INTRODUCTION

LITERATURE REVIEW

1.1 Pain and Sleep

Sleep disruption can be caused by both internal and external factors. One of the most common causes of sleep disruption, as reported by patients in clinical practice, is pain. According to the International Association of the study of pain (Mersky *et al*., 1979), pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain can either be acute or short-lasting, such as postoperative pain, or chronic, lasting more than several weeks or months, such as arthritic pain. Pain impacts quality of life and also sleep. Chronic pain is associated with an increased risk for insomnia: 44 % of patients with chronic pain report insomnia compared with 19 % of subjects without pain (Lavigne *et al*., 2010). The existing hypothesis that describes the interaction between sleep and pain suggests that pain has an arousal-enhancing influence that prevents the initiation and maintenance of sleep (Cooper, 1993; Roehrs, 2009). This influence leads to excessive daytime sleepiness (Roehrs, 2009). Sleep can also influence the perception of pain. The nociceptive and sleep-wake pathways have common neurobiological systems that include serotonergic transmission such that sleep can impact pain processing (Roehrs, 2009). Having fewer hours of sleep (< 6 hours per night) or poor quality sleep is associated with increased pain perception (Lavigne *et al*., 2010). The relationship between sleep and pain is, therefore, bidirectional.

The association between sleep and pain has been explored from different angles. There are experimental studies that have been conducted on pain-free subjects to assess how manipulating sleep influences pain perception and how experimental pain impacts sleep. Other studies have been carried out on animals to assess the mechanisms underlying the relationship between pain

and sleep. Some research studies have been carried out on clinical pain patients like in fibromyalgia, rheumatoid arthritis, orofacial pain, and other clinical pain conditions to explore the relationship between chronic pain and sleep.

Sleep disturbance in individuals with no medical condition, but stimulated with a noxious or non-noxious painful stimulus has been confirmed in some studies (Bedyoun *et al*., 1993; Drewes *et al.*, 1997; Bentley, 2003). The effect of painful stimulation on sleep varies depending on the stage of sleep and on the pain stimulus used. Studies that have been conducted during sleep using thermal pain showed that the threshold that triggers cortical arousals and increased heart rate was lower in light sleep stages 1 and 2 when compared to deep sleep (stage 3 and 4) or REM sleep (Bentley *et al*, 2003; Lavigne *et al.*, 2000) at 50° intense pain (50° thermal stimulus) was needed to arouse pain-free patients from SWS and REM sleep (Bentley *et al*., 2003). Whilst it is evident that a noxious stimulus causes awakenings across all sleep stages, a non-noxious stimulus is more likely to cause microarousals (Muzet, 2007; Bentley, 2007; Lavigne *et al*., 2001). The common outcome of the two types of stimuli is that of fragmented sleep (Lavigne *et al*., 2001). Different pain stimuli induce different EEG responses during sleep (Drewes *et al*., 1997). Muscle pain, induced with hypertonic saline during deep sleep, is associated with a reduction in slow-frequency delta waves (corresponds with deep sleep) and an increase in fast-frequency alpha which presents itself at 8 to 12Hz (associated with an awake state) and beta waves, commonly at 16 to 25Hz frequency (also associated with heightened wakeful state and anxiety) (Thunberg *et al*., 2005). Joint pain, induced with a pneumatic stimulator during deep sleep, is associated with a reduction in delta activity, presenting itself at 0.5 to 3.5Hz frequency and theta waves appearing at 4 to 7Hz frequency (associated with drowsiness) and an increase in alpha, sigma waves (at 12.5 to 14Hz), and beta waves (Thunberg *et al*., 2005). Sigma waves are also associated with wakeful state (Thunberg *et al.*, 2005). Cutaneous pain, induced with an Argon laser during deep sleep, however, had no effect on the sleep EEG (Drewes *et al*., 1997).

The validity of the studies on experimental pain is limited by the difference in pain modalities between experimental pain and clinical pain (Daya and Bentley, 2009). The influence of experimental pain on changes in sleep architecture can therefore not be extrapolated to neuropathic or clinical pain (Daya and Bentley, 2009). Due to the heterogeneous cognitive and

biochemical changes that are difficult to reproduce in an ethically acceptable way, it has also been difficult to carry out human experimental protocols for the study of chronic pain in humans (Bentley in Lavigne *et al.,* 2007). Experimental studies about pain and sleep, therefore, are poor models for the effects of chronic clinical pain on sleep.

1.1.1 Clinical pain and sleep

At least 50 % of patients with diverse chronic pain conditions complain of sleep disturbances (Smith and Haythornthwaite, 2004). In many diseases, pain is the leading cause of insomnia (Drewes and Arendt-Nielsson, 2001). Evidence is available confirming that pain contributes to sleep disturbance and that disruption of sleep contributes to pain, with sleep disruption shown to be increased with increased pain (Cole *et al*., 2007; Morin, 1998). For example, poor sleep quality is significantly correlated with mechanical pain thresholds in patients with Fibromyalgia, suggesting that increased pain sensitivity is associated with greater sleep disturbance (Agargun *et al*., 1999).

Objective polysomnographic studies have also shown strong relationships between sleep and pain. There are several sleep abnormalities found in patients with chronic pain, with fragmented sleep and a decrease in sleep efficiency and slow wave sleep being commonly found (Drewes and Arendt-Nielsson, 2001). A number of studies have found abnormalities in the general sleep architecture of Fibromyalgia patients (Modolfsky, *et al*., 1993; Branco *et al.,* 1994; Landis *et al.,* 2004). Fibromyalgia patients have a shorter total sleep time, reduced sleep efficiency, and shorter duration of slow wave sleep and REM sleep. There is also a general shift of EEG activity from slow wave (Delta) to faster (Alpha) activity ("alpha intrusion") indicating increased state of arousal. Fibromyalgic patients also show a more fragmented sleep (Modolfsky, *et al*., 1989). Other types of pain are also associated with disturbed sleep as objectively measured with the polysomnograph. Patients with lower back pain have a lower sleep efficiency and less slow wave sleep (Drewes and Arendt-Nielson, 2001). Patients with osteoarthritis have more Stage 1 sleep and less Stage 2 sleep than age- and sex-matched controls (Leigh *et al.,* 1988). Women with dysmenorrhoea have a lower sleep efficiency and more time spent awake, moving and in light

Stage 1 sleep when they have menstrual pain compared to other times of the menstrual cycle and compared to healthy controls (Baker *et al*., 1999). There are not many studies available that have researched CTS pain and subjective and objective measures of sleep as well as the influence of treatment of CTS pain on sleep, as discussed later in Section 1.4.

Studies about sleep in chronic pain patients have often found a strong association between mood, sleep and pain. Chronic pain in humans with fibromyalgia, rheumatoid arthritis as well as chronic orofacial pain has been found not to be only largely associated with sleep disturbance, but also emotional distress (Modolfsky, 1975; Call-Schmidt *et al.*, 1983; Riley *et al.*, 2000). According to Sayar *et al*., 2002, anxiety and depression explain about one-third of the variance in the relationship between poor sleep and pain. Also, the recall of patient sleep time has been found to be shorter than that objectively recorded in the sleep laboratory (Lavigne *et al*., 2007). Perceptions of sleep, therefore, may differ from laboratory-based measures of sleep in chronic pain patients.

Research conducted in the field of sleep and pain offers its own challenges due to complexities associated with sleep deprivation as well as pain perception (Lavigne *et al*., 2004). These factors may include medication, mood and depression, other undiagnosed conditions, pain perception and insomnia (Daya and Bentley, 2009). It is therefore essential to comprehend the basic construct of normal sleep and sleep pattern to be able to understand theability of pain to interfere with sleep. The following part of the discussion deals with normal sleep.

1.2 Sleep

As described by Aschoff (1965), sleep is controlled by light and darkness through the circadian rhythm and humans spend two thirds of their life span awake. The rest of the time human spend asleep. Sleep is essential for many of life's physiological, chemical and psychological processes that take place (Edgar *et al*., 1993). Since the discovery of electroencephalogram (EEG) by Berger in 1929 (Berger, 1929), and later work by other researchers including Carskadon and

Dement, 1987; Shapiro *et al.*, 1984; Dement *et al*., 2002, to name a few, immense knowledge has been collected regarding the profound alteration in brain pattern to regulate sleep-wake pattern. Reticular activation system is responsible for wakefulness and alertness (Cooper, 1993). The sleep/wake pattern is promoted by a two process system (Saper *et al.*, 2005). The one promotes sleep (process S), and the other one promotes wakefulness (Process C) (Saper *et al*., 2005). Neurons found in the pre-optic area of the hypothalamus inhibit neuronal communication and turn off arousal systems during sleep (Cooper, 1993, Gallopin *et al*., 2000, Saper *et al*., 2005). Ascending reticular formation system also promotes the release of noradrenalin and acetylcholine responsible for cortical activation (Cooper, 1995). Neurons in the pons are responsible for the switch over that takes place between REM and Non REM sleep through-out the night (Saper *et al.*, 2005).. Other neurotransmitters that are responsible for the sleep-wake process in the brain include dopamine, glutamine and histamine (Gilman and Newman, 1996; Spriggs, 2002).

External factors also play an important role in the control of sleep and in particular the sleep-wake pattern. The 'zeitgeibers' (time givers) play an important role in the essential control of the sleep-wake pattern. The two processes that are essential in the regulation of sleep within a 24 hour cycle are the homeostatic control and the circadian rhythm (Borbély, 1982). The homeostatic control is the regulation of sleep by exponential increase of sleep drive during waking and subsequent decrease during sleep (Borbély, 1982). The circadian rhythm represents the control of the tendency to sleep within a 24 hour period, regulated by the bio-physiological clock embedded in the suprachiasmatic nucleus (SCN) in the hypothalamus, as well as the retino-hypothalamic tract linking the retina to the SCN (Cooper, 1993; Moore, 1999). The circadian rhythmicity is therefore influenced predominantly by the cycle of light and darkness. Any type of pain may disturb sleep physiology including the homeostatic and circadian control of sleep.

Within sleep, two separate states have been defined on the basis of physiological parameters. The stages are, non-rapid eye movement (NREM), and rapid eye movement (REM) sleep. The REM and NREM phenomenon exists in virtually all mammals (Carskadon and Dement, 20002; Shapiro *et al*., 1984). NREM sleep is conventionally divided into four stages. It is characteristically synchronous with such sleep components as sleep spindles, K complex, high

slow wave sleep. The four NREM sleep stages are 1 constituting 2-5% of total sleep time (TST), and stage 2 constituting 45 to 55% of TST, and stages 3 and 4 (SWS) occupies 13 to 23% and lastly REM sleep usually occupies 20-25% of TST (Carskadon and Dement, 2002; Hirshkowitz, 2004). I have to mention that the stated proportions of sleep staging apply well to normal young and healthy subjects between the ages 18-30yrs (Van Cauter *et al.*, 2000). My CTS subjects had a mean age of 52, suggesting that they may have had lesser SWS and spent more time awake than the younger and more healthier subjects (Van Cauter *et al*., 2000). Most research has shown that there is significant decrease in SWS at mid-life (36-50), which is replaced by light sleep, with further decrease in SWS in later adulthood accompanied by an increase of 28 minutes in wake time per decade towards late adulthood (Van Cauter *et al*., 2000).

REM sleep is defined by EEG activation, muscle atonia, and episodic bursts of rapid eye movement. The mental activity of REM sleep in humans is associated with dreaming based on vivid dream recall reported after approximately 80 percent of arousals from this state (Carskadon and Dement, 2002). The important step toward the understanding of human sleep has been established on the basis of the electroencephalographic correlates of sleep and wakefulness. This has further helped in providing basic paradigm of studying human sleep and sleep disorders (Hirshkowitz, 2004).

Sleep stages are cyclical and they occur at between 3 and 5 cycles per night and each cycle lasting for between 70 and 120 minutes on average. The following stages are defined according to Rechtschaffen and Kales, (1968) and represented on a hypnogram in Figure 1.

Stage 1

- This stage begins with the disappearance of the alpha rhythm and the appearance of 4-7Hz slower frequency waves (Theta activity).
- Low amplitude activity of mixed frequencies.
- Paradoxical alpha rhythm may occur.
- A variety of sudden medium to high amplitude with delta, theta and alpha activity may occur in transition to stage 1 and 2.

Stage 2

- Characterised by presence of either sleep spindles of 0.5s duration, K complex or both.

- Sleep spindles are bursts of activity consisting of 12-16 Hz waves that occur for 0.5 to 1.5 seconds.
- K-complexes are waveforms that show an initial sharp negative deflection followed by a high-voltage slow wave of at least 0.5 seconds.
- Slow waves of less than 2Hz absent or not predominant. Positive occipital sleep transients (POSTs) which are characterised by the presence of sharp bi-occipital sharp wave mixed with bi-central short-lived 12-16 Hz bursts are also predominant.

Stage 3

Moderate amounts of slow waves and high amplitude activity present. If 20-50% of an epoch (30s of recording) is occupied by waves 2Hz or less of over 75μV amplitude recorded in C3-A1 or C4-A2, stage 3 is confirmed. K complex is often present. There is reduced muscle tone.

Stage 4

For Stage 4 sleep to be scored, over 50% of the 30s epoch should be occupied by slow wave sleep of at least 2Hz or less that are 75μV in amplitude. This activity is recorded on C3-A1 or C4-A2 and POSTs and spindles may be present but rare.

REM (rapid eye movement) Sleep

REM sleep is characterised by low voltage EEG patterns, with rapid eye movements, as well as reduced muscle activity (atonia). REM sleep is present when more than 50% of a 30s epoch contains low voltage EEG activity with theta activity as well as rapid eye movements. It is associated with vivid dreaming.

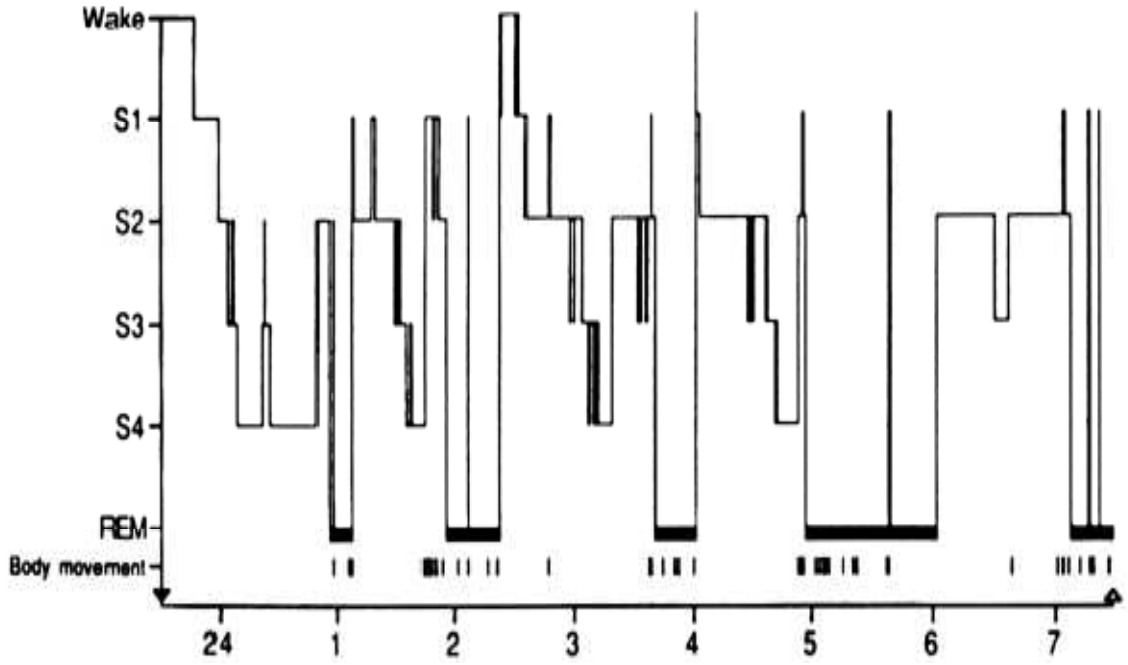

Figure 1: Progression of sleep stages during a complete night of sleep in a Normal healthy adult represented on a hypnogram (Hirschkowitz 2004).

1.3 Carpal tunnel syndrome and pain

The following section focuses on one of the neuropathic conditions that presents with numerous reports of sleep disturbance as well as daytime pain, the carpal tunnel syndrome.

1.3.1 Carpal tunnel syndrome

Carpal tunnel syndrome is a localised entrapment neuropathy of the median nerve at the wrist caused by the mechanical irritation from nerve impingement (Binnie *et al.,* 2004). It is the second most common industrial injury in America, surpassed only by lower back pain (Wall and Melzack, 1994). Carpal tunnel syndrome represents a localised injury on the median nerve (Smorto and Basmajian, 1979, Goodgold and Eberstein, 1983). The injury to the nerve may be due to constant irritation because of an impinging anatomical space due to increased wrist pressure as may be witnessed in rheumatoid arthritis, gout, ganglion tumours and pregnancy amongst many precursors (Goodgold and Eberstein, 1983; Wall and Meltzack, 1994; Binnie *et al*., 2004). As an entrapment neuropathic syndrome CTS is a well-known condition.

There is no South African statistical evidence on the prevalence of carpal tunnel syndrome. A stratified sample of 3000 subjects (Age range 25-74 years), randomly selected was surveyed in the region of Southern Sweden with a population of 170000 (Atroshi *et al*., 1999). There was a response rate of 83% (n=2466, 46%). Of the symptomatic respondents, 81% underwent clinical examination (Atroshi *et al*., 1999). Based on the clinical and symptomatic data, 1 in5 (20%) of subjects had CTS based on clinical examination and electrophysiological testing (Atroshi *et al*., 1999). Other epidemiological studies have also shown an increase incidence of CTS with age, women showing more presentation of CTS than their male counterparts (McCabe *et al*., 2007). Males have shown increased prevalence rate at 55-64 years of age, and females at 45-54 years of age (McCabe *et al*., 2007). The McCabe study also showed that increased BMI, diabetes and pregnancy are associated with CTS (McCabe *et al*., 2007).

The pain presented by carpal tunnel syndrome was given attention soon after World War II when patients presented with what was referred to as the ‘acroparaesthesia’ syndrome (Kremer *et al*., *1953*; Binnie *et al*., 2004) . The painful condition was reported largely from middle-aged women

who undertook manual labour due to wartime circumstances (Binnie *et al.,* 2004). In 1949, it was McArdle who suggested that the pain might be from the compression of the median nerve at the wrist area. McArdle also pioneered the first CTS operation which is done by the division of the flexor retinaculum at the wrist (Binnie *et al.,* 2004). Around 400 000 surgical operations are conducted in the USA alone on the CTS (Binnie *et al*., 2004).

The major symptoms reported by CTS patients are numbness, tingling of the fingers, pain and weakness of the fingers as well as signs of atrophy of the thenar muscles (Steven, 1987; Goodgold and Eberstein, 1983, Binnie *et al.,* 2004). According to Dawson *et al.,* 1983, there are three main types of documented categories of pain related to CTS. "*Group I is the mild form of intermittent pain and numbness at the median nerve distribution with no abnormal electrophysiological findings. Group II is characterised by tactile sensation (hyperesthesia) accompanied by clumsiness, loss of dexterity and weakness of the pinch with more nocturnal burning sensation and swelling in the hand. The conduction studies are abnormal in this group. Group III is characterised by severe sensory loss and significant functional impairment. There is thenar muscle wasting as well as reported severe sleep disturbance*". Group III patients have poor prognosis (Goodgold, 1983). The CTS pain can be distributed to the whole hand, forearm, elbow, shoulder and sometimes with neck discomfort being experienced (Dawson *et al.,* 1983; Goodgold and Eberstein., 1983; Binnie *et al.,* 2004). The compression of the median nerve may also be associated with many conditions other than CTS, including Raynaud's phenomenon, vascular lesions, systemic amyloidosis, pregnancy, granulomas, and vitamin (pyridoxine) deficiency as well as traumatic conditions (Dawson *et al*., 1983). Carpal tunnel syndrome surgery has reported success varying from 70% to 90% (Wilder-Smith *et al*., 2006).

It is however, of significant importance to understand the relationship between CTS and the effect it has on other physiological processes such as sleep. Understanding CTS objectively measured variables and the process of recovery was important in this study in order to understand the time-linked interaction between CTS pain, recovery period and the subjective reports from patients in a clinical setting for a comprehensive understanding and management of CTS pain. The following section will focus on the anatomical position as well as the physical entrapment of the median nerve.

1.3.2 The median nerve compression

The median nerve arises from the branches of the medial and lateral cords of the brachial plexus and is derived from the cervical nerve roots C5, C6, C7, C8, T1 (Romanes *et al.,* 1981, Gilman and Newman, 1996). The cords then unite anteriorly to the third part of the axillary artery, a continuation of the subclavian artery (Romanes *et al.,* 1981). The median nerve continues along the lateral aspect of the brachial artery at the mid-humerus to lie on its medial side and in the forearm, it enters between the heads of pronator teres and gives off an anterior interosseous branch (Romanes *et al.,* 1981). In the wrist, the median nerve becomes superficial on the ulnar side of the flexor carpi radialis, where it then passes deep to the floor of the flexor reticulum giving off branches to the thenar muscles, radial to two lumbricalis and cutaneous branches of the thumb, index, middle and the radial half of the ring finger (Romanes *et al.,* 1998; Gilman and Newman, 1996; Binnie, 2004).

Entrapment occurs where a nerve passes through an osseofibrous tunnel or through a slit of fibrous tissue (Eberstein and Goodgold., 1983). Carpal tunnel syndrome is prevalent primarily in people constantly engaged in excessive use of hands for activities requiring fine motor control, such as knitting, fitting and turning or meat packing amongst other activities (Dawson *et al.*, 1983, Russel, 2006). CTS can also be secondary to other conditions, like pregnancy, rheumatoid arthritis, any tenosynovial proliferation, wrist joint abnormality and muscular anomaly. (Dawson *et al*., 1983).

The examination of the carpal tunnel/wrist in patients with CTS reveals an impairment of the cutaneous sensation in the hand's median nerve distribution and if motor involvement has occurred, there is weakness and wasting of the abductor policis brevis and opponens policis muscles (Aminoff, 1986). The anatomical position of the median nerve makes it easily susceptible to compression compared to other entrapment neuropathies, like those affecting the ulnar and the radial nerve (Dawson *et al*., 1983). To properly diagnose CTS, other disorders which may co-exist with CTS, like tendinitis, fibromyalgia and cervical radiculopathy need to be excluded (Wilder-Smith *et al*., 2008).

1.3.3 Electrophysiology

A description of the loss of sensation by the patient is a very important part in the gathering of clinical information geared towards a proper diagnosis of the CTS. Electrophysiological measurements confirm and give evidence to complete the diagnosis of the carpal tunnel syndrome (Thomas *et al*., 1967; Goodgold and Eberstein, 1980).

During clinical examination, tests can help identify whether the patient has CTS or not before electrophysiological examination is performed. Tinel's test is undertaken by gently tapping over the wrist crease (Buchthal *et al*., 1974; Dawson *et al.*, 1983). A positive response for this test is a tingling sensation felt and extending to some or all median nerve innervated fingers (Dawson *et al.*, 1983; Goodgold and Eberstein., 1983; Wilder-Smith *et al*., 2008). In Phalen's test, the wrist is bent into flexion for 30 to 60 seconds (Dawson *et al.*, 1983; Wilder-Smith *et al*., 2008). The positive response here will be the exacerbation of symptoms in the affected hand (Dawson *et al.*, 1983; Goodgold and Eberstein., 1983). Abduction of the abductor policis brevis muscle is the commonly used technique to test the weakness of the median nerve innervated muscles (Dawson *et al.*, 1983). The thumb is brought up perpendicular to the palm and the patient is requested to produce a resistance force that is directed to the distal phalanx (Dawson *et al.*, 1983). The power of the thenar muscle is then compared to the power of the opposite side (Dawson *et al.*, 1983; Goodgold and Eberstein, 1983)

Carpal tunnel syndrome is best diagnosed by nerve conduction studies, which is the electrophysiological study of the nerves, performed according to the guidelines suggested by the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) Rochester, 2004. Early or mild compression may not lead to any electrophysiological abnormalities, but, more than 90% of CTS patients have localised slowing of conduction of sensory fibers (Dawson *et al.*, 1983; Binnie *et al.*, 2004). The study of the median nerve sensory conduction latency done at the wrist and distal motor conduction latencies as well as the sensory and motor response amplitude turned out to be the most sensitive criteria in the diagnosis of CTS (Dawson *et al.*, 1983; Goodgold and Eberstein., 1983). To a lesser extent when compared to nerve conduction studies, needle examination is also useful in the diagnosis of CTS (Dawson *et al.*, 1983). There is commonly no correlation between the degree of abnormality in the nerve conduction studies and the degree of severity of the symptoms (Binnie *et al*., 2004). Dawson *et al.*, (1983) suggests that

more pain may be caused by ischemia than by demyelination at the carpal tunnel site. The median nerve supplies sensation to the radial aspect of the palm, the volar aspect of the thumb, index, middle fingers and the radial half of the ring finger (Dawson *et al.,* 1983; Gilman and Newman, 1996). Dorsally, the supply of the median nerve extends to proximal interphalangeal joints of the second, third, third as well as the radial half of the fourth digit (Dawson *et al.*, 1983). The sensation to the aforementioned areas of the hand will be affected during the carpal tunnel syndrome (Fig 2).

1.3.4 Treatment

There are different forms of treatment for carpal tunnel syndrome. When the complaints are first reported, the conservative approach might take a form of job modification, avoiding the activity that precipitates the condition, night splints, non-steroid anti-inflammatory drugs (NSAIDS), occasional steroid injection, and trial of diuretics, especially when symptoms are premenstrual (Goodgold and Eberstein., 1983; Dawson *et al.,* 1983).

An alternative to conservative treatment is surgical treatment. An absolute indication for surgery includes failure of non-operative forms of treatment or clinical evidence of thenar atrophy. A relative indication for surgery is if there is persistent sensory loss. (Dawson *et al*., 1983). Surgery for carpal tunnel syndrome is said to be one of the most successful operations that can be performed on the hand and the complications of the operation and poor results are almost uniformly related to poor surgical technique (Dawson *et al*., 1983, Gorsche *et al.,* 1999). The surgical incision is a curved interthenar incision along the bisected line through the fourth digit. The transverse carpal ligament is then released (Dawson *et al.,* 1983). Rare complication of the ligament incision is injury to the superficial palmar arch as well as laceration of the motor branch of the median nerve (Dawson et al., 1983; Binnie *et al.,* 2004). The operation is otherwise known to have a good success rate (Dawson et al., 1983) with reported immediate relief in nocturnal pain symptoms (Binnie *et al*., 2004).

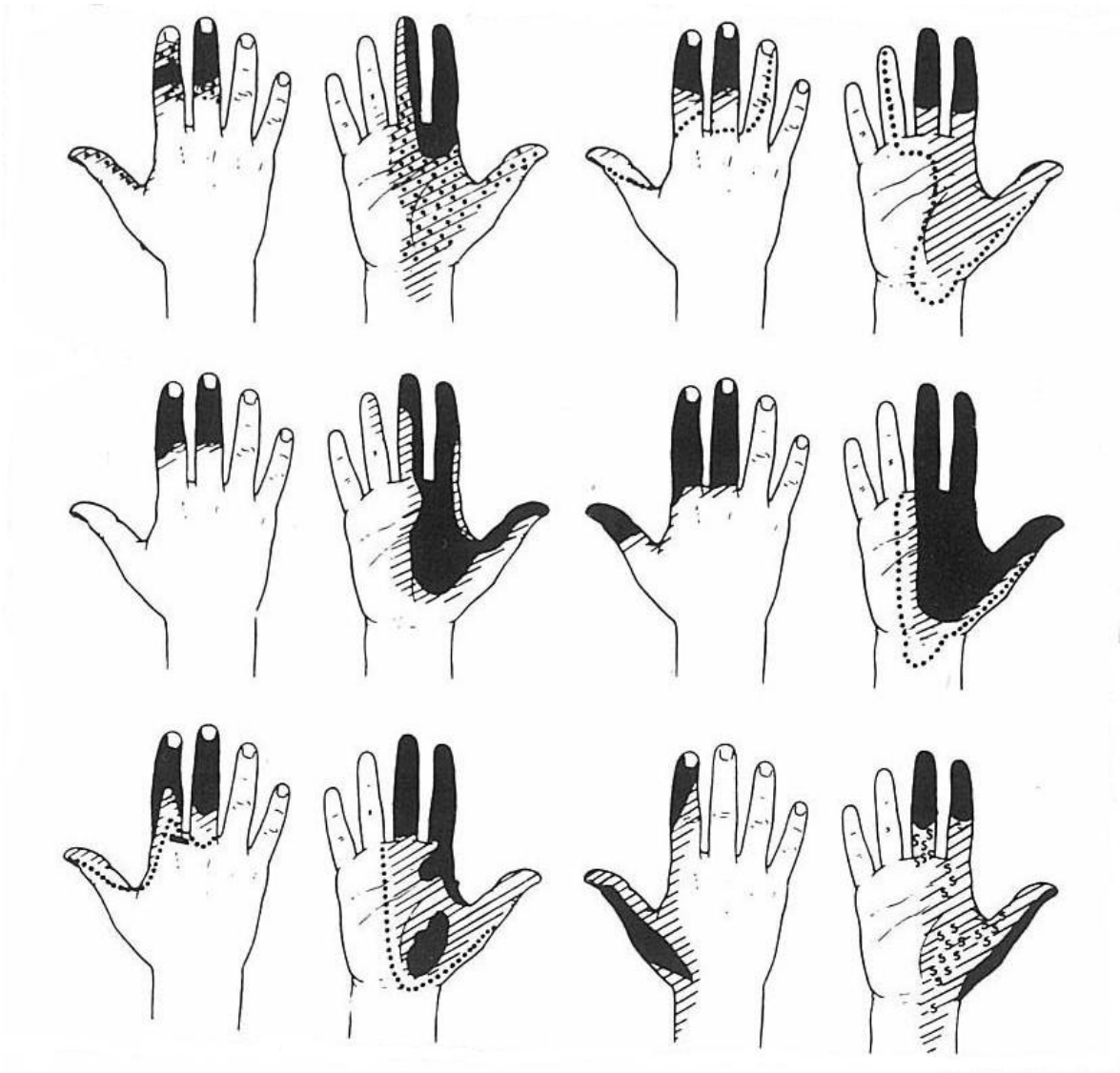

Figure 2. Areas of sensory loss affected by the complete lesion of the median nerve. Adapted from L.J. Pollock and L Davis, *Peripheral nerve injuries*, New York: Hoeber, 1933 p. 8 *(Dark shaded areas represent complete sensory loss and numbness. Hatched areas indicate partial loss of sensation)*

1.4 Carpal tunnel syndrome pain and sleep

Reports of nocturnal pain that wakes patients up in the early hours of the morning are very common in patients with carpal tunnel syndrome (Lavigne *et al*., 1996; Binnie *et al*., 2004). However, there are few studies that have investigated sleep disturbances in any detail in patients with CTS. One study found that patients with CTS scored an average of 11 on the Pittsburgh Sleep Quality Index, where a score of greater than 5 is considered an indicator of poor sleep (White *et al*., 2003). I conducted a pilot study of subjective sleep quality in 33 untreated patients with CTS (Mdluli *et al*., 2004, See Appendix). The majority of patients (> 85 %) reported that they had trouble falling asleep, awoke during the night, and had a restless sleep at least sometimes because of CTS pain. In the most detailed study of sleep in CTS patients, Lehtinen and colleagues (1996) compared the responses to a sleep questionnaire in 36 patients with CTS to those of a normal Finnish population. All patients reported waking up at night because of pain and numbness of the affected hands and fingers. Patients with CTS were more likely to report a poorer sleep quality, have a more fragmented sleep with longer awakenings, and suffer from more daytime sleepiness compared with the general population. CTS patients were also more likely to have symptoms of insomnia and to use sleeping pills compared to the general population (Lehtinen et al., 1996). Six of these patients were studied with objective measures of motor activity during the night both before and 6 months after an operation to treat their CTS. Motor activity was measured in the laboratory with a static-charge-sensitive bed that can monitor gross body movements and respiratory and heart-related movements. Patients showed a reduction in motor-active wakefulness and shorter movement periods during the post-operative night compared to the pre-operative night. Total hand movement time also decreased after the operation (Lehtinen et al., 1996). Limitations of this study are that sleep stages in the patients were not assessed with polysomnography and a control group was not included. As far as I am aware, there are no polysomnographic studies that have evaluated sleep quality in patients with CTS before and after treatment.

1.5 Thesis Aims

My study sought to further explore the association between CTS pain and sleep disturbance by doing subjective as well objective neurophysiological measurements on CTS patients and compare those with control subjects before and after surgery in order to measure changes in pain domain and sleep architecture. I hypothesized that untreated patients with CTS would report a poorer sleep quality and show a lower sleep efficiency and less slow wave sleep than age- and gender-matched control subjects who were not suffering from pain. I also hypothesized that subjective and objective polysomnographic measures of sleep quality would improve after surgical treatment of CTS in association with pain alleviation in CTS patients and that no change in sleep measures would be seen in the control group of patients after a surgical procedure in the absence of pain.

METHOD

This chapter describes the sample of subjects and the design of the study. A detailed description of procedures and instruments used for the collection of data is set out. The method that was used to analyse the data is also described. The study was carried out at the Wits Dial-a-Bed sleep laboratory of the Brain Function Research Group of the Faculty of Health Sciences, University of the Witwatersrand. Prior to commencement of this research project, ethical approval was obtained from the Committee for Research on Human Subjects of the University of the Witwatersrand (ethical clearance number is M01-09-13), which adheres to the principles of the Declaration of Helsinki (Appendix 1). All subjects signed an informed consent form.

2.1 Patients

2.1.1 Carpal tunnel syndrome patients

Patients between the ages of 35-75 years old (Table 1) who suffered from carpal tunnel syndrome, were recruited from an EEG and neurophysiology laboratory in the private sector in Gauteng, South Africa as well as from orthopaedic surgeons who operate on the condition, mainly in private hospitals in Gauteng, South Africa. All patients underwent a routine clinical examination by the referring physician. The median duration of persistent symptoms of CTS in the patients was 6 months. I performed nerve conduction studies on these patients according to guidelines suggested by the American Association of Electrophysiological Medicine (1993), to confirm the diagnosis of carpal tunnel syndrome. Only patients who had abnormal median/sensory conduction speed, abnormal sensory inter-peak latencies between the median and the ulnar nerves, as well those with absent responses were considered for the study. Surgical relief of the pressure on the median nerve was deemed necessary for all the subjects.

Table 1. The demographics of patients and control subjects

	CTS patients	Control patients
Number of patients	7	6
Male	2	1
Female	5	5
Caucasian	3	3
African ancestry	4	3
BMI (kg/m^2)	27±3	27±5
Median age(y)	52	49

2.1.2 Control patients

Age, gender and weight-matched control patients, who needed to undergo a minor dental surgical procedure, were recruited from local clinics (Table 1). Only patients with non-painful conditions at the time of surgery were considered. For those who had had acute pain, the pain would be alleviated long before they came for the operation. Further, the necessary surgical procedure had to be of a similar duration to that of the CTS release operation, and to require only regional anaesthesia. Six control patients who met our criteria agreed to participate in the study. Three of the control patients had surgical operations for tooth repair, and the other three had surgery for tooth extraction. Nerve conduction studies were not done on the control patients. None of these subjects reported any clinical symptoms suggestive of CTS. The post- surgical evaluation was done on the control patients at almost the same time (within two months) as CTS patients.

2.1.3 Screening interview

To confirm the suitability of candidate CTS and control patients for the study, all individuals were interviewed and completed a questionnaire about their medical history, use of chronic medication, sleep habits, possible presence of sleep disorders, and history of CTS, where applicable. None of the CTS or control patients suffered from comorbid diseases such as polymyopathies, polyneuropathies, or had had previous wrist surgery or any other inflammatory disease processes. None of the CTS patients or control patients reported or complained of symptoms of sleep disordered breathing. None of the subjects interviewed used pain medication in the form of morphinics or anti-epileptic drugs. There were therefore, no anticipated sleep changes from pain medication on these patients. Finally, none of the patients reported suffering from any chronic disease. None of the controls reported taking any pain medication. Four of the seven CTS patients, however, typically took some form of analgesic to reduce their pain before going to bed.

Female patients were also asked about their reproductive status. Five of the CTS patients had had a hysterectomy and one was taking hormone replacement therapy. Of the control female patients, three were peri-menopausal and three were post-menopausal. None of the control patients was taking hormone replacement therapy, but one woman was taking oral contraceptives. None of the women in either group reported severe mood and physical symptoms associated with their hormonal status.

All CTS patients complained about pain, described as one or more of the following: irritating pain accompanied by numbness and /or pins and needles in the median nerve distribution, weakness of the abductor policis brevis muscles, pain in the wrist sometimes radiating to the shoulder and scapula as well as dropping things easily from the hand. All the CTS patients also complained about the fact that the pain woke them up during the night, and got more severe subsequent to using their hand, either driving or doing fine motor movement tasks.

2.2 Measures and procedures

2.2.1 Nerve conduction studies

To measure the action potential response required to determine the median motor nerve latency, each patient was asked to lie down in a supine position. I used surface silver/silver chloride recording electrodes over the abductor policis brevis (APB) as indicated in Figure 3. To identify the muscle, I asked the patient to abduct the thumb, raise it at right angle to the hand**.** I then placed the three cup electrodes (Figure 3). The active electrode, I placed on the belly of the muscle (APB), halfway between the distal wrist crease and the first metacarpophalangeal joint. The ground electrode, I placed between the muscle being tested and the stimulator (see Figure 3). The reference electrode (R), I placed distal to the first metacarpophalangeal joint, 30-40mm distal to the muscle. For distal stimulation, cathode (C) was placed 80mm proximal to the active electrode, in a line between the midpoint of the distal wrist crease and a point slightly ulnar to

the tendon of the flexor carpi radialis. For proximal stimulation, I placed the cathode (C) slightly medial to the brachial artery pulse in the antecubital region. The anode was placed 15-20mm proximal to the cathode. Stimulation of the peripheral nerve at two points, distally and proximally, separated by a known distance, allows for the calculation of the motor conduction velocity.

Conduction time = Proximal motor latency – Distal motor latency

Motor conduction velocity (m/s) = Conduction distance (mm) / Conduction time (ms).

(Buschbacher and Prahlow, 2006)

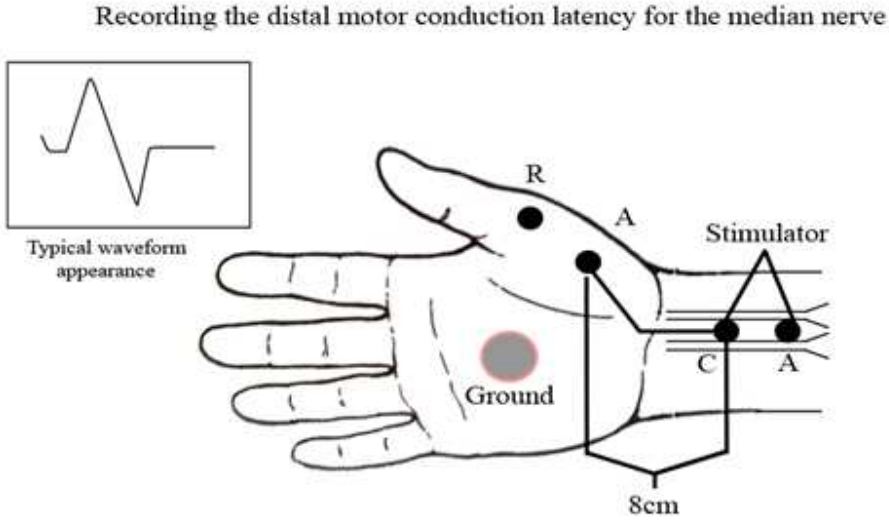

Figure 3. The orthodromic recording of the distal motor latency (DML) for the median nerve. Adapted from Buschbacher and Prahlow, 2006

Table 2. Parameter settings for the median and sensory nerve conduction studies

	Motor	Sensory
Sensitivity	10mV/division	5µV/division
Time base:	20ms	10ms
Sweep speed:	1ms/division	1ms/division
Stimulus rate	1-2 pulse per second	1-2 pulse per second
Low frequency filter	3Hz	20Hz
High frequency filter	10Hz	2 KHz
Stimulus duration	100µs	100µs

Orthodromic sensory conduction recording and palmar stimulation

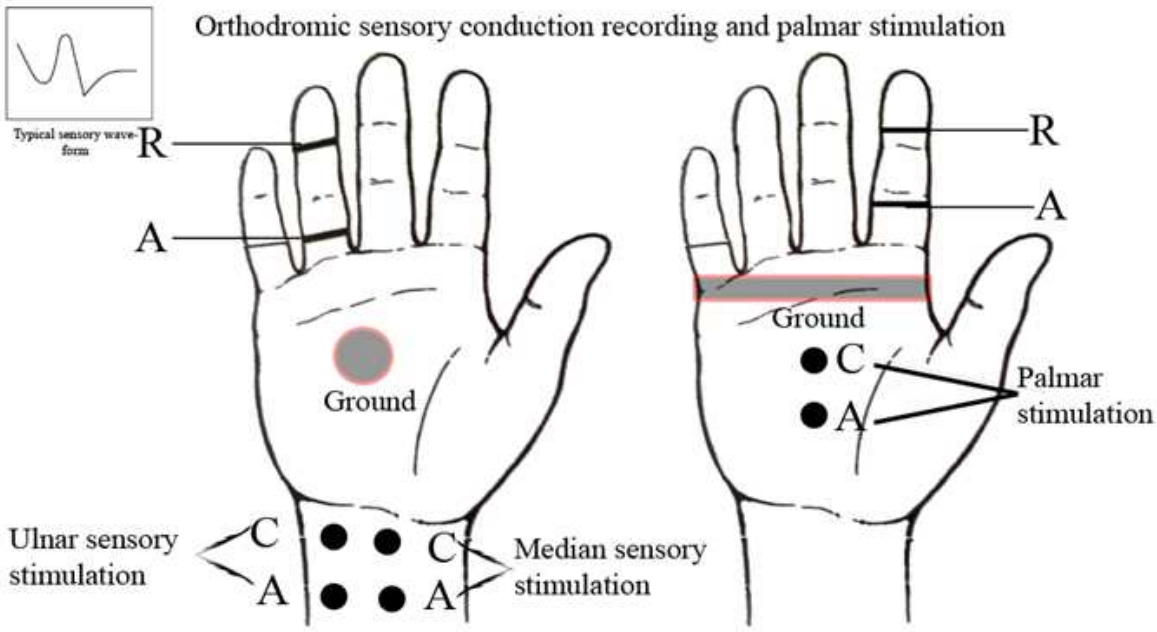

Figure 4a

Figure 4b

Figure 4a: The recording of orthodromic median/ulnar sensory conduction latencies and Figure 4b shows a palmar stimulation of the median nerve.

C-Cathode, A- Anode R-Reference, A-Active

2.2.1.1 Sensory conduction

To do the sensory nerve conduction study I asked each patient to lie in a supine position. To measure sensory conduction velocity, for orthodromic digital nerve stimulation and recording, I used ring electrodes soaked in saline or sometimes coated with electro-conductive paste. I placed the ring electrodes around the digits and the recording electrode on the midline section of the wrist. I placed the electrodes, on the patient's hand as depicted in Figure 4a and 4b. The active electrode (A) was placed slightly distal to the fourth metacarpophalangeal joint. The reference electrode (R) ring electrode was placed 40mm distally on the same digit. For median nerve stimulation, the cathode (C) was placed 140mm proximal to the active electrode and made slightly ulnar to the tendon of the flexor carpi ulnaris. For ulnar nerve stimulation, the cathode (C) was placed 140mm proximal to the active electrode, slightly radial to the tendon of the flexor carpi ulnaris. The anode (A) was placed proximally. The ground electrode was placed midway between the recording and the stimulation site. I then recorded the action potential using the technique described below to obtain supra-maximal response.

2.2.1.2 Stimulation and recording

I performed nerve conduction studies on all patients with suspected CTS using a Sapphire, Medelec 1L EMG 2 channel (Vickers Medical, Surrey, England). The criteria used to confirm a diagnosis of CTS are given in Table 3. Ulnar and radial nerve motor and sensory conduction latencies, velocities, response amplitude defects were considered for the study to exclude more diffuse nerve pathology.

To produce action potentials, I used constant current stimulation. I used the standard parameters as described in Table 2, for motor and sensory nerve conduction time, response amplitude and conduction speed determination. The technique I applied was slowly to increase the stimulus

intensity to threshold, observing the initial motor/sensory action potential, from the baseline. I then increased the stimulus current to between three and five times the threshold value to achieve supra-maximal stimulation of all the nerve/muscle activity with a moderately vigorous twitching of the muscles. I measured latency from the initial time of stimulation from baseline in milliseconds and peak latency was measured for distal/proximal sensory conduction latencies. Amplitude was measured from peak (negative) to peak (positive) in millivolts for motor conduction and microvolts for sensory conduction. Duration was measured from the initial deflection at the beginning of the action potential to the last deflection back to baseline at the end of the action potential in a single sweep in milliseconds. The supra-maximally stimulated action potential was reproduced at least three to four times at the same stimulus intensity and super-imposed to exclude artefact.

Another technique that I used to confirm the presence of localized wrist entrapment of the median nerve was that of comparing the inter-peak latency difference between the median and the adjacent ulnar nerve. By stimulating the nerves as indicated in Figure 3, a sensory recording on the digits of the fingers for the respective nerves was obtained and conduction latency measured at peak amplitude. The inter-peak latency differences for the adjacent radial and the ulnar nerves, as well as the palmar stimulation difference to median and ulnar nerves were combined to give the combined sensory index (Table 4).

2.2.2 Electromyography

Electromyography was performed using a 0.37mm, bipolar concentric Teflon disposable needle electrode inserted in the relaxed belly of the tested muscle. One reason for doing the EMG was to assess the muscular atrophic and/fibrotic abnormalities, which would allow one to gauge whether the CTS was chronic or not (Binnie *et al.,* 2004). A second reason was to exclude the involvement of the cervical compressive lesions by sampling specific cervical root myotomes to look for fasciculation potentials, fibrillations and other abnormalities. Lastly it was to exclude any abnormal muscular abnormality patterns in these patients. EMG examination of the abductor

policis brevis muscle particularly was used to grade the severity of the CTS. Reduction in muscle volume contraction was graded as the indication of either chronic denervation or conduction block of motor units. To exclude a diffuse/proximal EMG pattern compatible with a cervical compressive pathology or a muscular abnormality pattern, I sampled the deltoid, the biceps, the brachioradialis, flexor carpi radialis, and the first dorsal interosseous muscles. (Goodgold and Eberstein, 1983)

Table 3. Criteria to confirm a diagnosis of clinically suspected CTS, based on the guidelines of the American Association of Electrophysiological Medicine, (1993).

Measured variable	Value
Median motor distal latency	>4.4ms
Median palmar latency	>3.6ms
Median/Ulnar difference	>1ms
Palmar median/ulnar difference	>0.3ms

Diffuse neuropathy and myopathic pattern excluded. All criteria in Table 3 met for the diagnosis of suspected CTS. . Mild CTS: Abnormal sensory conduction latencies; Moderate CTS: Abnormal sensory and motor conduction latencies; Severe CTS: Abnormal sensory and motor conduction latencies, abnormal response amplitude and needle examination patterns.

Table 4. The calculation of the combined sensory index between the radial, ulnar and median nerves. (American Academy of Neurology, 1993).

Nerves for inter-peak latency Determination	Latency difference
Median digit IV-Ulnar digit IV	0.4ms
Median digit-Radial Digit I	0.5ms
Median Palmar-Ulnar Palmar	0.3ms

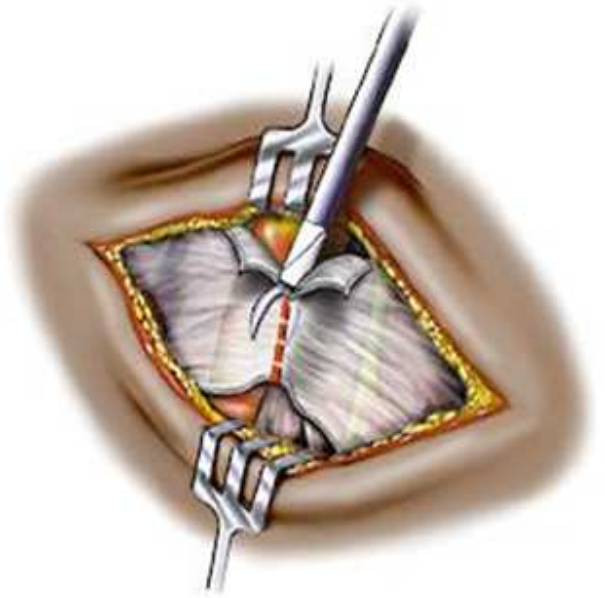

Figure 5. Position of the median and ulnar nerves and the incision of the carpal ligament to decompress the pressure on the median nerve. *Adapted from Nucleus Communications Incorporated (1998)*

2.2.2 Patients' surgical procedure

2.3.1 CTS operation

All CTS patients underwent an open carpal tunnel decompression (see Figure 5). The procedure involved a small palmar incision to visualize the carpal ligament and the median nerve. The transverse carpal ligament was then sectioned to provide relief on pressure on the median nerve at the carpal tunnel site (Dawson *et al*, 1983; Goodgold and Eberstein, 1980). The surgical procedure lasted between 30 – 60 min and was performed under regional anaesthesia (Auerbach, Southern California Orthopaedic Institute, 2004).

2.3.2 Control operation

All control patients underwent a minor operation which predominantly involved the removal/extraction of a tooth. Once the anaesthetic had taken effect, the dentist or oral surgeon would widen the socket using a tool elevator or a pair of special forceps. The tooth would then be moved the from side to side until it was loose enough to be removed completely. No patient had gums or jawbone deformities. The procedure lasted for about 30 minutes.

2.4 Polysomnography

After screening, both the patients and controls were asked to spend four nights in the Wits Dial-a- Bed Sleep Laboratory, two nights pre-operatively and two nights post-operatively. The first night served as an adaptation night, on each occasion. All procedures were identical to those followed on recording nights, however, data was not collected. Pre-operative recordings were made between three days and four weeks before the operation, and post-operative recordings were made between 10 days and two months after the operation for all the subjects (patients and

controls). The average time for post-operative recording was 34 ±15days for CTS patients and 36 ± 15 days for control subjects.

I asked patients to keep to their regular sleep-wake schedules during the week before each visit to the laboratory. Most of my subjects did not adhere to this request. They completed morning questionnaires to record their bedtimes, wake times, and subjective sleep quality. I also asked the patients not to exercise, drink coffee or other caffeinated beverages, or take sleeping tablets on each day before coming to the laboratory. Finally, I asked patients not to take any pain medications in the evening of their overnight recordings. Patients arrived at the laboratory 2-3 hours before bedtime so they could familiarise themselves with the laboratory. All the patients were encouraged to go to bed at their normal sleep time, which ranged between 21:00 and 22:30. Spontaneous wake-up time ranged between 05:30 and 07:30.

2.4.1 International 10/20 System

On each visit to the sleep laboratory standard electroencephalographic, electrooculographic, and electromyographic recordings were made on a computerized electroencephalograph (Medelec DG 20, Vickers Medical, Surrey, England) at a virtual speed of 15mm/s. The standard International 10/20 System was used for electrode placement (Spriggs, 2002).

EEG was recorded from two leads, C3 and C4, referenced to an indifferent electrode placed on the contralateral mastoid (A1 and A2). Bipolar submental electromyographic (EMG) and referential electro-oculographs were also recorded (Figure 6). The electro-oculograph leads were placed 10 mm out from the outer canthus, with one placed slightly above and one placed slightly below the horizontal plane to allow for the symmetric recording of both the vertical and the horizontal oscillatory movements of the eyes (Spriggs, 2002; Chokroverty, *et al*, 2005). These electrodes were referenced to the indifferent electrode on the opposite side of the head (A1 or A2).

For the recording of chin EMG, leads were placed flat against the skin to ensure stability throughout the night. Lead A was placed over submental muscles on one side and B on the

opposite side of the jaws to measure the muscle contraction (Spriggs, 2002). See Figure 6 for electrode placement.

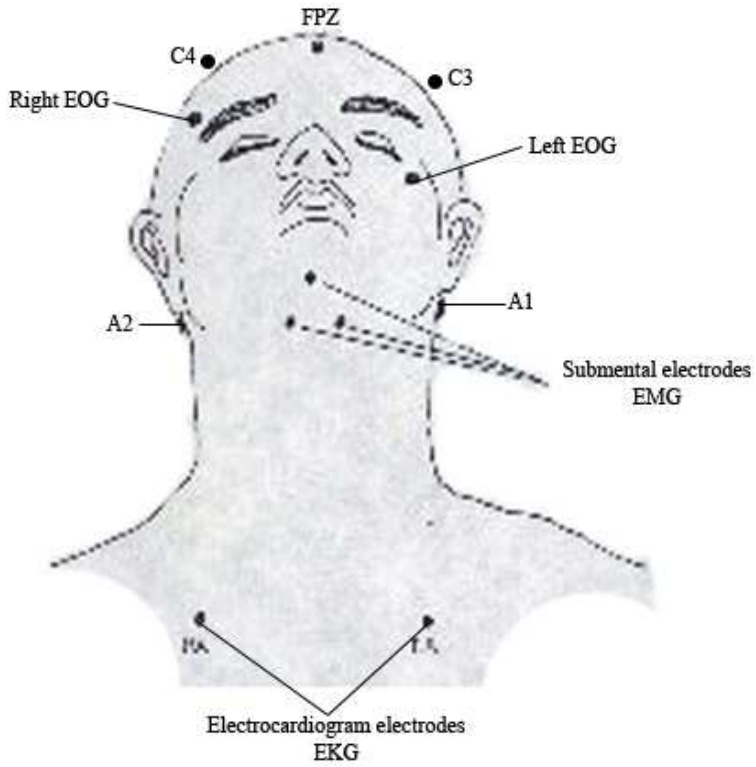

Figure 6. The 10-20 electrode placement system for a polysomnogram recording.

Table 5. Recording parameters used for Polysomnograph

Channel	Low frequency filter	High frequency filter	Sensitivity
EEG/EOG	.5Hz	35Hz	7μV/mm
EMG	10Hz	70Hz	5μV/mm

Electrode resistance- less than 10kiloOhms

2.4.2 Sleep variables and subjective data

Thirty-second epochs were scored according to the standard criteria (Rechtschaffen and Kales, 1968) by me. A selection of records was double-checked by Dr. Alison Bentley, a scorer blind to the identity and condition of the subjects. Sleep onset latency (SOL) was calculated as the time from lights out to the appearance of the first two consecutive epochs (60s) of stage 2 sleep. The sleep period was defined as the time from sleep onset until lights-on, including any intervening wakefulness. Total sleep time (TST) was computed as the amount of actual sleep time within the time in bed interval, equal to the total recording time from lights out to lights-on minus the sum of total wake/movement time. Sleep efficiency was calculated as the proportion of sleep time to total time spent in bed, expressed as a percentage.

Slow wave sleep latency was calculated as the time from sleep onset to the first of at least 60 seconds of stage 3 sleep. The REM onset latency was calculated as the time between sleep onset and any indication of the first continuous 30 second epoch of REM sleep. Time spent in REM sleep, stage 2 sleep, stage 3 and stage 4 sleep combined (slow wave sleep), stage 1 sleep, and wakefulness/movement time, were calculated as a percentage of the sleep period.

Transient arousals were scored independent of Rechtschaffen & Kales, 1968 epoch scoring. An arousal differs from wake time, defined in Rechtschaffen and Kales, 1968, which lasts 15 seconds or longer in a 30 second epoch. In contrast, an EEG arousal lasts between 3 and 15 seconds and is as an abrupt shift in EEG frequency, which may include theta, alpha and/or frequencies greater than16Hz but not spindles (Mathur and Douglas, 1995). The subject needs to be asleep for at least 10 continuous seconds before an arousal can be scored. Arousals in REM sleep are scored only when they are accompanied by an increase in submental EMG amplitude. Delta waves, K complex and artefacts are not counted as arousals unless accompanied by a frequency shift (Chokroverty, 2006). Arousal index was calculated according to the recommended polygraphic parameters for arousal scoring based on a preliminary report from

Sleep Disorders Atlas Task Force of the American Sleep Disorders Association (1995). The arousal index was recorded as the number of arousals per hour.

2.5 Subjective Assessments

On each visit to the sleep laboratory, patients assessed their pain severity, mood, and sleep quality using validated questionnaires and visual analogue scales. I assessed the quality of their pain in the evening and morning using the McGill Pain Questionnaire, which has been used extensively to describe different pain types (Wall and Melzack, 1989). The questionnaire consists of 78 adjectives arranged into 20 groups, reflecting similar pain quantities. The patients selected a word that best described their pain from each applicable group. Because of the language barrier in most of the patients regarding the words used, pain rating index (PRI), which is a verbal scale pain intensity measurement index, could not be used. The patients also assessed the severity of their pain in the evening before bed, and in the morning, when they woke up, by making a mark on a 100mm visual analogue scale (VAS) anchored at their 'worst pain' ever experienced and 'no pain' at all (Collins *et al*., 1997). All the subjects were comfortable with and could comprehend the visual analogue scale.

Patients were asked to complete the Beck Depression Inventory (Beck *et al*., 1961) to assess their psychological status on each visit to the laboratory. The Beck Depression Inventory consists of 21 questions and is widely used to assess depression. The conventional cut-off points for mild, moderate and severe depression used on the BDI in a psychiatric setting are: <10 minimal depression, 10-19 mild depression, 20-29 moderate depression and >30 severe depression (Beck *et al*, 1961). The BDI was used to describe the way the patients had been feeling the previous week, including the day of filling in the form.

The profile of mood states (POMS) questionnaire was used to assess the instantaneous mood state of the subjects at each laboratory visit. All the subjects had a fair comprehension of the words used in POMS. The POMS consists of 65 words or brief phases (McNair *et al.,* 1971). It was developed by Mcnair, Lorr and Droppleman in 1971. The POMS consists of 65 adjectives to

which participants respond on a 5-point scale, from 1 (not at all) to 5 (extremely) based on how they are feeling right then (McNair *et al*., 1971). Six dimensions of mood are evaluated from the POMS, including tension-anxiety, depression-dejection, anger-hostility, vigour-activity, fatigue-inertia, and confusion-bewilderment. A total mood score is calculated by summing the scores of the six dimensions, with vigor weighted negatively.

Finally, in the evening of each recording night, patients completed a questionnaire describing the events of that day and indicated their evening anxiety on a VAS, with anchors of 'terrible agitation' and 'utterly calm and peaceful'. After each recording night, subjective sleep quality was assessed with a VAS, anchored at 'worst ever' and 'best ever' sleep quality. Similarly, morning vigilance was assessed with a VAS, anchored at 'worst ever' and 'best ever'. Patients also reported their subjective sleep onset latency, and the perception of the number and duration of awakenings during each night.

2.6 Data analysis

All results are reported as mean ± standard deviation. Arcsin square-root transformation was done on all visual analogue scale ratings to normalize the scores before analysis. A repeated-measures analysis of variance at a 95% confidence interval was used to investigate the effect of surgical intervention on polysomnographic and subjective sleep and mood variables. The effect of surgical intervention on VAS pain ratings in the evening and morning was determined using a repeated-measures ANOVA with treatment (pre-operation versus post-operation) and time (evening versus morning) as factors.

RESULTS

This chapter describes the results of different tests done on carpal tunnel syndrome (CTS) patients before and after the carpal tunnel decompression treatment. The CTS patients' results are compared to those of the control subjects before and after their minor surgical procedure for tooth extraction. The data presented in the main body of results will exclude the results obtained from one of the 7 CTS patients who participated in the study. I will later come back to this patient and present the results separately. Results include the nerve conduction studies data that were used to confirm the diagnosis of CTS on these patients. The sleep section consists of the objective polysomnographic measurements, as well as the subjective sleep assessment results that are comprised of visual analogue scale (VAS) rating as well as questionnaires on sleep behaviour before and after treatment for both the CTS as well as the control patients. Results of the ratings of the quality and the intensity of pain in all the subjects are also presented. The section on mood assessment describes results obtained from the profile of mood states (POMS) and the Beck depression inventory (BDI) instruments as well as assessment of evening levels of anxiety based on VAS in all patients before and after treatment. The last section on this chapter describes the CTS patient that was excluded from the study due to the fact that this patient reported no changes in his condition and continued to experience pain after CTS treatment.

3.1 Nerve conductions

The average median nerve distal motor conduction latencies for the patients with carpal tunnel syndrome before and after treatment are shown in Figure 7. Table 6 shows values before and after CTS treatment. The nerve conduction measurements were done at least 2 months after surgery on all our patients. The antidromic median nerve distal sensory tests showed absent conduction in 5 of the 6 patients, indicating a severe compressive neuropathy of the median nerve in these patients (Table 6). There was a slight increase in the incidence of fibrillation

potentials as well as nascent low amplitude polyphasic potentials on the abductor policis brevis muscles in 4 out of the 6 CTS patients, during post-operative electromyography. Five of the patients had a unilateral carpal tunnel syndrome of either the right or the left hand (Table 6), and one patient had a bilateral carpal tunnel syndrome. Out of the five patients who came back for a nerve conduction study post-operatively, only two showed an improvement in both sensory and motor conduction latencies with recovery in median nerve antidromic sensory conduction and also distal motor response amplitude and latency. There was no significant improvement shown by motor conduction amplitude response, post-operatively (Table 6). Before surgery the two CTS patients had absent distal sensory action potential, which returned after treatment

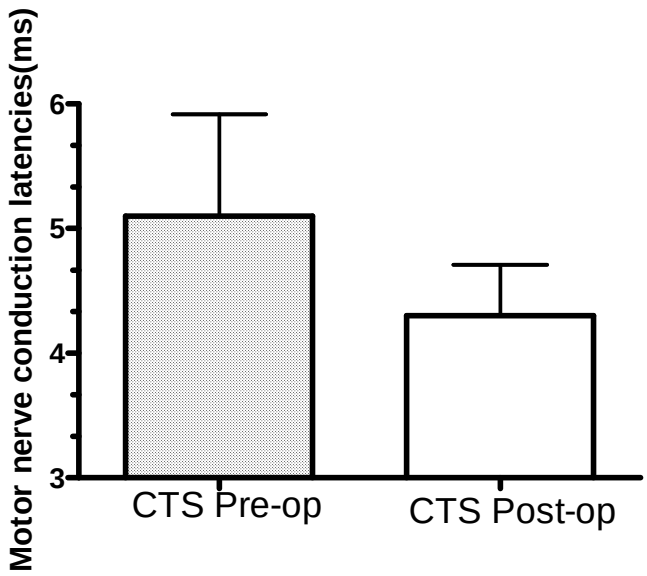

Figure 7. Distal motor conduction latency on 5 CTS patients recorded before and after the CTS operation was performed. Post-operative reduction in latency was statistically significant t=1.980, p=0.04.

Table 6. Distal motor conduction amplitude on 5 CTS patients recorded before and after the CTS operation was performed.

Subject	Pre-op amplitude (mv)	Post-op amplitude (mv)
1	1.5	1.9
2	1.8	2.2
3	1.5	1.4
4 R	No response	*15μv*
L	2.5	3
5	2.9	3.4

Table 7. Median nerve distal sensory latency and amplitude on 5 patients with carpal tunnel syndrome before and after treatment.

Subject	**Distal sensory latency (ms) and amplitude(μv)**	
	Pre-op	Post-op
1	R-No response	2.4(14μv)
2	R-No response	No Response
3	R-No response	3.0(19μv)
4	R-No response	No Response
5	R-Low amplitude	No Response
	L-No response	No Response
6	R-No response	-

R=Right hand L=Left hand

3.2 Sleep

3.2.1 Polysomnogram

This section describes the results obtained from polysomnograms from two recording nights, one pre-operative and one post-operative night. Results are compared between the CTS and control patients before and after surgery (See Table 8).

There were no significant differences in time in bed, total sleep period, total sleep time, sleep onset latency, latency to REM sleep or latency to slow wave sleep either between patient groups or before compared to after treatment (Table 8). There was a significant treatment effect with no significant interaction effect for sleep efficiency with both groups having better sleep efficiency while spending less time awake/moving after the operation (Table 8). CTS patients spent more time awake/moving both before and after their operation compared to controls (Table 8). The CTS patients showed significant group-by-treatment effect when compared to the control group (Table 8). The CTS patients also had a larger arousal index than did the control patients, and that arousal index was reduced after surgery particularly for the CTS patients. There were no differences in percentage time spent in Stage 1 sleep, Stage 2 sleep, or REM sleep either between subject groups or before and after the operation. However, the CTS patients had less slow wave sleep than did the control patients, but there was no significant change in percentage slow wave sleep after surgery.

3.2.2 Subjective sleep assessment

Subjective ratings of sleep quality by the CTS and control patients are shown in Table 9. The CTS patients reported that they woke up more frequently and spent more time awake than did controls on both nights. There was also a significant treatment and interaction effect for awake time, with the time spent awake being reduced following the operation particularly in the CTS patients. CTS patients also rated their sleep quality as significantly poorer than control patients overall and reported that their sleep quality was improved after the operation (Table 9). There were no differences in perceived time to fall asleep between groups or as a result of treatment in either group. Finally, there were significant subject and treatment effects for morning vigilance, with a tendency for an interaction effect ($p = 0.07$). Patients with CTS reported lower levels of morning vigilance than controls and both groups reported higher levels of vigilance after the operation, which tended to be more pronounced in CTS patients. The CTS patients reported not using pain medication for CTS pain after surgery, other than for other pain related conditions.

Table 8. Sleep variables (mean±SD) derived from the polysomnogram for six patients with carpal tunnel syndrome before and after a carpal tunnel release operation compared with six control patients before and after a minor surgical procedure for a non-painful dental condition.

	CTS patients		**Control patients**		**Repeated measures**
Variable	**Before**	**After**	**Before**	**After**	**2 way ANOVA**
TIB (min)	465±12	471±16	471±14	468±23	Subjects F(1,10)=0.04, P=0.9 Treatment F(1,10)=0.03, P=0.9 Interaction F(1,10)=0.3, P=0.6
Total sleep Period (min)	451±12	458±17	456±14	450±24	Subjects F(1,10)=0.04, P=0.8 Treatment F(1,10)=0.01, P=0.9 Interaction F(1,10)=0.6, P=0.5
TST(min)	385±16	400±15	397±16	404±19	Subjects F(1,10)=1.7, P=0.2 Treatment F(1,10)=2.2, P=0.2 Interaction F(1,10)=0.3, P=0.6
Sleep efficiency (%)	82.7±1.7	84.9±1.4	84.4±3.2	86.4±0.8	Subjects F(1,10)=2.8, P=0.1 Treatment F(1,10)=10.2, P=0.01* Interaction F(1,10)=0.01, P=0.9
Awake/ Movement (%)	15±1	13±1	12±2	11±1	Subjects F(1,10)=13.1, P=0.005* Treatment F(1,10)=10.5, P=0.009* Interaction F(1,10)=0.7, P=0.4
Stage1 (%)	7±1	6±2	5±1	6±2	Subjects F(1,10)=2.7, P=0.1

					Treatment F(1,10)=1.1, P=0.3 Interaction F(1,10)=2.0, P=0.3
Stage2 (%)	41±2	41±3	40±2	42±2	Subjects F(1,10)= 0.3, P=0.6 Treatment F(1,10)=1.7, P=0.2 Interaction F(1,10)=1.4, P=0.3
SWS (%)	19±0.8	20±1	21±2	22±2	Subjects F(1,10)=6.0, P=0.03* Treatment F (1,10) =0.6, P=0.5 Interaction F (1,10) =0.01, P=0.9
REM (%)	18±2	21±4	20±0.9	20±0.9	Subjects F(1,10)=0.4, P=0.5 Treatment F (1,10) =2.7, P=0.1 Interaction F (1,10) =3.1, P=0.1
SOL(min)	14±2	13±2	15±1	18±4	Subjects F(1,10)=4.6, P=0.06 Treatment F(1,10)=0.6, P=0.5 Interaction F(1,10)=2.7, P=0.1
ROL(min)	71±10	66±9	69±5	72±6	Subjects F(1,10)=0.4, P=0.5 Treatment F(1,10)=0.07, P=0.8 Interaction F(1,10)=1.3, P=0.3
Latency to Stage 3(min)	15±2	14±2	15±2	12±2	Subjects F(1,10)=0.4, P=0.5 Treatment F(1,10)=4.0, P=0.07 Interaction F(1,10)=1.3, P=0.3
Arousal Index (number/hour of sleep)	7±3	3±2	2±2	2±1	Subjects F(1,10)=33.1, P<0.01* Treatment F(1,10)=29.7, P<0.01* Interaction F(1,10)=29.7, P<0.01*

Time spent in each sleep stage or wake/movement is expressed as a % of Total Sleep Period

Table 9. Subjective assessments of sleep and morning vigilance (mean±SD) for CTS and control patients before and after their operation.

Question	**CTS patients**		**Control Patients**		**Repeated measures 2 way ANOVA**
	Before	After	Before	After	
How long do you think it took to fall asleep? (min)	45±24	33±14	28±12	23±10	Subjects F(1.10)=2.7, P = 0.1 Treatment F(1.10)=3.5, P=0.09 Interaction F(1.10)=0.8, P=0.4
How many times did you wake up?	4±2	2±1	3±1	2±1	Subjects F (1.10)=26.1, P=0.01* Treatment F (1.10)=2.91, P=0.37 Interaction F (1.10)=2.91, P=0.37
If you woke up how long were you awake for (min)?	45±17	22±9	15±4	16±6	Subjects F(1.10)=28.4, P<0.001* Treatment F(1.10)=5.5, P=0.04* Interaction F(1.10)=06.4, P=0.03*
VAS: Sleep quality (Worst ever to best ever)	71±8	88±6	98±2	98±3	Subjects F(1.10)=47.1, P<0.001* Treatment F(1.10)=10.1, P=0.01* Interaction F(1.10)=7.2, P=0.023*
VAS: Morning vigilance (Worst ever to best ever)	71±8	88±5	96±3	98±3	Subjects F(1.10)=57.7, P<0.001* Treatment F(1.10)=16.2, P=0.002* Interaction F(1.10)=4.0, P=0.07

3.3 Pain

3.3.1 Pain intensity

The CTS patients rated their pain on a VAS as significantly lower after the carpal tunnel release operation in both the evening and morning (ANOVA treatment effect: $F(1,5) = 468.0$, $p < 0.001$). There was no significant difference in pain ratings between evening and morning (ANOVA time effect: $F(1,5) = 2.5$, $p = 0.2$) and no significant interaction between treatment and time (ANOVA interaction effect: $F(1,5) = 2.0$, $p = 0.2$). All patients rated their evening and their morning pain as being low or absent after surgery (Figure 8). None of the control patients reported pain during their visit to the sleep laboratory either before or after their operation.

3.3.2 Pain quality

3.3.2.1 The McGill Pain questionnaire

The MPQ was administered in English for all the subjects. All the subjects tested could speak English, but it was not necessarily their first language. All words chosen were explained to the patients in their own language. The primary comparison was that of the MPQ before and after the operation in all CTS patients. See Table 10 for words chosen to describe the CTS pain by the patients on the pain questionnaire. On the McGill pain questionnaire, all six patients with CTS described the pain as “pricking” (Table 10). The next most common words used to describe the pain were “sharp” and “numb”, used by four out of six subjects. All the patients reported the night-time as the time when their pain is at its worst. The control patients did not select any words on the McGill pain questionnaire as they did not report any pain.

Table 10.. All the words chosen by the CTS patients in the McGill pain questionnaire before the CTS operation, including the most common words.

Words chosen	Number of patients Before	Number of patients After
Pricking	6	0
Sharp	4	0
Numb	4	0
Shooting	3	0
Cramping	3	0
Sore	3	0
Dull	3	0
Piercing	3	0
Sharp	3	0
Annoying	3	0
Burning	3	0
Tingling	2	0
Stinging	1	0
Tight	1	0

3.4 Mood

3.4.1 Profile of Mood States (POMS)

CTS patients had higher POMS scores, reflecting poorer mood, when compared to control patients regardless of treatment (Subject: $F(1,10) = 40.7$, $p < 0.001$). The significant treatment ($F(1,10) = 13.1$, $p = 0.005$) and interaction ($F(1,10) = 8.8$, $p = 0.014$) effects showed that there was significant improvement in mood for the CTS patients after surgery but little change in mood in the controls (See Figure 9).

3.4.2 Beck Depression Inventory

CTS patients had higher scores on the Beck Depression Inventory, reflecting greater levels of depression, compared to control patients (Subject: $F(1,10) = 64.8$, $p < 0.001$) (Figure 10). The significant treatment ($F(1,10) = 10.4$, $p = 0.009$) and interaction ($F(1,10) = 14.1$, $p = 0.004$) effects showed that the CTS patients were less depressed after their operation with little change seen in controls.

3.4.3 Evening anxiety

There were significant treatment ($F(1,10) = 14.2$, $p = 0.004$), subject ($F(1,10) = 6.4$, $p = 0.03$) and interaction ($F(1,10) = 9.0$. $p = 0.01$) effects for evening anxiety, as rated on a visual analogue scale before subjects went to sleep. CTS patients were more anxious before their operation (83±7

mm) compared to after the operation (96±4 mm), and compared to control patients (pre-operation: 95±3 mm; post-operation: 96±3 mm).

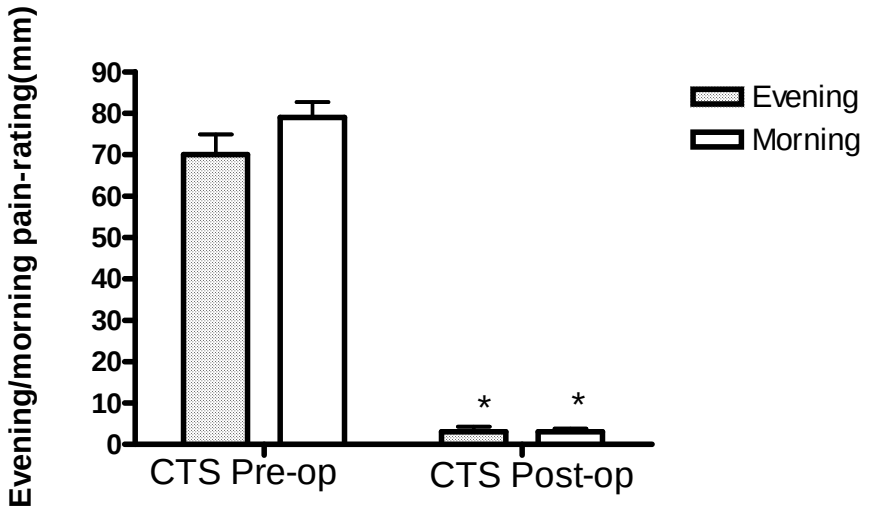

Figure 8: Ratings of evening and morning pain severity on a 100 mm visual analogue scale in 6 patients with carpal tunnel syndrome before and after a carpal tunnel release operation. * $p < 0.001$ compared to before the operation.

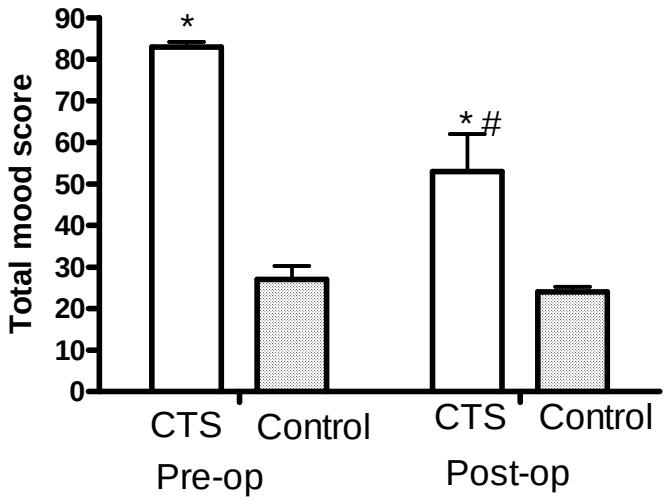

Figure 9. Total Mood Score (mean±SD) calculated from the POMS in six patients with CTS and six patients with non-painful dental complaints before and after treatment.

*significantly different from controls, $p < 0.001$; # significantly different from pre-operatively.

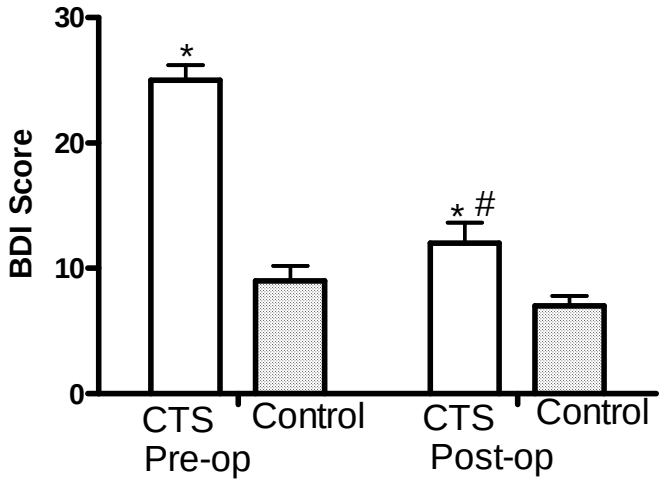

Figure 10. Beck Depression Inventory Score (mean ±SD) for six patients diagnosed with carpal tunnel syndrome and six patients with non-painful dental complaints before and after treatment**.**
* significantly different from controls, $p < 0.001$; # significantly different from pre-operative.

3.5 The excluded patient

This 72 year old patient had had clinical symptoms of carpal tunnel syndrome for more than two years. He had complained of pins and needles, numbness, as well as unbearable pain on the median and ulnar nerve sensory distribution as well as along the arm up to the neck. There was no evidence of cervical radiculopathy noted on needle examination that had been done three weeks before this patient entered my study. The patient reported no known sleep problem in the oral interview for the sleep studies. The patient showed absent sensory and motor conduction latencies with minute sensory and motor response amplitude for the median and ulnar nerves, bilaterally. Needle examination showed fibrillation potentials, positive sharp activity, and increased insertional activity with reduced recruitment pattern on the thenar muscles.

Table 13 shows a comparison of data collected in this patient compared with the other CTS patients. The polysomnogram on this patient showed that he had a very high percentage of Stage 1 sleep, a longer sleep onset latency, and a lower sleep efficiency than the other patients. The patient reported continuous poor sleep quality with no noticeable changes before and after the operation (35mm before and 32mm after operation on the sleep quality VAS). The patient also had very high BDI and POMS scores, indicating severe depression, which did not change after treatment (Table 11). This patient still reported severe pain long after the surgery and the PSG were done. This reported pain was accompanied by no change in both sensory and motor conduction latency (Table 11).

Table 11. Variables for the CTS patient that was excluded from the study

Polysomnogram	**Before Treatment**		**After treatment**	
	This subject	Other subjects	This subject	Other subjects
TIB (min)	474	465±12	444	471±16
Total sleep period(min)	446	451±12	419	453±17
TST(min)	356	385±16	339	400±15
Sleep efficiency (%)	73	82.7±1.7	76	84.9±1.4
Awake/movement (%)	19	15±1	18	13±1
Stage 1%	29	7±1	21	6±2
Stage 2%	30	41±2	33	41±3
SWS (%)	18	19±0.8	20	20±1
REM (%)	11	18±2	12	21±2
SOL (min)	28	14±2	25	13±2
ROL (min)	95	71±10	88	66±9
Latency to stage 3 (min)	25	15±3	22	14±2
Arousal index (Number/hours of sleep)	8	7±3	6	3±2
Other measurements				
POMS	110	83±3	104	53±22
BDI	43	25±7	41	13±4
VAS pain rating	91	90±8	93	10±2
VAS Sleep quality	35	71±8	32	88±6
Median nerve distal sensory latency	Absent	5.8±2	Absent	3.6±1
Median nerve distal motor latency	Absent	Absent	Absent	3.8±2

Discussion

I investigated the changes in sleep architecture, subjective sleep assessment, mood and pain in patients with carpal tunnel syndrome before and after CTS decompression. I compared CTS patients with control subjects who underwent a minor dental surgical procedure of similar magnitude to carpal tunnel decompression. This study is the first, as far as I am aware, to use polysomnography to record sleep architecture in patients with CTS before and after surgical treatment. All patients who participated in the study had electrophysiological features of CTS. I showed that my patients with CTS had significant abnormalities in the distal sensory motor latencies, velocities and sensory/motor response amplitude. All patients that took part in the study had absent sensory conduction latencies and sensory action potential response amplitude and grossly delayed distal motor conduction latencies. I discovered that the sensory action potential response amplitude had partially recovered in these patients after CTS operation with accompanying recovery in distal sensory latencies. The CTS patients had shown some improvement in the electrophysiological CTS features, but the condition had not been completely cured, following surgery. The nerve conduction studies were still abnormal. Despite very little change in electrophysiological measures, the CTS patients reported an almost complete eradication of pain post-operatively compared to pre-operatively. I discovered that after surgery, CTS patients reported a better sleep quality, improved morning vigilance and less perceived wakefulness during the night compared to the pre-operative recording. They also showed dramatic improvements in mood post-operatively. CTS patients showed signs of moderate depression pre-operatively, which was reduced to minimal/mild depression post-operatively based on Beck Depression Inventory scores. Age- and gender-matched control patients who underwent an operation of similar duration showed no significant change in subjective sleep assessments or mood post-operatively. I have, therefore, shown that the improvement in mood and subjective sleep quality is likely due to the eradication of pain post-operatively in CTS patients. Despite the dramatic improvements in subjective sleep perception, there was very little change in objective polysomnographic measures post-operatively compared to pre-operatively in the CTS patients. The only variable that showed an interaction effect was arousal index, which was lower in CTS patients post-operatively. The CTS patients showed an

improvement in sleep efficiency and a reduction in time spent awake or moving post-operatively, however, this effect was also seen in the control patients and therefore was not specific to the removal of pain in the CTS patients. The improvement in sleep efficiency was small, being only two percentage points, on average, in both groups.

My study demonstrated that the CTS patients' subjective perception of their pain and sleep improved after surgery disproportionately with respect to any objective measure of neurophysiology or sleep architecture. Minimal changes were noted in the objective measurement of sleep, the overnight polysomnogram. Even though the CTS patients showed some changes in sensory and motor conduction studies, these were just residual deficits. The perceived improvement in pain after the CTS surgery exceeded the neural improvement measured in conduction studies. These findings are strengthened by the inclusion of a comparison group of subjects in my study to control for any effects of surgery or other factors on sleep that may have changed over the pre-operative to post-operative time interval. The control patients had no pain and no symptoms of depression or anxiety either before or after treatment. Psychological problems may therefore be dependent on whether patients undergoing surgery are in pain or not, amongst other variables, as was evidenced in CTS patients.

The study had several limitations. The first was that of the language barrier particularly on the subjective instruments used in the study. Most patients did not use English as their first or second language even though all spoke the language. The language barrier was more or less similar for the CTS patients. The language barrier posed a problem in most questions that depended on rigorous understanding of the language in order respond to questions. The McGill pain questionnaire was particularly difficult because of its absolute reliance on language proficiency of the subjects making it difficult to get a comprehensive analysis of the questionnaire. It was therefore not possible to compute the pain rating index. Although some explaining had to be done on the other subjective questionnaires like the POMS and the BDI, these questionnaires seemed better understood than the McGill pain questionnaire by the subjects.

The second limitation on the study was that no other objective measurement was done on all the patients to exclude any other sleep problem. Incidental sleep disorders were excluded only by

interviews and sleep questionnaires. Some patients may have had some undiagnosed sleep problems that may have disturbed their sleep. Screening for sleep breathing disorders like sleep apnoea or snoring would have been one way helpful to exclude conditions which may significantly alter sleep architecture including the patient's sleep efficiency and periodic sleep disruptions. I also did not analyze the microstructure of sleep, such as delta and alpha activity in the EEG. It is possible that the CTS patients may have shown improvements in the microstructure of sleep post-operatively that may have influenced the subjective perception of sleep.

Thirdly, my patients had generally increased BMI. There is no available research-based evidence linking the increase in BMI directly to the prevalence of CTS. The same cannot, however, be said with the relationship between increased BMI and sleep apnea, where strong correlation can be found in literature. One can then argue that the exclusion of sleep apnea though objective screening would have been helpful in my patient sample.

A fourth limitation was the sample size. A bigger sample of both CTS and control patients would have provided a more comprehensive analysis of the results than the sample size considered for this study. A fifth limiting factor was the fact that no actigraph logs were used to properly compute the sleep-wake schedule for these patients. The pitfall with the sleep diaries was that they were not all properly filled up to be able to get a proper analysis of the estimated sleep duration. Lastly, there is a need for a long-term follow up for post-operative re-testing for CTS patients in particular, to accommodate neural recovery time lag after CTS surgery.

Few studies have investigated sleep quality in patients with CTS and no other study has investigated sleep architecture in patients with CTS before and after treatment with which to compare my results. An extensive study of CTS sleep disruption was conducted by Lehtinen *et al.,* (1996). Similar to my results, that study found that CTS patients reported a poorer sleep quality with a more fragmented sleep and longer awakenings. Although polysomnographic recordings were not made, objective measurements of gross body movements during sleep were made in six patients with CTS before and after surgical treatment (Lehtinen *et al.,* (1996). Patients had less motor-active wakefulness, less movement time and shorter movement periods post-operatively compared to pre-operatively (Lehtinen *et al*., 1996). Similarly, I found that CTS patients had fewer microarousals and less awake/movement time post-operatively. However, a

control group of patients in my study showed a similar small decrease in awake/movement time post-operatively suggesting that the decrease in awake/movement time was not only related to the removal of CTS pain. The study by Lehtinen et al (1996) did not have a control group of subjects.

Nerve conduction variables were also recorded on the symptomatic arm in the evening before patients went to bed, during the night when subjects woke up due to numbness, as well as in the morning in the study by Lehtinen *et al*. (1996). The nerve conduction studies showed significant improvement in the patients after CTS surgery, a trend also confirmed in my study. All variables measured including distal sensory/motor conduction latencies, conduction velocities and response amplitude showed significant improvement (Lehtinen *et al*., 1996). There was a longer interval (6 months) between the surgery and follow-up recordings in that study (Lehtinen *et al.*, 1996) than in my study (< 2 months), allowing more time for recovery. .

In the objective measurements obtained using a polysomnograph in my study, there was no noticeable change in Time in bed, Total sleep time, ROL, SOL, latency to SWS, percentage of stage1, 2 and REM sleep pre-operatively compared to post-operatively despite the improvements in subjective sleep quality and no difference between CTS and control subjects. The relative resistance to change in REM duration has been observed in other pain-related disorders like rheumatoid arthritis, fibromyalgia as well as chronic fatigue syndrome (Modolfsky *et al.,* 1975, Modolsky (2001), Modolsky and MacFarlane (2005), Nicassio *et al.,* 2002). The observation also concurs with other findings on experimentally induced pain which found no change in REM duration in response to pain in the experimental subjects (Daya and Bentley, (2009), Drewes *et al.,* 1997, Velluti (1997). I established that percentage time spent awake/moving was significantly greater in CTS patients than controls. This finding supports that of other studies about chronic pain: The most consistent finding in chronic pain diseases is a greater amount of time spent awake after sleep onset compared to healthy controls (Drewes and Arendt-Nielsen, 2001). Although wake/movement time decreased significantly post-operatively in the CTS patients in my study, it still remained higher than controls showing that factors other than pain may be disturbing their sleep. Also, controls showed a similar reduction in wake/movement time post-operatively despite not having any pain pre-operatively. Possibly, all patients were more comfortable in the laboratory on their fourth overnight (post-operative recording) than on their

second overnight (pre-operative night) despite having an initial adaptation night. I also found that SWS (as a percentage of total sleep period) was marginally less in the CTS subjects compared to controls on both pre and post-operative nights. Other studies have reported lower levels of SWS in some patients with chronic pain, such as low back pain, compared to controls (Drewes and Arendt-Nielsen, 2001). The percentage time spent in SWS, however, did not change after treatment and alleviation of pain in the CTS patients in my study showing that the lower amount of SWS was not simply related to the presence or absence of pain. All my CTS patients were categorised as having a severe form of CTS. The CTS severity is characterised by the absence or delay in both sensory and motor conduction latencies accompanied by reduction in sensory and motor response amplitude, as well as abnormal electromyographic patterns (Dawson, 1995). The pain exhibited by my CTS patients was typical of the pain experienced by most neuropathic pain patients. I discovered that the most complained about pain descriptions by my CTS patients were numbness, pricking, and burning sensation and shooting on the median nerve myotomes. Others have also reported that patients with CTS report symptoms such as shooting, burning sensation and numbness, pricking and shooting on the McGill pain questionnaire (Nashed *et al.*, 2010; Iida *et al.*, 2008). The CTS patients also presented with similar reported characteristic daytime and night-time symptoms which were relieved following surgical decompression (Higgs *et al*., 1997; Iida *et al.*, 2008). Previous studies have confirmed complete or marked (80 to 100%) relief of CTS symptoms following surgery (Townshend *et al*., 2004; Richer *et al*., 2004). In one study, 100% complete pain relief was achieved in patients with early CTS symptoms, 94% in the moderate symptom group and 50% in patients with severe CTS (Iada *et al*., 2008). All my CTS patients were categorised as having a severe form of CTS. The CTS severity is characterised by the absence or delay in both sensory and motor conduction latencies accompanied by reduction in sensory and motor response amplitude, as well as abnormal electromyographic patterns (Table 3) (Dawson, 1995). Similarly, the CTS patients in my study reported subjective pain relief following surgery. The reported improvement in pain symptoms has been reported, particularly in “paraesthesia” following surgery (Mirone *et al*., 2008; Wilder-Smith, 2008). Other studies have shown improvements in psychological parameters after CTS decompression surgery, similar to my findings. CTS patients have lower depression and anxiety scores after surgery compared to pre-operative levels, suggesting that the chronic pain of CTS causes, at least in part, psychological distress (Hobby *et al*., 2005). Indeed, there is a strong correlation between

pain severity and depressive symptoms and people with chronic pain have a high prevalence of depressive disorders (Landis et al., 2004, Pagano et al., 2004, Wilson et al., 2002). Chronic pain, psychological distress, and sleep disturbances often co-exist (Riley *et al*., 2001) and it is difficult to determine direction of causality. Morin *et al.*, 1998, found a self-reported sleep disruption as well as a psychological and mood disturbance in patients with chronic pain. Patients with lower back pain, fibromyalgia as well as orofacial pain patients were investigated using subjective sleep measurement questionnaires, as well as mood and anxiety scales to determine the influence of chronic pain on sleep and mood. The Beck Depression Index, the Pain Anxiety symptom scale and the Pittsburgh Sleep Quality Index were the subjective questionnaires used in that study. These patients had had chronic pain for longer than 6 months, and others for as long as 5 years. They did not find any difference in depression or anxiety comparing patients with and without sleep disturbance, suggesting that sleep disturbance is not always associated with an underlying mood disturbance in chronic pain patients (Morin *et al*., 1998). However, there is other evidence suggesting that pain increases negative mood over time and that the negative mood makes a more substantial contribution to poor sleep quality than does pain (Riley *et al*., 2001). In my study, it is therefore possible that the improvement in the subjective perception of sleep quality in CTS patients post-operatively was partially mediated by the improvement in their mood.

I also found no direct relationship in the recovery of the median nerve or the improvement of the median nerve, post-operatively in the CTS patients, to the reported improvement in sleep quality. The CTS patients reported improvement in sleep quality long before the median nerve recovery was complete. We found no direct relationship between the actual recovery duration of the sensory/motor fibers of the median nerve based on the nerve conduction studies and the subjective perception of pain and sleep quality improvement amongst the CTS patients. There is no documented report about the extent of CTS recovery and sleep quality in the study of CTS patients conducted by Lehtinen *et al., (*1996). The 2 groups were evaluated at almost the same time within the two month period post-surgically.

According to Dellon (2000), the recovery of the CTS post-operatively is characterised by two stages. Firstly, the improvement of the symptoms (numbness, pain, pins and needles) is due to the physical release of pressure on the nerve and the immediate improvement of the blood flow.

Secondly, it is due to the recovery of the inside of the nerve and from the actual loss or degeneration of nerve fibers and nerve wasting. The nerve fibers must regenerate from the site of the nerve injury to the finger tips, and it is not immediate. Depending on the severity of the CTS, it may take six months to a year. I conducted the electrophysiological measurements about 2 months post-operatively, when the nerve fibers were likely still recovering.

In our study we have successfully shown that even though the clinical presentation and the relief of pain symptoms of carpal tunnel syndrome are dependent on the surgical procedure to decompress the median nerve, physiological post-operative recovery takes place long after reported pain relief, confirming the possibility of continued existence of CTS immediately after surgery. The continued existence of the objectively measured abnormality on the EMG and nerve conduction studies shortly after surgery, despite the reported subjective improvement could provide an explanation for the recurrence of CTS in these patients. The recurrence of carpal tunnel syndrome has been reported as a common occurrence in the CTS patients (Dyck *et al*., 1971; Amadio, 2009). Most common causes are due to incomplete release of carpal ligament, post-operative adhesions, intra-neural fascicular scarring, and tethering of the median nerve with the carpal canal (Raimbeau *et al*., 2008). The percentage of recurrence has been reported at ranging from 3 to 12 and 3 to 19 percent (Raimbeau *et al*, 2008). This recurrence percentage may be higher as my study has shown that all my CTS patients had no short-term improvement in EMG and nerve conduction studies compared to normal benchmark values. Most patients in my study were seen again for re-testing of the EMG and nerve conduction studies about two months after surgery for decompression. None of my patients were followed up afterwards for sufficiently long to confirm whether or not they had recurrence of CTS. The lack of improvement in polysomnogram, EMG and nerve conduction studies, post-operatively whilst there is an almost complete subjective pain relief, offers an interesting case to argue the failure of CTS surgery to completely treat CTS on a short term basis. It also may provide the basis for the recurrence of CTS in some patients that are treated with decompression, depending possibly on the severity of the CTS, opening another question for further research.

Having considered and stated the various limitations in my research, my study did, however, manage to conclusively show that the reported improvement in subjective pain relief, subjective sleep quality and psychological improvement and vigilance are independent of the objectively

measured results of the polysomnogram and the electrophysiological recovery as well as the integrity of the median sensory and motor fibers. A lot more research can still be done based on our significant findings. This further research may for instance explore the usage of language to promote the better understanding of the language-dependant subjective instruments as I discovered some barriers in the comprehension of some of the words used in the questionnaires used for my research for non-English speakers. More emphasis should also be placed on stricter exclusion criteria for incidental sleep disorders that may significantly alter sleep variables and cause periodic sleep disruptions and other sleep distortions. A provision for a much bigger sample size may also help in improving the statistical analysis of the results. Lastly, a future direction would be to explore the recovery rate and integrity of the median nerve over a longer period of time following CTS surgery, as well as whether there are any subsequent changes in sleep architecture given a longer period of recovery for the median nerve following surgery.

Conclusion

The overall purpose of my dissertation was to do explore the association between CTS pain and sleep disturbance. I compared subjective and objective data between CTS patients and a control group of patients that underwent a surgical procedure of the same magnitude as CTS patients, pre and post-operatively. To achieve this purpose I recorded overnight sleep before and after CTS surgery as well before and after a minor dental surgical procedure. I also took nerve conduction measurements in CTS patients before and after CTS surgery. Subjective data was collected through subjective questionnaires and visual analogue scales. My study produced a number of interesting observations that may need to be taken into account in the overall management and, possibly, treatment of patients with carpal tunnel syndrome.

The first important observation I made was that sleep disruption is not directly correlated to pain severity in carpal tunnel syndrome. Whilst all my CTS patients reported decreased pain after CTS decompression, this decrease did not translate into any observable improvement in the PSG. Nevertheless, the CTS patients complained of sleep disruption and reported that the CTS decompression improved their sleep. But because of lack of observable improvement in the PSG (except a modest improvement in sleep efficiency, wakefulness/movement and slow wave sleep), one cannot completely rely on subjective reports to determine whether or not sleep architecture has been improved.

The second observation in my study is that even though the CTS patients reported improvement in pain severity and no sleep disruptions, that improvement was not paralleled by neurophysiological improvement in nerve conduction studies performed a few weeks after surgery. This observation suggests that the severity of the CTS symptoms cannot be completely correlated with severity of the nerve conduction measurements, since the nerve conduction studies still showed an abnormality in the face of improved pain reports from the CTS patients, particularly within the first few weeks after surgery. There was some neurophysiological improvement, however, following decompression: sensory conduction responses that were all absent during the pre-operative conduction studies were recorded in 2 of the 5 patients that were

re-examined in follow up study. All these patients reported improved pain and discomfort, post-operatively. The improvement in sensory conduction is therefore not solely responsible for the improvement in reported pain and discomfort amongst the CTS patients. The "container" hypothesis postulates that factors other than damage to the median nerve, particularly the connective tissue in the carpal tunnel space, may play a role in the symptoms associated with CTS. Therefore the pain severity pre-operatively and pain relief post-operatively may be dependent not only on the damage and recovery of the sensory/motor fibers of the median nerve, but also on the damage or the recovery of the carpal tunnel space connective tissue. The awareness of these possibilities may be an important issue to be taken into consideration in clinical practice when evaluating pain symptoms and pain relief pre and post-operatively in CTS patients. It may also help in effective pain management as well as attending to patients' expectations before and after surgery.

The third important observation in my study is that despite the fact that there were minimal changes in overnight PSG, and the nerve conduction studies, the subjective reports of improvement in sleep disruption and in pain were profound. The reason why this improvement was not recorded in objective measurements to the same magnitude as with the subjective reports is still unclear. This observation conclusively established that even though the CTS patients got pain relief and improved quality of life from the decompression surgery, the objective measurement showed that they still had disturbed sleep, and residual nerve damage, so subjective improvement is no guarantee of the success of the procedure.

The fourth observation in my study is that all CTS patients showed evidence of depressive mood, and increased anxiety levels before the CTS operation with notable improvement after CTS operation. The improvement in the depressive mood as well as anxiety, presumably, is a result of the removal of pain. There was no correlation between the depressive mood, anxiety improvement and the objective measurement of sleep, except that the CTS patients had reduced wakefulness/movement time, and slightly reduced slow wave sleep following surgery.

Future management strategies of carpal tunnel syndrome patients should consider a number of pertinent issues when dealing with CTS patients in clinical and surgical practice. These issues are that the operative treatment of CTS does improve the patient's sleep quality significantly, but there is a limited association between this improvement and the patient's actual sleep

architecture. In the management strategy, one can therefore not rely on the overnight PSG, and the patient's self-reports do not necessarily spell out an improvement in the patient's CTS condition, post-operatively. Further, even though nerve conduction studies should still be used as a diagnostic tool, there should be less reliance on the nerve conduction measurements as a management benchmark for improvement, particularly within first few weeks after surgery as there won't be any significant immediate change in nerve conduction studies despite reports of reduction in pain and discomfort from these patients.

The depressive mood, increased anxiety levels, and non-restorative sleep reports from the CTS as a result of chronic pain may in themselves suggest that the CTS patients may benefit from non-pharmacological treatment options like cognitive behavioural therapy (CBT) or cognitive behavioural therapy for insomnia (CBT-I) used widely for the management of pain. In CTS patients, however, it would be much more beneficial to still consider CTS surgery as a primary option considering the success rate of the operation in reducing pain and discomfort in these patients. Cautionary measures should be taken into account regarding the possibility of the recurrence of symptoms at a later stage considering that these patients are physiologically not readily cured of the CTS.

In conclusion, my study established the relative discrepancies between subjectively and objectively measured variables in relation to improvement in sleep, reduction in pain and discomfort in CTS patients post-operatively. Future research may still need to do comparative sequential study of sleep studies and neurophysiological measurements over longer periods of time post-operatively, in order to track the possible causes of the dissociation between the subjective and objective results of this particular research.

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Subjective sleep quality and psychological status in patients with carpal tunnel syndrome.

Carpal tunnel syndrome is a mono-neuropathy in which the median nerve is compressed in the space that is formed by the wrist and the carpal ligament, which results in a mechanical irritation that causes pain. Carpal tunnel syndrome is prevalent in people constantly engaged in extensive use of hands for activities requiring fine motor control, such as knitting, fitting and turning, or meat packing, amongst other activities (Gorsche, 1999; Uchiyama, 2005). The patients with carpal tunnel syndrome commonly complain of increased pain severity during the night. The pain often radiates to the median nerve sensory distribution of the thumb, index, and the middle finger. Pain radiating proximal to the wrist as well sensory symptoms outside the median nerve distribution has also been reported (Cupta and Benstead, 1997). The aim of this particular study was therefore to explore the CTS patients' subjective sleep quality, particularly mood and psychological status and how the sleep quality is being affected by the carpal tunnel syndrome pain.

MATERIALS AND METHODS

Patients

Patients recruited for this study were those referred for nerve conduction studies to the Neurophysiology laboratory in Gauteng. There were 33 age and gender-matched patients recruited for the study (Table 1). The patients came from different centres around Gauteng that deal with neurological as well as orthopaedic conditions including carpal tunnel syndrome. The diagnosis of carpal tunnel syndrome was made based on clinical examination as well as nerve conduction studies. On clinical examination, sensory disturbance was evaluated by the area of hyperaesthesia and paraeththesia and by using the Phalen's and the Tinel's tests. I conducted

nerve conduction studies on these patients in accordance with the recommended guidelines of the American Association of Electrophysiological Medicine, 1993. Patients were interviewed to establish any known sleep problems. The suitable patients were afterwards given questionnaires relating to the history of CTS, pain severity, sleeping and social habits. Patients included in the study were therefore those without any other known sleep problems other than the reported sleep problems related to CTS. Clinical symptoms used were those of tingling or numbness, in a distribution including the hand, or pain in a region, including the hand or weakness in the median nerve distribution and abnormal conduction studies.

Table 1. Gender and age of participants in the study

Subjects	**Number**	**Age (Yrs±SD)**
Male	14	43±11
Female	19	41±10

Electro-diagnostic investigation

Standard nerve conduction studies techniques were carried out on these patients using surface stimulating electrodes. Standard practice recommended by the American Academy of Electrophysiological medicine for the evaluation of CTS was followed. Nerve conduction stimulation was obtained by using an electrical stimulator with a narrow pulse of between 100 and 500 microseconds in width. The stimulation repetitive rate used for the sensory and motor conduction studies was between 1 and 2 pulses per second. A Sapphire, Medelec IL EMG 2 channel Electromyography (Vickers Medical Surrey, England) was used to record nerve conduction studies.

The severity of carpal tunnel syndrome was defined based on the results of nerve conduction studies. Normal: normal median nerve conduction velocity and normal distal conduction latencies; mild: slow sensory conduction velocity and normal median nerve distal motor latencies; moderate: slow sensory conduction velocity, prolonged median nerve distal latencies; severe: absent sensory action potential and prolonged or absent motor distal latencies. Normal radial and ulnar nerve motor and sensory conduction as well as "F" wave conduction time were used to exclude other nerve lesions and confirm the absence of diffuse neuropathy.

A subjective questionnaire

All patients were asked to complete a questionnaire. The questionnaire was aimed at the subjective assessment of the sleep, as well as mood states. The first questions were separated into four main categories.

- The history of CTS and pain experienced
- The pain severity which was measured using the visual analogue scale
- The sleeping habits and social habits

History of CTS and pain experienced

Patients were asked the duration for which they had experienced CTS and whether they had had a previous CTS operation. Patients were asked if they had experienced any of the following symptoms; headaches, shoulder pain, neck pain, pins and needles, numbness, muscle weakness on regular basis.

Pain severity and sleep habits

The subjective severity of CTS was measured using the visual analogue scale anchored from “no pain” to “unbearable pain”. The subjects were also asked whether their sleep was being disturbed by the CTS pain and how they were affected. They were also asked whether they had trouble falling asleep, needed medication to fall asleep, or were frequently awakened by pain. The patients were asked to describe their sleep habits and the presence of any sleep disorders. Patients were asked whether they stopped breathing when they slept or if they woke up gasping for breath or if they snored or if they had restless sleep. They were also asked how often they experience sleep problems like non-refreshing sleep or sleepiness that interfered with daily activities. Patients were also asked about their smoking habits, their drinking habits and other health problems in general and whether or not they took any medication.

The women subjects were asked additional questions that related to their reproductive hormonal status. The question related to whether they had irregular menstrual cycle, or if they suffered from severe pre-menstrual tension, or if they had any sleep complaints associated with menstrual cycle, or if they were pregnant. The patients were also asked if they were taking any medication that had hormones, or if they were menopausal, or had any operation that caused their periods to stop completely as well as whether both ovaries were removed.

Data Analysis

All results are reported as mean ± standard deviation. Arcsin square-root transformation was done on all visual analogue scale ratings to normalize the scores before analysis.

Results

The CTS patients had had symptoms for carpal tunnel syndrome for between 2 weeks and 6 months (42%), between 6 months and 2 years (30%) and over 2 years (28%). None of these patients had had previous carpal tunnel release surgery.

Latencies: Most CTS patients (68%) showed severe carpal tunnel syndrome with either absent or grossly prolonged distal sensory and/motor conduction latencies. The rest (32%) had moderate CTS with median nerve distal motor latency and median palmar sensory conduction (Table 2)

Pain severity: The patients rated their pain severity on a 100mm visual analogue scale that was anchored from "no pain at all" to "unbearable pain". Patients reported their pain as being significantly greater during the night than it was during the day (paired t test, $p<0.03$). The mean was 74±24mmSD during the night, and 46±24mmSD, during the day. The majority of these patients (91%) reported that their sleep was disturbed by pain. Most of these patients reported that they woke up during the night (88%), they had trouble falling asleep (94%), and they had experienced restless sleep (94%), at least sometimes because of CTS pain.

Sleep habits: A small percentage of these patients (27%) reported excessive sleepiness, during the day as determined by the score of greater than 10 on the Epworth Sleepiness score (ESS). Scale on the ESS were not significantly correlated with the VAS pain rating (Pearson's correlation ($r=0.2$, $P=0.3$) whether during the day or night. Some of these patients (45%) reported taking some form of medication regularly in order to fall asleep, whilst 33% reported not taking any form of medication to fall asleep, and 21% of these patients sometimes did take medication.

General health and mood: A quarter of the patients had altered psychological status indicated by a very high score on the General Health Questionnaire (GHQ). The mean score was 7±7meanSD which is higher than that of the normal population. This relationship confirmed that the CTS is not only associated with sleep disruption, but also with altered mental status. There was no significant correlation associated between the psychological status and pain severity, particularly during the night as measured on GHQ (Pearson's correlation, $r=0.2$ $p>0.05$). Eight of the patients who were being regularly awakened by CTS pain also showed sign of depression with the GHQ=8±5SD.

Table 2. Conduction latencies for distal median sensory and motor nerve.

Type fibers stimulated	**Conduction latency (mean±SD)**
Median nerve distal motor latency (ms)	4.7±1.4
Median palmar sensory conduction latency (ms)	3.4±0.3

CONCLUSION

In my pilot study I established that the CTS patients had reported disturbed sleep. There was no correlation between the alteration of the psychological status of these patients and pain severity. Some of these patients used some one form of pain-killers or another in order to subdue pain, a factor that may have influenced some of my findings on the influence of pain during sleep.

In conclusion, I have shown that patients with carpal tunnel syndrome had trouble falling asleep and maintaining sleep because of nocturnal pain. Most patients reported an increase in daytime sleepiness. Patients with CTS also did have disturbed mental health although independent of pain severity. Similar to other pain-related diseases, therefore, neuropathic pain in patients with CTS is associated with disturbed sleep and psychological status.