before TENS or placebo stimulation in session, and across the 12 treatment sessions (6 days) after the operation. (ii) Next, repeated measures ANOVA was used to compare the difference in the normalized range of knee flexion at 2 time intervals (before and after TENS or placebo stimulation) between the two groups in each treatment session. This was followed by an analysis of the difference in the normalized range of knee flexion obtained before each TENS or placebo stimulation across the 12 treatment sessions (6 days) after operation. (iii) Paired t-test was used to analyze the difference in the doses of PCA morphine consumption and the rates of epidural fentanyl at 6, 12 and 24 hours after operation between the TENS and placebo groups. (iv) For the length of hospital stay in the days needed by the patients to reach the criteria for discharge, paired t-test was used to compare the means between the TENS and placebo groups. Significant levels in all statistical methods were set at $p=0.05$ with Bonferroni adjustment.

5.4 Results
5.4.1 Relevant Demographic Data

Forty-four patients with osteoarthritic knee pain participated in session. Two patients each from the TENS and placebo group dropped out due to medical problem; so that 42 patients completed the 20 treatment sessions, administered twice a day, 3 days before, 1 day during and 6 days after total knee replacement. Table 5.1 presented the relevant characteristics of these 42 patients who were randomly allocated to a TENS (n=21) or placebo group (n=21). The ages of patients were 70.1±S.D.7.8 yr. and 65.6±9.5 yr. respectively in the TENS and placebo groups. Their genders (F; M) were 15; 6 and 17; 4. Their weights were 62.6±11.8 and 61.5±13.2 kg, and their heights were respectively 152.3±10.1 and 151.3±9.1 cm. The patients had moderate knee pain before operation; the mean values of their VAS scores were 5.3±1.5 and 5.4±0.8 respectively in the TENS and placebo groups. The ranges of knee flexion measured before operation were 102.2±17.4 and 104.1±19.5 degrees respectively in the TENS and placebo groups. In each group, 12 had unilateral total knee replacement surgery, whereas 9 received bilateral surgery. Furthermore, 14 and 7 patients in each group received the analgesic routes by PCA morphine and epidural fentanyl infusion respectively. The operation times for the total knee replacement surgery were 180.3±64.7 and 166.6±60.7 min respectively in the TENS and placebo groups. In other words, the demographic data and other relevant variables were similar between the TENS and placebo groups.

5.4.2 Subjective Post-operative Knee Pain Intensity
In each treatment session, repeated measures ANOVA was used to analyze the difference in the normalized VAS scores of subjective post-operative knee pain intensity between the TENS and placebo groups at 9 levels of time. Significant differences were found when comparing the measurements among the 9 levels of time in each group (p=0.000), as well as combined group-time effect (p=0.000). In other words, an interaction was found between the two main factors of group and time. Due to the probability of an interaction effect, a contrast test was done to further compare the measurements obtained among the 9 levels of time within each group. An independent samples t-test was then used to compare the measurements between the two groups, and the alpha adjustment was set at p=0.006 (0.05/9).

On day 1 after surgery (session1), a significant between-group difference in the decrease of VAS scores was found at 20 min (p=0.003), 40 min (p=0.000) and 60 min (p=0.000) during, and at 20 min (p=0.001), 40 min (p=0.001) and 60 min (p=0.002) after TENS but not placebo stimulation (Fig. 5.1A). The pre-stimulation baseline VAS score of the TENS group gradually dropped from 100% to 83.3% (S.D.±14.9%) at 60 min during, and to 85.7% (±16.1%) at 20 min after TENS, with a gradual return to 94.3% (±7.8%) at 60 min after TENS (Table 5.2). These scores were significantly smaller than those recorded in the placebo group, which showed negligible changes from the baseline value.

On day 2 after surgery (session1), a significant between-group difference in the further reduction of the VAS scores of the post-operative knee pain intensity was demonstrated at 20 min (p=0.001), 40 min (p=0.000) and 60 min (p=0.000) during, and at 20 min (p=0.000), 40 min (p=0.001) and 60 min
(p=0.002) after TENS stimulation, when compared with that of placebo stimulation (Fig. 5.1B). The decrease to 59.3% (±22.0%) at 60 min during and to 66.7% (±20.1%) at 60 min after TENS stimulation was found to be significantly greater than the decrease to 87.6% (±20.6%) at 60 min during and to 84.9% (±14.8%) at 60 min after placebo stimulation (Table 5.2).

On day 4 after surgery (session_4), a further reduction was found in the VAS scores which dropped to 50.1% (±23.2%) at 40 min (p=0.001) during, to 48.2% (±22.9%) at 60 min (p=0.001) during, and to 52.0% (±22.4%) at 20 min (p=0.005) after TENS stimulation (Fig. 5.1C). These scores were significantly less than those recorded in the placebo group, which showed a decrease to 71.9% (±16.7%) at 40 min during, to 69.3% (±15.6%) at 60 min during, and to 69.9% (±16.1%) at 20 min after placebo stimulation (Table 5.2).

On day 6 after surgery (session_12), there was a further decrease of the VAS scores to 31.5% (±22.9%) before, 25.6% (±20.6%) at 60 min during, and 27.3% (±19.9%) at 60 min after TENS stimulation (Fig. 5.1D). These scores were significantly less than those recorded in the placebo group, which showed a decrease to 50.0% (±12.3%) before, 47.6% (±12.9%) at 60 min during and 47.5% (±13.2%) at 60 min after placebo stimulation. Indeed, the VAS scores recorded at all the 9 time intervals before, during and after stimulation were significantly more reduced in the TENS than the placebo group, with p value ranging from 0.000 to 0.003 (Table 5.2).

For across the sessions, repeated measures ANOVA was used to analyze the difference in the VAS scores obtained before TENS or placebo stimulation across the 12 treatment sessions (6 days) after total knee replacement. Significant
differences were found when comparing the measurements among the 6 levels of
days in each group (p=0.000), as well as combined group-time effect (p=0.000).
In other words, an interaction was found between the two main factors of group
and day (or session). Due to the probability of an interaction effect, a contrast test
was done to further compare the measurements obtained among the 6 levels of
days within each group. An independent samples t-test was then used to compare
the measurements between the two groups, and the alpha adjustment was set at
p=0.008 (0.05/6).

A cumulative decrease in the VAS score of the post-operative pain
intensity was found in the TENS group, from 100% obtained before treatment
session, to 31.5% obtained before treatment session12 (Table 5.2). This decrease
was significantly more than that found in the placebo group (p=0.002), which
showed a reduction of the VAS score obtained before treatment session12 to only
50.0% of the pre-stimulation value in session1.

5.4.3 Range of Knee Flexion

The means and standard deviations of the range of knee flexion on each
day after operation in the TENS and placebo groups were shown in Table 5.3.
The range of knee flexion before and after TENS application progressively
increased from 22.1±9.8 and 27.4±11.3 degrees on day 1, to 65.5±11.2 and
69.2±11.4 degrees on day 6. The range of knee flexion before and after placebo
application also progressively increased from 28.8±11.6 and 29.3±12.5 degrees on
day 1, to 64.5±10.4 and 65.9±10.0 degrees on day 6.
Each data point was then normalized with respect to the initial range of knee flexion on day 1 after operation (range of knee flexion / initial range of knee flexion x 100%). The difference in the normalized values of the range of knee flexion before and after TENS or placebo stimulation was then calculated (= after – before treatment), and presented in Table 5.3. One way ANOVA was used to compare the range of knee flexion before and after TENS or placebo across the different sessions within each group. An independent samples t-test was then used to analyze the (after – before) difference in the range of knee flexion between the TENS and placebo groups at a given session.

For within-group comparison, a significantly improved range of knee flexion was found after TENS when compared with before TENS in each of the 6 days after operation (Fig. 5.2A). The improvement in the knee flexion range before and after TENS was 5.2, 5.3, 5.0, 3.7, 4.5 and 3.6 degree respectively on each of 6 days after operation (Table 5.3). By comparison, a significantly improved range of knee flexion after placebo stimulation was found only on day 3 (p=0.020) and day 6 (p=0.024) (Fig.5.2B). The improvement in the knee flexion range before and after placebo stimulation was also smaller, being 1.1 and 1.4 degree on day 3 and 6 after operation (Table 5.3).

For between-group comparison, a significantly improved range of knee flexion before and after TENS stimulation was found on each of 6 days after operation, when compared with that of placebo stimulation (Table 5.3, Fig.5.2C), with the p values ranging from 0.000 to 0.006.

5.4.4 Analgesic Consumption
Twenty-eight patients were administered general anesthesia. The PCA morphine taken in the TENS (n=14) and placebo groups (n=14) were respectively 17.7±12.3 and 21.8±8.2 mg at 6 hours, 23.5±16.0 and 30.8±10.9 mg at 12 hours, and 30.6±19.1 and 51.3±29.8 mg at 24 hours after operation (Table 5.4). No significant differences were found in the PCA morphine consumption between the TENS and placebo groups at 6, 12 and 24 hours after operation, despite a trend for increased consumption in the placebo group.

Fourteen patients received epidural anesthesia. The epidural fentanyl was administered to these patients at different rates of infusion, ranging from 5 to 15 ml/hour. The rates of infusion in the TENS (n=7) and placebo groups (n=7) were respectively 7.7±1.5 and 7.7±1.0 ml/hour at 6 hours, 7.7±1.5 and 8.9±1.2 ml/hour at 12 hours, and 7.1±2.6 and 9.6±2.6 ml/hour at 24 hours after operation (Table 5.4). Again, no significant differences in the rates of epidural infusion at 6, 12 and 24 hours after operation were found between the 2 groups.

5.4.5 “Length of Hospital Stay”

No statistically significant difference was found in the number of days needed by the patients to reach the discharge criteria between the TENS and placebo groups (p=0.382). However, the TENS group showed a tendency to have a shorter stay than the placebo group, being 17.4±5.3 and 19.8±6.0 days respectively. In other words, the patients receiving repeated TENS stimulation reached the discharge criteria an average of 2.4 days earlier than those receiving placebo stimulation.
5.5 Discussion

5.5.1 Antinociceptive Effect of 60 min of TENS on Post-operative Knee Pain Intensity

Our findings showed a gradual onset and offset of TENS analgesic effects on the post-operative pain during and after a single session of TENS. A significant decrease of VAS scores at 20, 40 and 60 min during and at 20, 40 min and 60 min after TENS was found, when compared with the respective time intervals of placebo stimulation in the first day after operation. The VAS scores in the TENS group dropped gradually from 100% before stimulation to 83.3% (±14.9%) at 60 min during TENS. They gradually returned to 85.7% (±16.1%) and 94.3% (±7.8%) respectively at 20 min and 60 min after TENS (Table 5.2). In agreement with the findings by Cheing and Hui-Chan (1999) in patients with knee OA, TENS produced analgesic effects with a typical time course of gradual onset and offset on the post-operative pain in these patients as well.

In rats, Han and his co-investigators showed that the onset of TENS-induced analgesia was slow, with the pain threshold reaching a maximum (56-95% above the baseline) in approximate 20-30 minutes during stimulation (Han et al. 1989). This pain threshold gradually returned to the baseline value at 45 minutes after stimulation. In human studies, Liu and Chan (1993) found that 60 min of TENS to the low back significantly inhibited experimental electrical pain in normal subjects when compared with placebo stimulation (p<0.05). The analgesic effect also showed a gradual onset and offset, with the VAS score of the low back pain intensity decreased gradually to 91.7% of the baseline value during
and to 85.2% after TENS. Cheing and Hui-Chan (1999) further demonstrated that 60 min of TENS application to the acupoints around the knee joint produced a similar time course of analgesic effects on osteoarthritic knee pain. It reduced the VAS score from 100% before TENS, to 72.1% during, and to 63.1% (p<0.001) after TENS, in contrast to the negligible changes shown during and after placebo stimulation. The analgesic effect produced by TENS in these patients had a gradual onset (time to peak maximum inhibitory effect=60min) and offset (more than 60 min post-stimulation). Please refer to a discussion of the possible mechanisms for the gradual onset and offset of TENS analgesia in Chapter 3.

5.5.2 Cumulative Analgesic Effect of Repeated TENS Applications on Subjective Post-operative Knee Pain Intensity

Repeated TENS applications for 60 min, twice daily, 3 days before, 1 day during and 6 days after total knee replacement surgery, produced a marked decrease in the post-operative pain intensity in patients with knee OA. Briefly, the pre-stimulation VAS score decreased from 100% in session₁, to 31.5% in session₁₂. This decrease was significantly more than that produced by placebo stimulation, which reduced the post-operative VAS score from 100% in session₁, to 50.0% in session₁₂ (p=0.002).

Recent studies on daily TENS, repeated 5 times per week over a 2- to 4-week period, have shown that it produced cumulative inhibitory effect on chronic clinical pain. Briefly, Cheing and Hui-Chan (1996) reported that, in contrast to placebo stimulation, 2 weeks of TENS produced a decrease of 48.8% chronic low back pain (p<0.01). A subsequent study by the same investigators demonstrated
that the mean VAS score of osteoarthritic knee pain was decreased to 68.4% of
the control value after 2 weeks of TENS, and was further decreased to 54.1% after
4 weeks (Cheing and Hui-Chan 1998). More reduction in the VAS score (to
31.5%) of the post-operative knee pain after total knee replacement was
demonstrated in our study, when 60 min of TENS was applied twice daily for 12
sessions or 6 days after total knee replacement surgery. It should be noted that
TENS was actually started 3 days before, 1 day during and continued for the 6
days after surgery. Hence, TENS analgesic effects could have been cumulated
from the treatment administered before and during surgery (see below). The
medication for pain control after surgery would also have contributed to the better
analgesic effect seen in this study. Alternately, the different magnitude of pain
relief could be due to the different nature of pain: acute post-operative knee pain
in our study versus chronic pain of knee OA in the study by Cheing and Hui-Chan
(1998). Certainly, there is substantial evidence to show the elevation of pain
threshold in patient with chronic pain by other investigators (e.g. Defrin et al.
1999).

The effect of continuous pre-emptive administration of opioids has been
studied in surgical cases. This approach is based on the hypothesis that it will
prevent the central sensitization resulting from the continuous transmission of
sensory nociceptive stimuli after surgery. The underlying hypothesis requires that
an appropriate pharmacological intervention is applied before pain occurs, rather
than in response to it after its occurrence. The timing of the drug administration is
aimed to prevent the spinal cord from reaching a hyper-excitabale state that leads
to excessive response to afferent pain nerve impulses (Wassef 1998). In rat
experiments, various investigators have shown that pre-operative administration of opiates was more effective than post-operative administration, in reducing the excitability generated by experimental inflammation through neurophysiological recordings from rat dorsal horn neurons (Coderre et al. 1987, 1990, Dickenson 1987, Woolf and Wall 1986a,b). In human study, the dose of opiate required during the first 24 post-operative hours was reduced by 50% in the patients undergoing knee joint surgery, in whom femoral nerve block with 20 ml of 0.5% bupivacaine was given before rather than after surgery (Ringrose and Cross 1984). Along this line of thinking, TENS applied before, during and after surgery could have more effectively suppressed the development of post-operative pain or its persistence with time. The findings of this study are consistent with this proposition. As discussed in Chapter 4, the cumulative inhibitory effect of repeated TENS application could also be explained by an increase in the release of endogenous opioids (Luo et al. 1996), or possible plastic changes in the nervous system (Romita et al. 1997).

5.5.3 Placebo effect?

Pre-stimulation VAS scores decreased from 100% in session, to 50% (±12.3%) in session, of placebo stimulation 6 days after surgery. While spontaneous pain reduction certainly occurred over the post-operative period, placebo effects could not be entirely ruled out without a real control group in our design. This is because placebo analgesia has been demonstrated and can at least partly be explained by the release of endorphins (Levin et al. 1979) or non-opioids via e.g. the adrenergic pathways (Amanzio and Benedetti 1999). It could also be
the result of an interaction between the neural changes induced by the experience of receiving placebo stimulation and the learning effect of being treated (Fields and Price 1997).

Thorsteinsson et al. (1978) reported that 30% of clinical improvement could be explained by placebo effects. Aside from spontaneous recovery, the higher placebo analgesic effect demonstrated in our study could be further attributed to a drug effect (morphine or fentanyl administration). It could also be associated with other factors such as learning and memory. Age, diagnosis, variation in subject groups, study design, therapist and patient relationship or culture differences may all contribute to the extent of placebo response and spontaneous recovery. Despite the findings of a possible placebo effect in our study, it is noteworthy that the effects of real TENS stimulation were significantly more than those of placebo stimulation.

5.5.4 Effect of Repeated TENS on Range of Knee Flexion

The results demonstrated a significant improvement in the range of knee flexion after 60 min of TENS application on each post-operative day, and across the 6 post-operative days when compared with placebo stimulation. The effect of repeated TENS applications on the improvement of knee mobility after TENS could partly be due to a significant cumulative inhibitory effect of repeated TENS on the post-operative knee pain, thereby improving knee range. Furthermore, TENS at an intensity of 2-3 times the sensory threshold has been shown by Levin and Hui-Chan (1993) to activate large diameter Aαβ fibers. These fibers are known to consist of two major components, sensory and motor (Wall and
Melzack 1994). Thus, the significant improvement in knee flexion demonstrated in this study could be, at least partly, explained by activation of the large motor fibers by TENS. Active mobilization, which usually commenced at 24 hours post-surgery, might also play a major role. It included assisted and active exercises for the knee muscles, getting out of bed, plus standing and walking with a frame under the supervision of a therapist. Any increase in the power of knee muscles and other joint muscles of the lower extremities could enhance knee mobility during walking.

5.5.5 Effect of Repeated TENS on Analgesic Consumption

The results showed no significant differences in PCA morphine consumption and the rates of epidural fentanyl infusion at 6, 12 and 24 hours between the patients in the TENS and placebo groups after total knee replacement.

Using analgesic consumption as an outcome measure, Wang and his co-investigators (1997) demonstrated a significant analgesic effect of transcutaneous acupoint electrical stimulation, applied to the patients after abdominal surgery for 30 min every 2 hours on the first day. The frequency of stimulation was set in the standard dense-and-disperse mode, alternating electrical stimulation at 2 Hz and 100 Hz every 3s. The post-operative PCA morphine consumption at 8-16 hours and the total amount in 24 hours were respectively 15±15mg and 52±46mg in the placebo group (n=25), which was significantly more than 5±4mg and 21±11mg in the stimulation group (n=25).
In this study, the post-operative PCA morphine consumption in the TENS and placebo groups were respectively 23.5±16.0 and 30.8±10.9 mg at 12 hours after operation, and 30.6±19.1 and 51.3±29.8 mg at 24 hours after operation. Although there was no statistically significant difference in the morphine consumption between the TENS and placebo groups, the placebo group tended to receive more morphine, respectively by 7.3 mg (30.8 – 23.5 mg) and 21.3 mg (51.3 – 30.6 mg) at 12 and 24 hours after operation. When comparing with the results by Wang et al. (1997), there was more post-operative PCA morphine consumption in our study. The difference could be partly due to the 2 different types of surgery, abdominal surgery versus total knee replacement. Since older patients who had undergone total knee replacement were more likely to report intense pain when compared with other orthopedic and abdominal surgeries (Hall-Lord et al. 1999, Wilkie et al. 1990), these patients may need more pain medication, e.g., morphine, to obtain relief from the more intense post-operative pain. The different races of population (Chinese in our study versus American in the study by Wang et al.), patient’s background, different knowledge of pain medication, or sample size may have contributed to the negative results in our study.

5.5.6 Effect of Repeated TENS on “Length of Hospital Stay”

Because health care expenditure is escalating, there is an increasing need to decrease the cost of health care while maintaining quality. The length of hospital stay was considered one of the important indicators in the cost of health care and various measures have been taken to shorten it.
Major medial expenses for total knee replacement surgery include the prosthesis, anesthesia/operating room, and nursing/hospital room (Meyer et al. 1996). Meyer and co-investigators (1996) reported that the average total medical cost was $12,561±2,596 for 87 patients who had undergone total knee replacement in one American hospital, from 1991 to 1992. Among the total medical cost, prosthesis represented 29% of the cost, anesthesia/operating room represented 21%, and nursing/hospital room represented 23%. These investigators found a strong linear relationship between the total medical cost and the length of hospital stay. If certain costs can be standardized, especially with regard to the prosthesis, the total cost is then directly correlated with the length of hospital stay (Sommers et al. 1990). Tidswell (1998) remarked that the length of hospital stay depends on the patient’s capabilities, their safety in mobilization, the range of motion achieved at the knee joint and the absence of any complications.

The Hong Kong Authority reported that the average medical cost for the total knee replacement surgery, from 1997 to 1999, was about HK$ 3,100 per patients per day. Our study showed that the patients receiving repeated TENS stimulation tended to be discharged an average of 2 days earlier than the patients receiving placebo stimulation. Possible saving was therefore HK$ 6,200 (= HK$ 3,100 x 2 days) per patient. According to a report by the Queen Mary Hospital, about 100 patients will receive total knee replacement every year. If so, the total amount saved will be HK$ 62,000 (= HK$ 6,200 x 100 patients) in one hospital in Hong Kong each year. Therefore, TENS, a simple, economic and non-invasive approach could provide a simple means to reduce the cost of medical care expenditure through a tendency towards shortened hospital stay.
5.6 Limitations of this study

First, no control group was included in the design of this study. A control group is important to assess possible placebo effects through a comparison of the different effects between the control and placebo groups. The initial plan did involve a control group in our study design, but some factors, in particular, the ethical issue and difficulty in patient recruitment, resulted in failure to include this group in my Ph.D. study due to its inherent time limitation. Secondly, pre-emptive and repeated TENS or placebo stimulation was applied to the patients before, during and after total knee replacement. To determine the pre-emptive (and continuous cumulative) inhibitory effect of TENS on post-operative pain, it is necessary to add two more groups receiving post-operative TENS and placebo stimulation. Finally, it is desirable to conduct a multi-center trial to determine the generalization of the present findings in the Queen Mary Hospital to other institutions, where different surgical approaches could have been adopted for total knee replacement. Neither of the latter two limitations was addressed due to the reasons presented above.

5.7 Conclusion

The findings from the main study of the thesis show that TENS applied for 60 min, 2 times each day for 10 days (3 days before, 1 day during and 6 days after total knee replacement), reduced post-operative knee pain and improved knee flexion range significantly more than placebo stimulation. Furthermore, patients receiving repeated TENS applications tended to reach the criteria for discharge 2
days earlier on the average than those receiving placebo application. These findings unequivocally demonstrated that TENS application to acupoints before, during and after total knee replacement produced significant beneficial effects in patients with osteoarthritic knee pain, in terms of a significant improvement in their sensori-motor functions and possible saving garnered from a tendency towards shortened hospital stay.⁴

⁴ Note: Part of this chapter will be submitted:

Wang Ninghua and Hui-Chan Christina W.Y. “Pre-emptive and continue transcutaneous electrical nerve stimulation (TENS) improve the management post-operative knee pain”. Anesthesiology
Table 5.1 A comparison of the patient characteristics between TENS and placebo groups

<table>
<thead>
<tr>
<th></th>
<th>TENS group (n=21)</th>
<th>Placebo group (n=21)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td>17</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>70.1±7.8</td>
<td>65.6±9.5</td>
<td>.094</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>62.6±11.8</td>
<td>61.5±13.2</td>
<td>.783</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>152.3±10.1</td>
<td>151.3±9.1</td>
<td>.733</td>
</tr>
<tr>
<td><strong>Gender (F;M)</strong></td>
<td>15;6</td>
<td>17;4</td>
<td>.197</td>
</tr>
<tr>
<td><strong>VAS scores (x/10)</strong></td>
<td>5.3±1.5</td>
<td>5.4±0.8</td>
<td>.847</td>
</tr>
<tr>
<td><strong>Range of knee flexion (degree)</strong></td>
<td>102.2±17.4</td>
<td>104.1±19.5</td>
<td>.746</td>
</tr>
<tr>
<td><strong>TKR</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>One side</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Two side</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td><strong>Analgesic routes</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PCA</td>
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<td>14</td>
<td></td>
</tr>
<tr>
<td>Epidural infusion</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>Operation time (min)</strong></td>
<td>180.3±64.7</td>
<td>166.6±60.7</td>
<td>.481</td>
</tr>
</tbody>
</table>

Values are means±S.D.

* indicates the p value when the relevant data were compared between TENS and placebo groups using independent t-test.
Table 5.2 A comparison the post-operative knee pain intensity between TENS (n=21) and placebo (n=21) groups on each day for 6 post-operative days

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th></th>
<th></th>
<th>During</th>
<th></th>
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<th>After</th>
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</thead>
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<tr>
<td></td>
<td>20 min</td>
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<td>0 min</td>
<td>20 min</td>
<td>40 min</td>
<td>60 min</td>
<td>20 min</td>
<td>40 min</td>
</tr>
<tr>
<td>TENS</td>
<td>8.3±1.8</td>
<td>8.4±1.8</td>
<td>8.4±1.8</td>
<td>7.4±2.0</td>
<td>6.9±2.3</td>
<td>6.9±2.4</td>
<td>7.2±2.2</td>
<td>7.5±2.0</td>
</tr>
<tr>
<td>(100±0.0)</td>
<td>(100.7±1.4)</td>
<td>(100.3±2.3)</td>
<td>(89.3±15.3)</td>
<td>(82.7±17.6)</td>
<td>(83.3±14.9)</td>
<td>(85.7±16.1)</td>
<td>(89.5±13.1)</td>
<td>(94.3±7.8)</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.2±1.8</td>
<td>8.3±1.8</td>
<td>8.3±1.8</td>
<td>8.2±1.8</td>
<td>8.2±1.8</td>
<td>8.2±1.9</td>
<td>8.2±1.8</td>
<td>8.3±1.8</td>
</tr>
<tr>
<td>(100±0.0)</td>
<td>(101.0±2.4)</td>
<td>(101.4±3.6)</td>
<td>(100.8±5.1)</td>
<td>(100.8±4.9)</td>
<td>(100.5±4.8)</td>
<td>(101.0±4.8)</td>
<td>(101.0±4.4)</td>
<td>(100.8±3.3)</td>
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<tr>
<td>p value</td>
<td>0.599</td>
<td>0.231</td>
<td>0.003*</td>
<td>0.000*</td>
<td>0.000*</td>
<td>0.001*</td>
<td>0.001*</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

| #3 - Day 2 |
| TENS      | 6.0±1.9| 6.0±1.9| 6.0±1.9| 5.4±2.0| 5.1±2.1| 4.9±2.1| 5.0±2.0| 5.3±2.0| 5.5±1.9|
| (73.0±20.5) | (73.3±20.2) | (72.9±20.6) | (65.4±19.4) | (60.7±20.4) | (59.3±22.0) | (61.3±21.9) | (64.0±20.3) | (66.7±20.1) |
| Placebo   | 7.1±1.6| 7.2±1.5| 7.5±1.5| 6.9±1.6| 7.1±1.6| 7.1±1.7| 7.1±1.6| 6.9±1.7| 6.9±1.6|
| (87.6±18.0) | (88.7±17.9) | (88.6±17.7) | (85.2±15.9) | (87.9±20.6) | (87.6±20.6) | (87.7±18.2) | (85.6±16.9) | (84.9±14.8) |
| p value   | 0.019  | 0.013  | 0.012  | 0.001* | 0.000* | 0.000* | 0.001* | 0.001* | 0.002* |

| #7 - Day 4 |
| TENS      | 5.1±1.9| 5.1±1.9| 5.1±1.9| 4.4±1.9| 4.1±2.0| 3.9±2.0| 4.2±1.9| 4.3±1.9| 4.5±1.9|
| (63.6±23.9) | (63.0±23.2) | (63.1±23.4) | (54.3±24.5) | (50.1±23.2) | (48.2±22.9) | (52.0±22.4) | (54.0±22.2) | (56.6±25.3) |
| Placebo   | 5.7±1.6| 5.8±1.5| 5.8±1.6| 5.7±1.5| 5.8±1.6| 5.7±1.6| 5.7±1.5| 5.8±1.6| 5.7±1.6|
| (70.6±16.1) | (71.8±16.7) | (71.2±17.6) | (70.4±17.1) | (71.9±16.7) | (69.3±15.6) | (69.9±16.1) | (71.8±17.6) | (70.7±17.0) |
| p value   | 0.268  | 0.165  | 0.212  | 0.018  | 0.001* | 0.001* | 0.005* | 0.007  | 0.041  |

| #12 - Day 6 |
| TENS      | 2.5±1.9| 2.4±1.9| 2.4±1.9| 2.1±1.8| 2.0±1.7| 2.1±1.8| 2.0±1.7| 2.1±1.6| 2.2±1.7|
| (31.5±22.9) | (30.8±22.0) | (31.0±22.3) | (26.2±21.1) | (25.1±19.8) | (25.6±20.6) | (25.3±20.7) | (27.0±20.2) | (27.3±19.9) |
| Placebo   | 4.1±1.2| 4.0±1.2| 4.0±1.1| 3.8±1.1| 3.9±1.1| 3.8±1.1| 3.7±1.2| 3.9±1.2| 3.8±1.2|
| (50.0±12.3) | (49.8±12.3) | (49.7±12.6) | (47.6±12.6) | (47.8±11.2) | (47.6±12.9) | (44.9±12.8) | (47.8±13.5) | (47.5±13.2) |
| p value   | 0.003* | 0.002* | 0.002* | 0.000* | 0.000* | 0.000* | 0.001* | 0.000* | 0.000* |

p value of session b 0.002*

Values are means ± S.D., normalized with respect to the initial VAS score (VAS score / initial VAS score x 100)

a indicates the p values when the VAS scores were compared before, during and after treatment between the TENS and placebo groups using independent t-test, with the alpha adjustment set at p = 0.006 (0.05/9).

b indicates the p values when the VAS scores obtained before treatment in session, were compared with that obtained in session 12 between the TENS and placebo groups

* denotes that the p value reached a significant level
Table 5.3 Summary of the range of knee flexion (degree) before and after TENS (n=21) or placebo (n=21) stimulation on each of the 6 post-operative days

<table>
<thead>
<tr>
<th>Flexion</th>
<th>#1 – Day1</th>
<th>#3 – Day2</th>
<th>#5 – Day3</th>
<th>#7 – Day4</th>
<th>#9 – Day5</th>
<th>#12 – Day6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TENS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>22.1±9.8</td>
<td>34.7±11.8</td>
<td>44.8±11.7</td>
<td>52.1±12.4</td>
<td>60.2±11.9</td>
<td>65.5±11.2</td>
</tr>
<tr>
<td>(100.0%)</td>
<td>(179.9%)</td>
<td>(239.2%)</td>
<td>(282.8%)</td>
<td>(327.4%)</td>
<td>(359.7%)</td>
<td>(359.7%)</td>
</tr>
<tr>
<td>After</td>
<td>27.4±11.3</td>
<td>40.1±13.1</td>
<td>49.9±12.6</td>
<td>55.9±11.9</td>
<td>64.8±12.1</td>
<td>69.2±11.4</td>
</tr>
<tr>
<td>(125.1%)</td>
<td>(205.9%)</td>
<td>(266.3%)</td>
<td>(300.4%)</td>
<td>(349.9%)</td>
<td>(378.3%)</td>
<td>(378.3%)</td>
</tr>
<tr>
<td>Difference (%)</td>
<td>5.2±2.5</td>
<td>5.3±8.2</td>
<td>5.0±3.5</td>
<td>3.7±2.7</td>
<td>4.5±3.4</td>
<td>3.6±2.3</td>
</tr>
<tr>
<td>p-value&lt;sup&gt;a&lt;/sup&gt;</td>
<td>.000*</td>
<td>.010*</td>
<td>.000*</td>
<td>.000*</td>
<td>.001*</td>
<td>.001*</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>28.8±11.6</td>
<td>40.1±9.5</td>
<td>46.6±12.0</td>
<td>54.5±9.6</td>
<td>60.3±11.1</td>
<td>64.5±10.4</td>
</tr>
<tr>
<td>(100.0%)</td>
<td>(156.0%)</td>
<td>(186.0%)</td>
<td>(217.7%)</td>
<td>(243.3%)</td>
<td>(262.4%)</td>
<td>(262.4%)</td>
</tr>
<tr>
<td>After</td>
<td>29.5±12.5</td>
<td>40.0±9.5</td>
<td>47.7±11.8</td>
<td>55.1±9.1</td>
<td>60.6±10.5</td>
<td>65.9±10.0</td>
</tr>
<tr>
<td>(102.0%)</td>
<td>(155.7%)</td>
<td>(189.6%)</td>
<td>(219.8%)</td>
<td>(243.6%)</td>
<td>(267.4%)</td>
<td>(267.4%)</td>
</tr>
<tr>
<td>Difference (%)</td>
<td>0.7±2.1</td>
<td>-0.3±1.6</td>
<td>1.1±1.6</td>
<td>0.6±2.0</td>
<td>0.2±1.6</td>
<td>1.4±1.2</td>
</tr>
<tr>
<td>p-value&lt;sup&gt;b&lt;/sup&gt;</td>
<td>.139</td>
<td>.833</td>
<td>.020*</td>
<td>.214</td>
<td>.514</td>
<td>.024*</td>
</tr>
<tr>
<td>p-value&lt;sup&gt;c&lt;/sup&gt;</td>
<td>.000*</td>
<td>.006*</td>
<td>.000*</td>
<td>.000*</td>
<td>.001*</td>
<td>.012*</td>
</tr>
</tbody>
</table>

Values are means ± S.D.
Values in ( ) were normalized with respect to the initial range of knee flexion on day 1 after operation (Range of knee flexion / initial range of knee flexion x 100%).
Difference = after – before TENS or placebo stimulation.

For within-group comparison,
- <sup>a</sup> denotes the p values when the normalized values were compared within the TENS group using one way ANOVA.
- <sup>b</sup> indicates the p values when the normalized values were compared within the placebo group using one way ANOVA.

For between-group comparison,
- <sup>c</sup> denotes the p values when the (after – before) difference in the knee flexion range was compared between the TENS and placebo groups, using independent t-test.
- * denotes that the p value reached a significant level.
Table 5.4 A Comparison of PCA morphine (mg) and the rate of epidural fentanyl infusion (ml/hour) at 6, 12, 24 hours between TENS and placebo groups

<table>
<thead>
<tr>
<th></th>
<th>6 hours</th>
<th>12 hours</th>
<th>24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCA morphine (mg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TENS n=14</td>
<td>17.7±12.3</td>
<td>23.5±16.0</td>
<td>30.6±19.1</td>
</tr>
<tr>
<td>Placebo n=14</td>
<td>21.8±8.2</td>
<td>30.8±10.9</td>
<td>51.3±29.8</td>
</tr>
<tr>
<td>p value&lt;sup&gt;a&lt;/sup&gt;</td>
<td>.303</td>
<td>.170</td>
<td>.129</td>
</tr>
<tr>
<td><strong>Epidural fentanyl</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ml/hr.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TENS n=7</td>
<td>7.7±1.5</td>
<td>7.7±1.5</td>
<td>7.1±2.6</td>
</tr>
<tr>
<td>Placebo n=7</td>
<td>7.7±1.0</td>
<td>8.9±1.2</td>
<td>9.6±2.6</td>
</tr>
<tr>
<td>p value&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00</td>
<td>.143</td>
<td>.109</td>
</tr>
</tbody>
</table>

<sup>a</sup> indicates the p value when the PCA morphine consumption was compared between the TENS and placebo groups using independent t-test.

<sup>b</sup> denotes the p value when the rate of epidural fentanyl was compared between the TENS and placebo groups using independent t-test.
(A): In session₁, a significant decrease of VAS scores was found at 20 min (p=.003), 40 min (p=.000) and 60 min (p=.000) during, and at 20 min (p=.001), 40 min (p=.001) and 60 min (p=.002) after TENS when compared with that of placebo stimulation.

(B): In session₂, a significant further reduction in the VAS scores at 20 min (p=.001), 40 min (p=.000) and 60 min (p=.000) during, and at 20 min (p=.000), 40 min (p=.001) and 60 min (p=.002) after TENS was demonstrated when compared with that of placebo stimulation.

(C): In session₇, a significant further reduction was found in the VAS scores at 40 min (p=.001) and 60 min (p=.001) during and at 20 min (p=.005) after TENS when compared with that of placebo stimulation.

(D): In session₁₂, there was a significant decrease of the VAS scores before, during and after treatment in the TENS than in the placebo group at all the 9 time intervals.
Fig. 5.2

(A): A significantly improved range of knee flexion was found within the TENS group on each of 6 days.

(B): A significantly improved range of knee flexion was found within the placebo group only on day 3 (p=0.020) and on day 6 (p=0.024).

(C): For between-group comparison, a significantly improved range of knee flexion before and after TENS was found on each day when compared with that of placebo stimulation.

* denotes significant difference in the range of knee flexion, n.s. 0.05/5=0.01

** denotes significant difference in the range of knee flexion, p≤0.01
CHAPTER 6

SUMMARY AND CONCLUSION
6.1 Introduction

Recent studies showed that TENS produced cumulative analgesic effects on the intensity of different types of pain. Briefly, Liu and Hui-Chan (1994) demonstrated that 60 min of TENS, repeated 5 times a week for 2 weeks, led to a decrease of 30% in electrically induced pain in young normal subjects. Cheing and Hui-Chan (1996) found that the same TENS protocol produced a decrease of 48.8% pain in patients with chronic low back pain. They further demonstrated that 2 weeks of TENS resulted in a decrease of 32.6% of knee OA pain, and that 4 weeks of TENS led to a further decrease (45.9%) of pain in older patients with chronic knee pain (Cheing and Hui-Chan 1998). The treatment protocol used in the above studies involved the application of TENS or placebo stimulation for 60 min, 5 times a week over a 2- to 4-week period. It should be noted that no study to-date has investigated the possible cumulative analgesic effect of repeated TENS applications on acute thermal pain, or more importantly, the use of pre-emptive and continued daily TENS on the post-operative pain after total knee replacement. This thesis set out to investigate these issues through of three inter-related studies with the following objectives.

The first objective of our study is to determine if the inhibitory effect of TENS applied to the acupuncture points, was specific to pain as measured by the heat pain threshold, when compared with tactile sensibility as measured by the vibration threshold. Second, we set out to examine whether repeated TENS applications to the acupoints produced more cumulative analgesic effects on the heat pain threshold in the older normal subjects than placebo stimulation. Finally, we tried to determine if repeated TENS applications to the acupoints before,
during and after total knee replacement surgery improved the post-operative pain management, in a manner similar to the use of pre-emptive and continuous opioid analgesia. Specifically, we attempted to delineate whether repeated TENS applications could exert cumulative inhibitory effects on the post-operative pain intensity, improve the range of knee flexion, reduce the analgesic consumption, and shorten the length of hospital stay more than placebo stimulation.

6.2 Methods

Study 1. Twenty young normal subjects, aged 20 to 39, participated in this study. They were randomly allocated to a TENS or placebo group. Thirty minutes of conventional TENS (200μs pulses at 100 Hz and 2-3 times sensory threshold) or placebo stimulation was applied to the acupuncture point (LI4) on each subject’s hand. Heat pain and vibration thresholds were measured using the Medoc TSA-2001 and the VSA-3000 respectively on the thenar eminence of each subject’s left hand. Both threshold measurements were performed at 10 min intervals, namely 30, 20 and 10 min before and 0, 10, 20, 30, 40 and 50 min after 30 min of TENS or placebo stimulation. Repeated measures ANOVA was used to analyze the data obtained at the differences time intervals (3 before and 6 after each TENS or placebo stimulation) between the two groups.

Study 2. Nineteen older normal subjects, aged 60 to 85, participated in this study. All the subjects were randomly allocated to a TENS or placebo group. Sixty minutes of TENS (200μs in pulses at 100 Hz with 2 – 3 times sensory threshold intensity) or placebo stimulation was applied to four acupoints: Extra36, Gb34, Sp9 and St35 around the knee joint twice daily over a 3-day period (=6
sessions in total). Heat pain threshold was measured at 30, 20 and 10 min before, 20, 40 and 60 min during, and 10, 20, 30, 40, 50 and 60 min after 60 min of TENS or placebo stimulation in session. It was also measured before and after TENS or placebo stimulation in the other 5 sessions, from session to session. For analyzing the effect of a single session, repeated measures ANOVA was used to analyze the difference in the heat pain threshold measured at 10 time intervals (1 time before, 3 times during and 6 times after TENS or placebo stimulation) in session. For analyzing the cumulative effect across sessions, repeated measures ANOVA was also used to analyze the difference in the pre-stimulation heat pain thresholds obtained in session, and session between the TENS and placebo groups.

**Study 3.** This study was carried out in 42 patients, aged 50 to 85, who were undergoing total knee replacement surgery. All the patients were randomly allocated to a TENS or placebo group. Sixty minutes of TENS (200µs pulses at 100 Hz with 2-3 times sensory threshold) or placebo stimulation was applied to 4 acupuncture points (Extra 36, St35, Sp9 and Gb34) around the knee joint, 2 times each day, 3 days before, 1 day during, and 6 days after surgery (= 20 sessions in total). Four outcome measurements were recorded: (1) subjective post-operative knee pain intensity, (2) range of knee flexion, (3) analgesic consumption and (4) length of hospital stay, defined as the number of days needed by the patients to reach the discharge criteria of the hospital. Repeated measures ANOVA was used to analyze the differences in the means of the following 2 values obtained before each treatment session between the TENS and placebo groups: (1) post-operative pain intensity measured by VAS and (2) range of knee flexion. Paired t-test was
used to analyze the difference in the doses of PCA morphine consumption and the rates of epidural fentanyl infusion at 6, 12 and 24 hours after operation between the 2 groups. The length of hospital stay was measured as the number of days needed by the patients to reach the discharge criteria; and paired t-test was used to compare the means between the TENS and placebo groups. Significant levels in all the statistical methods were set at $p=0.05$ with Bonferroni adjustment.

6.3 Results

Study 1. Our findings showed a significant increase in heat pain threshold by $0.8^\circ C$ and $1.5^\circ C$ respectively at 0 ($p=0.002$) and 20 min ($p=0.004$) after 30 min of TENS application to the LI4 acupoint in the young normal subjects, when compared with that of placebo stimulation. In contrast, no significant difference in vibration threshold was found between the TENS and placebo groups.

Study 2. In session 1, a significant increase in the heat pain threshold at 20 ($p=0.016$), 30 min ($p=0.007$) and 40 min ($p=0.005$) after TENS was found in the TENS group, in contrast to the negligible effects in the placebo group. Furthermore, the inhibitory effects on the heat pain threshold in the older normal subjects manifested a gradual onset and offset. By the finish of 6 treatment sessions, a significant increase in the pre-stimulation heat pain threshold was found, from $46.9^\circ C$ in session 1 to $48.6^\circ C$ in session 6, or by $1.7^\circ C$ in the TENS group ($p=0.007$), but not in the placebo group or between groups. Though the latter difference approached statistical significant.

Study 3. Our results showed that (1) 60 min of TENS application in session 1 produced a significant decrease of the post-operative knee pain intensity
during and after TENS, when compared with that of placebo stimulation ($p=0.000$ to $0.003$). Briefly, the baseline VAS score in the TENS group gradually dropped from 100% to 83.3% ($p=0.000$) at 60 min during, to 85.7% ($p=0.001$) and 94.3% ($p=0.002$) at 20 and 60 min after TENS, in contrast to the negligible changes shown during and after placebo stimulation. By the completion of 12 treatment sessions after the surgery, there was a further decrease to 31.5% before, 25.6% at 60 min during and 27.3% at 60 min after TENS application. These scores were significantly less than those recorded in the placebo group, which showed a decrease to 50.0% ($p=0.003$) before, 47.6% ($p=0.000$) at 60 min during and 47.5% ($p=0.000$) at 60 min after placebo stimulation. (2) Furthermore, a significant increase in the range of knee flexion was found between the TENS and placebo groups on each of the 6 days after operation ($p=0.000$ to 0.012). (3) However, no statistical difference in the analgesic consumption – either in the PCA morphine taken or in the rate of epidural fentanyl infusion, was found between the TENS and placebo groups. (4) A final finding was that the patients receiving repeated TENS tended to reach the hospital discharge criteria 2 days earlier than those receiving placebo stimulation, though the difference was not statistically different.

6.4 Conclusion

(1) In contrast to placebo stimulation, 30 min of TENS to the LI4 acupoint specifically increased the heat pain but not the vibration threshold in the young normal subjects. This result demonstrated that, like acupuncture, the effect of TENS on the acupoint is to reduce pain but not tactile (specifically vibration)
sensibility. In other words, TENS could inhibit the transmission of nociceptive information through the small diameter fibers, but not that of tactile sensation (vibration) through the large diameter fibers. Our finding suggest that TENS on acupoints would be preferable to needle acupuncture, by virtue of its non-invasive nature. (2) A single session of 60 min of TENS produced inhibitory effects on the heat pain threshold in the older normal subjects with a gradual onset and offset, similar that produced by to 30 min of TENS in the young normal subjects. Furthermore, repeated TENS application to the acupoints around the knee joint, for 60 min twice daily for 3 days, produced a cumulative antinociceptive effect on the heat pain threshold in the older normal subjects. Our results further showed that the difference in the heat pain threshold after treatment in session, between the TENS and placebo groups was almost but not yet significant (p=0.027). This finding suggested that application of TENS twice daily for more than 6 sessions may bring about a real between-group difference. (3) Indeed, TENS applied for 60 min, 2 times each day for 10 days (3 days before, 1 day during and 6 days after total knee replacement), reduced the post-operative knee pain and improved the knee flexion range significantly more than placebo stimulation. The existence of such a cumulative antinociceptive effect, as denoted by a significant decrease in the post-operative knee pain intensity obtained prior to treatment in session, after surgery, suggested possible plastic changes in the nervous system. It is noteworthy that the effects of real afferent stimulation via TENS were significantly more than those of placebo stimulation. In additions, patients receiving repeated TENS applications tended to reach the discharge criteria 2 days earlier on the average than those receiving placebo application. These findings
unequivocally demonstrated that TENS applications to the acupoints before, during and after total knee replacement produced significant beneficial effects to the patients with knee OA pain after the surgery, in terms of a significant improvement in their sensori-motor functions and possible saving garnered from a tendency towards shortened hospital stay.
References


(32) Cheing, G., & Hui-Chan, C.W.Y. "Repeated application of transcutaneous electrical nerve stimulation (TENS) produce cumulative effects on chronic


(294) Weller, R., Rosenblum, M., Conard, P., & Gross, J.B. “Comparison of epidural and patient-controlled intravenous morphine following joint


(316) Zoppi, M., Froncini, F., Maresca, M., & Procacci, P. "Changes of cutaneous sensory thresholds induced by non-painful transcutaneous
Appendix 1

The Hong Kong Polytechnic University
Department of Rehabilitation Sciences
Informed consent Form

**Project entitled:** Can Pre-emptive and Continuous Transcutaneous Electrical Nerve Stimulation Improve Post-operative Knee Pain?

**Investigators:** Ms Wang Ninghua, Prof. Christina W.Y. Hui-Chan, Dr. W Y Chiu

---

1. **Purpose and Design of the Study**

The purpose of this study is to investigate the effect of TENS on postoperative knee pain including subjective pain perception and heat pain threshold measured using Thermal Sensory Analyzer (TSA 2001), range of movement of knee joint, analgesic intake, and length of hospital stay when TENS is repetitively applied to the patients before, during and after Total Knee Replacement (TKR).

I understand that I will be assigned by chance to one of two groups. The results of each group will be unknown to me throughout the length of the study. Depending on the group that I am assigned to, I may receive either (1) standard TENS (2) sham TENS. It will cost me approximately 30 minutes, 2 times per day to receive TENS or sham TENS treatment before 3 days, during 1 day and after 5
days total knee replacement at the department of Orthopedic in the Queen Mary Hospital.

Before, during and after each treatment, I will register the intensity of my knee pain on a pain scale when resting and standing and the knee range of motion including passive and active. Analgesics intake will be measured at 3, 6, 12, 24, 48, 72 in completion of surgery. The total time required for each of treatment and assessment will be about 1.5 hour. During the study period, I agree to keep routine daily activity.

2. Advantages of Participation in the Study

I understand that I may experience postoperative knee pain relief, less analgesics and/or early discharged. However, I may receive no benefit from participating in the study if I do not respond to the treatment. Nevertheless, the results of this study will tell us whether repeated applications of TENS will produce relief of postoperative knee pain that will accumulate over time.

3. Disadvantages of Participation in the Study

The above treatment and testing produces have been well clinically and experimentally used and approved a safety method with no major side effect. I have been told that a few subjects may have temporary mild skin irritation to the conducting gel in the electrode used for TENS stimulation. Anti-irritation cream will be curable in one or two days.
4. Inquires Concerning the Study

I understand that all the questions about this study will be answered by Ms Wang Ninghua and/or Prof. Hui-Chan who can be reached at the Department of Rehabilitation Sciences, The Hong Kong Polytechnic University located at Hung Hom, Kowloon, or by telephone at 27667092 and 27666704.

5. Withdrawal from the Study and Confidentiality

I understand that my participation in this research study is strictly voluntary, and that I may withdraw at any time. I have been told that this study has been approved by the Ethics Committee of the Hong Kong Polytechnic University and The University of Hong Kong. In addition, any personal information obtained from me through this study will be confidential, and I will not be identified in any communication concerning this study. I am entitled to keep a copy of this consent for my future reference.
I, ___________________, understand the explanation of this research study and consent to participate in the experiment.

Signature of subject: ___________________ Date: ___________________

Signature of witness: ___________________ Date: ___________________

I, Wang Ninghua, certify that I have fully explained to the above-mentioned subject the nature of the experiment, the known risks involved in participating in this study, and the fact that he/she the right to withdraw from the study at any time.

Signature of researcher: ___________________ Date: ___________________
Appendix 2

Recording of Subjective Pain Intensity (VAS)

Name: _______  Age: _______  Gender: _______
Height: _______  Weight: _______  Group: _______

<table>
<thead>
<tr>
<th>VAS</th>
<th>Before- (min)</th>
<th>During- (min)</th>
<th>After- (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td></td>
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<td>40</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

Before surgery
Day 1
Day 2
Day 3

During surgery
Day

After surgery
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Appendix 3

Recording of Heat Pain Threshold Measurement

Name: ___________ Age: ___________ Gender: ___________
Height: ___________ Weight: ___________ Group: ___________

<table>
<thead>
<tr>
<th>Heat pain threshold (°)</th>
<th>Before- (min)</th>
<th>During- (min)</th>
<th>After- (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40 20 0</td>
<td>20 40 60</td>
<td>20 40 60</td>
</tr>
</tbody>
</table>

**Before surgery**
Day1
Day2
Day3

**During surgery**
Day

**After surgery**
Day1
Day2
Day3
Day4
Day5
Day6
Appendix 4

Recording of Range of Knee Flexion *Before* and *After* TENS/Placebo

Name: ______ Age: ______ Gender: ______ Bed: ______ Group: ______

<table>
<thead>
<tr>
<th>Days</th>
<th>Range of Knee Flexion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
</tr>
<tr>
<td><strong>Before surgery</strong></td>
<td></td>
</tr>
<tr>
<td>Day1</td>
<td></td>
</tr>
<tr>
<td>Day2</td>
<td></td>
</tr>
<tr>
<td>Day3</td>
<td></td>
</tr>
<tr>
<td><strong>During surgery</strong></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td></td>
</tr>
<tr>
<td><strong>After surgery</strong></td>
<td></td>
</tr>
<tr>
<td>Day1</td>
<td></td>
</tr>
<tr>
<td>Day2</td>
<td></td>
</tr>
<tr>
<td>Day3</td>
<td></td>
</tr>
<tr>
<td>Day4</td>
<td></td>
</tr>
<tr>
<td>Day5</td>
<td></td>
</tr>
<tr>
<td>Day6</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 5

Recording of Analgesic Consumption

Name: _________ Age: _________ Gender: _________

Bed: _________ Group: _________

Background infusion: _________ mg/hr

PCA bolus: _________ mg

1-hour-max: _________ mg

Lock out interval: _________ min

<table>
<thead>
<tr>
<th></th>
<th>PCA morphine (mg)</th>
<th>Epidural infusion rate (ml/hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
29th Annual Meeting
Society for Neuroscience

Saturday–Thursday
October 23–28, 1999

Miami Beach Convention Center
Miami Beach, Florida

Abstract postmark deadline
Monday, April 26, 1999
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HEAT PAIN THRESHOLD...IN YOUNG HEALTHY SUBJECTS: SENSITIVITY AND REPEATABILITY. Wang Ning Hua, Christina W.Y. Hui-Chan*, Department of Rehabilitation Science, The Hong Kong Polytechnic University, Hong Kong (SAR), China

Previous studies had shown high repeatability of heat pain threshold measurement (e.g. Yandinsky et al. 1995). We set out to systematically define the sensitivity simultaneously with repeatability of heat pain threshold, using the Medoc TSA 2001 device in our study.

The study on repeatability was performed on 8 young normal subjects on the knee, foot, hand and trunk, using the Method of Limits. Tests were repeated one and two weeks following the first one. In the study on sensitivity, 10 young healthy subjects performed subjective psychophysical estimates involving warm and hot cutaneous stimuli. Ten levels of temperature ranging from 32 to 50°C were applied for 10 seconds to the left knee in a random order. Subjects gave continuous ratings of perceived temperature and pain intensity using the visual analogue scale (VAS). Interclass correlation coefficient (ICC) and linear regression were used for data analysis in repeatability and sensitivity respectively.

Our results showed that ICC of the tested sites ranged from 0.87 to 0.93. There was a linear correlation between heat stimulus intensity and subjective thermal sensation, with a high value of r=0.93 and a slope of 5.04.

We concluded that heat pain threshold measurements were not only highly repeatable but also highly sensitive. Under the present experimental paradigm, heat pain processing by the nervous system appears to be a linear function of the stimulus intensity in young healthy humans.

The project was funded by the Hong Kong Polytechnic University.

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Abstracts
TENS ON ACUPOINT INDUCED INHIBITION OF HEAT PAIN BUT NOT VIBRATION SENSITIVITY IN NORMAL, YOUNG SUBJECTS

Ninghua Wang, Christina W.Y. Hui-Chan. Department of Rehabilitation Science, The Hong Kong Polytechnic University, Hong Kong

Introduction: There have been conflicting reports on the inhibitory effects of TENS on both the acute heat pain and vibration threshold. Such controversial could have arisen from different experimental protocols such as the duration, location and parameters of TENS being used in the different studying alternately. TENS could exert different effects on pain (mediated by small diameter fibers) and tactile sensation (mediated by large diameter fibers). This study set out to delineate the influence of TENS on pain (measured by heat pain threshold) and tactile sensation (measured by vibration threshold) with same subjects.

Method: Twenty normal, young subjects, aged from 20 to 39, participated in the study. They were randomly allocated into TENS and placebo groups. Thirty min of conventional TENS (200μs pulses at 100 Hz, and 2-3 times sensory threshold) or placebo stimulation was applied to the acupuncture points (Li4) on each subject's left hand. Heat pain and vibration thresholds were measured using Medoc TSA-2001 and VSA-3000 respectively on the thenar eminence of each subject’s left hand. These assessments were done at 30, 20 and 10 min before and 0, 10, 20 and 30 min after 30 min of TENS or placebo treatment. Repeated Measures ANOVA was used to analyze the data.

Results: This study showed a significant increase in heat pain threshold, by 0.81°C and 1.54°C respectively at 0 (p=.002) and 20 min (p=.004) after 30 min of TENS application to the Li4 acupoint of young healthy subjects, compared with placebo stimulation. Interestingly, no significant difference in vibration threshold was found between TENS and placebo groups.

Conclusion: In contrast to placebo stimulation, 30 min of TENS to the Li4 acupoint increased the heat pain but not vibration threshold. This result demonstrated that, like acupuncture, the effect of TENS on the acupoint is to reduce pain but not tactile (specifically vibration) sensibility. In other words, TENS could inhibit the transmission of tactile sensation (vibration) through large diameter fibers.
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Abstract: REPEATED TENS PRODUCED CUMULATIVE INHIBITORY EFFECT ON HEAT PAIN THRESHOLD IN HEALTHY ELDERLY SUBJECTS. N. Wang, C.W.Y.Hui-Chan*. Department of Rehabilitation Science, The Hong Kong Polytechnic University, Hong Kong (SAR), China

Our previous study showed that low-intensity transcutaneous electrical nerve stimulation (TENS), repeated daily for 2 weeks, led to a decrease of 30% in electrically induced pain (Liu and Hui-Chan, 1994). We therefore set out to delineate the possible cumulative inhibitory effect of repeated TENS on another type of pain induced by heat. Nineteen healthy elderly subjects, aged 60 to 90, participated in this study. They were randomly allocated to a TENS or placebo group. Sixty minutes of TENS (200μs pulse at 100Hz at 2 - 3 times sensory threshold intensity) or placebo stimulation was applied to four acupoints: Extra36, Gb34, Sp9 and St35 around the knee joint, twice a day for 3 days. Heat pain threshold was measured using the Medoc TSA-2001 device before and after TENS or placebo stimulation to each subject's knee. The results obtained were analyzed using repeated measures ANOVA. In contrast to placebo stimulation, our findings showed a significant increase in the heat pain threshold, measured prior to the 1st session to that measured prior to the 6th session of TENS, from 46.9 ±3.1 to 48.6 ± 1.8°C (p=.007). These results demonstrated that afferent conditioning stimuli, repeated twice daily for 3 days, produced a cumulative antinociceptive effect on heat pain threshold in healthy elderly subjects.

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