

**THE EFFECTIVENESS OF
ELECTROACUPUNCTURE IN REDUCING
POSTOPERATIVE PAIN, ANALGESIC
REQUIREMENT AND PREVENTION OF
POSTOPERATIVE NAUSEA AND VOMITING
POST TOTAL ABDOMINAL HYSTERECTOMY
SURGERY**

By

DR S PRAVEENA D/O SEEVAUNNAMTUM

**DISSERTATION SUBMITTED IN PARTIAL
FULFILLMENT OF THE REQUIREMENT FOR THE
DEGREE OF MASTER OF MEDICINE
(ANAESTHESIOLOGY)**



UNIVERSITI SAINS MALAYSIA

2015

ACKNOWLEDGEMENTS

Firstly, I would like to express my gratitude to Lord Ganesha for blessing me with the wisdom and dedication to accomplish this dissertation.

I would also like to extend my deepest appreciation to both my supervisors, Dr. Kavita Bhojwani and Professor Dr. Nik Abdullah Nik Mohamad. Dr. Kavita has helped in many ways with the support needed to conduct this study in Hospital Raja Permaisuri Bainun, Ipoh. She inspired me to do a study based on acupuncture in clinical practise as well as sorted the logistics of it. Professor Dr. Nik Abdullah Nik Mohamad has also given constant support, encouragement and guidance in completion of this dissertation. With his invaluable advice, I have managed to successfully accomplish this task with confidence.

My sincere appreciation also goes to Sister Choo Wai Ling for helping with recruitment as well as the collection of data. I am also grateful to the support team consisting of medical officers of Anaesthesia Department and Intensive Care of Hospital Raja Permaisuri Bainun Ipoh and nurses from the Acute Pain Service (APS) for helping in conducting this study as well.

Finally, I would like to thank my dearest family for their unconditional love and patience. I dedicate this dissertation to my pillar of support, my beloved husband, Dr. Allan Ravi.

TABLE OF CONTENTS

TITLE	Page
ACKNOWLEDGEMENTS	ii
TABLE OF CONTENTS	iii
LIST OF TABLES	vii
LIST OF FIGURES	viii
LIST OF ABBREVIATIONS	xi
ABSTRACTS	
ABSTRAK	xiii
ABSTRACT	xv
CHAPTER 1: INTRODUCTION	
1.1 Postoperative pain and its challenges	1
1.2 Acupuncture	4
1.3 Electroacupuncture	9
1.4 Use of Electroacupuncture in this study	12
CHAPTER 2: LITERATURE REVIEW	
2.1 Pain	14
2.1.1 Pain perception	14
2.1.2 Pain pathway	16
2.1.3 Gate Control Theory	18
2.1.4 Neurotransmitters and Pain	20

2.1.5	Acute Pain post Hysterectomy	22
2.1.6	Validation of Numerical Rating Scale	23
2.2	Acupuncture	26
2.2.1	History of Acupuncture	26
2.2.2	Types of Acupuncture	27
2.2.3	Electroacupuncture and how it works	29
2.3	Postoperative nausea and vomiting	33
2.3.1	Definition of postoperative nausea and vomiting	33
2.3.2	Physiology of vomiting	34
2.3.3	Risk factors for PONV	37
2.3.4	Strategies to reduce PONV	40
2.4	Morphine	42
2.4.1	History of opioids	42
2.4.2	Opioid Receptors	44
2.4.3	Pharmacokinetics of morphine	48
2.4.4	Pharmacodynamics of morphine	50
2.5	Patient controlled analgesia	52
2.6	Objectives	56
2.7	Research Hypotheses	57
 CHAPTER 3: METHODOLOGY		
3.1	Study design	58

3.2 Inclusion Criteria	59
3.3 Exclusion Criteria	59
3.4 Sample Size Calculation	60
3.5 Research Methodology	64
3.5.1 Preoperative	64
3.5.2 Intraoperative	66
3.5.3 Postoperative	71
3.6 Measurement Tools	73
3.7 Methodology Flow Chart	75
3.8 Data Collection and Statistical Analyses	76
3.8.1 Specific Objective 1	76
3.8.2 Specific Objective 2	77
3.8.3 Specific Objective 3	77
3.9 Ethical Consideration	78
 CHAPTER 4: RESULTS	
4.1 Profile of Sample	79
4.2 Comparison of mean pain score via Numerical Rating Scale (NRS)	84
4.3 Comparison of mean total PCA Morphine demand and dose within 24 hours	87
4.4 Incidence of nausea	89
4.5 Incidence of antiemetic usage	92

CHAPTER 5: DISCUSSION

5.1	Subject Recruitment	95
5.2	Analgesic effect of electroacupuncture as adjuvant therapy	96
5.3	Electroacupuncture as adjuvant therapy	99
5.4	Electroacupuncture to reduce incidence of PONV	102
5.5	Electroacupuncture to reduce usage of pharmacological antiemetics.	104
5.6	Clinical Practice Implications	106
5.7	Limitations	107

CHAPTER 6 : SUMMARY AND CONCLUSION

6.1	Summary	109
6.2	Conclusion	110

CHAPTER 7: RECOMMENDATIONS FOR FUTURE STUDY

REFERENCES

APPENDICES

Appendix A:	Letter of Ethical Approval from NMRR	116
Appendix B:	Letter of Ethical Approval from USM	120
Appendix C:	Patient Information Sheet and Consent Form	122
Appendix D:	Maklumat Kajian dan Borang Keizinan Pesakit	127
Appendix E:	Data Collection Sheet	132

LIST OF TABLES

		Page
Table 2.1	Endogenous opioid peptides and their sensitivity for the different subtypes of opioid receptor.	46
Table 4.1	Demographic data between electroacupuncture and control group.	79
Table 4.2	Demographic data between electroacupuncture and control group	82
Table 4.3	Comparison of mean pain score via Numerical Rating Scale (NRS) between electroacupuncture and control group	84
Table 4.4	Comparison of mean total PCA Morphine Demand and Dose within 24 hours between electroacupuncture and control group	87
Table 4.5	Comparison of incidence of nausea at various intervals between electroacupuncture and control group.	89
Table 4.6	Comparison of incidence of antiemetic usage at various intervals between electroacupuncture and control group	92

LIST OF FIGURES

		Page
Figure 1.1	Mappings of body structures and functions by points along the outer ears, on the nose, in the scalp, on the hands, on the feet, at the wrists and ankles	5
Figure 1.2	Pericardium Meridian point 6 (p6)	6
Figure 1.3	Large Intestine Meridian point 4 (p4)	7
Figure 1.4	Acupuncture needles attached to small clips to deliver the electric pulses	10
Figure 1.5	Hwato electronic acupuncture treatment instrument (model No SDZ-V, Suzhou Medical Appliances Co., Ltd, Suzhou, China)	10
Figure 1.6	An electroacupuncture procedure	11
Figure 2.1	Pain pathway	17
Figure 2.2	Descending pathways from the brain close the gate by inhibiting the projector neurons and diminishing pain perception	19
Figure 2.3	Visual Analog Scale	23

LIST OF FIGURES, continued

		Page
Figure 2.4	Numerical Rating Scale	24
Figure 2.5	Verbal Rating Scale	25
Figure 2.6	Afferent and Efferent pathways affecting the vomiting centre	36
Figure 2.7	G protein receptors and its mechanism of action	44
Figure 2.8	Structure of Morphine	48
Figure 2.9	The difference between PCA doses and conventional intramuscular (IM) doses of opioid in relation to opioid concentration and effect versus time	53
Figure 3.1	Location of Pericardium Meridian p6 point (Neiguan)	67
Figure 3.2	Location of The Large Intestine p4 point (Hegu)	68
Figure 3.3	Example of setting up of the electroacupuncture needles	69
Figure 3.4	Numerical Rating Scale tool	73

LIST OF FIGURES, continued

Page

Figure 4.1	Comparison of mean Numerical Rating Score at various time intervals between electroacupuncture and control group	86
Figure 4.2	Comparison of incidence of nausea at various time intervals between electroacupuncture and control group	90
Figure 4.3	Comparison of incidence of antiemetic usage at various time intervals between electroacupuncture and control group	93

LIST OF ABBREVIATIONS

BMA	British Medical Association
CGRP	Calcitonin gene related peptide
CNS	Central nervous system
CSF	Cerebrospinal Fluid
CTZ	Chemoreceptor trigger zone
cAMP	Cyclic adenosine monophosphate

DOP	Delta orphanin peptide
D2	Dopamine 2
EA	Electroacupuncture
ERAS	Enhanced Recovery After Surgery
fMRI	Functional magnetic resonance imaging
Hz	Hertz
H1	Histamine 1
IASP	International Association of Pain
IUPHAR	International Union of Pharmacology
I.V	Intravenous
KOP	Kappa orphanin peptide
p4	Large Intestine Meridian point 4
MEAC	Minimum effective analgesic concentration
MTC	Minimum toxic concentration
MOP	Mu orphanin peptide
mGCA	Multivariate Granger causality analysis

LIST OF ABBREVIATIONS, continued

NIH	National Institute of Health
NOP	Nociceptin orphanin peptide
NRM	Nucleus raphe magnus
NRS	Numerical Rating Scale
PCA	Patient controlled analgesia
PAG	Periaqueductal grey

p6	Pericardium Meridian point 6
PACU	Post Anaesthesia Care Unit
5HT3	Serotonin
STG	Superior temporal gyrus
TCM	Traditional Chinese Medicine
VAS	Visual Analog Score
VRS	Verbal Rating Scale
WHO	World Health Organization

ABSTRAK

KEBERKESANAN ELEKTROAKUPUNKTUR UNTUK MENGURANGKAN RASA SAKIT DAN MENGELAKAN RASA LOYA DAN MUNTAH SELEPAS PEMBEDAHAN HISTEREKTOMI

Pengenalan: Kami menyelidik kaedah alternatif menggunakan elektroakupunktur untuk mengurangkan sakit, loya dan muntah terhadap pesakit selepas pembedahan histerektomi.

Objektif: Ini adalah kajian prospektif secara rawak di mana kami meletakkan pesakit dalam salah satu kumpulan yang menerima rangsangan elektroakupunktur atau tidak. Pesakit tidak mengetahui samada mereka menerima rangsangan elektroakupunktur atau tidak. Kami menyelidik samada penggunaan rangsangan elektroakupunktur semasa pembedahan mengurangkan sakit, loya atau muntah selepas pembedahan histerektomi. Kajian ini dijalankan di Hospital Raja Permaisuri Bainun, Ipoh.

Kaedah kajian: Seramai 64 wanita dibahagikan secara rawak samada menerima rangsangan elektroakupunktur atau tidak. Rangsangan elektroakupunktur diberikan semasa pembedahan sehingga tamat pembedahan. Semua pesakit menerima bius am dan ubat tahan sakit dikawal pesakit iaitu morfin. Kami mengumpul maklumat selepas pembedahan mengenai Numerical Rating Scale, kejadian loya dan penggunaan ubat tahan muntah pada 30 minit, 2 jam, 4 jam dan 24 jam selepas pembedahan. Kami juga mencatatkan permintaan untuk morfin dan jumlah penggunaan morfin dalam 24 jam pertama. Penilaian data ini dibuat oleh kakitangan jururawat yang tidak mengetahui jika pesakit menerima rangsangan elektroakupunktur atau tidak.

Keputusan: Kami mendapati bahawa skor kesakitan lebih rendah secara signifikan buat pesakit yang menerima rangsangan elektroakupunktur pada 30 minit ($p=0.004$). Min skor kesakitan pada kumpulan elektroakupunktur adalah 2.75 ± 2.34 berbanding min skor kesakitan kumpulan kawalan iaitu 4.50 ± 2.37 . Pada 2 jam, skor kesakitan lebih rendah secara signifikan buat pesakit yang menerima rangsangan elektroakupunktur ($p=0.002$). Min skor kesakitan pada kumpulan elektroakupunktur adalah of 2.25 ± 1.80 berbanding min skor kesakitan kumpulan kawalan iaitu 3.88 ± 2.21 . Min permintaan morfin dalam 24 jam adalah jauh lebih rendah secara signifikan dalam kumpulan yang menerima elektroakupunktur ($p=0.003$). Min permintaan morfin adalah 27.28 ± 21.61 kali diminta berbanding 55.25 ± 46.85 kali diminta dalam

kumpulan kawalan. Min penggunaan morfin dalam masa 24 jam dalam kumpulan elektroakupunktur adalah lebih rendah secara signifikan ($p=0.006$). Min penggunaan morfin dalam 24 jam dalam kumpulan elektroakupunktur adalah 21.38 ± 14.38 mg berbanding 33.94 ± 20.34 mg dalam kumpulan kawalan. Kadar loya selepas pembedahan pada 30 minit adalah lebih rendah iaitu 15.63 % berbanding 46.88 % dalam kumpulan kawalan. Nilai ini adalah signifikan ($p=0.007$).

Kesimpulan: Kajian ini mendapati bahawa dengan penggunaan elektroakupunktur semasa pembedahan terdapat pengurangan ketara dalam skor kesakitan sehingga 2 jam selepas pembedahan, permintaan morfin dan penggunaan morfin dalam 24 jam pertama dan kadar loya dalam 30 minit selepas pembedahan.

Kata kunci: Electroakupunktur, sakit selepas pembedahan, mual selepas pembedahan, muntah selepas pembedahan, penggunaan opioid, pembedahan ginekologi

ABSTRACT

THE EFFECTIVENESS OF ELECTROACUPUNCTURE IN REDUCING POSTOPERATIVE PAIN, ANALGESIC REQUIREMENT AND PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING POST TOTAL ABDOMINAL HYSTERECTOMY SURGERY

Introduction: We explored the use of intraoperative single session low frequency (2 Hertz) electroacupuncture stimulation to show an opioid sparing effect whilst having better analgesic profile and reduction of postoperative nausea and vomiting (PONV) in

patients recovering from hysterectomies. The tiny focused electrical current is postulated to modulate the pain pathway via release of endogenous opioid substances and stimulation of descending pain inhibitory pathways.

Objectives: This was a prospective, double blinded randomized study of the effect of intraoperative electroacupuncture on postoperative pain, analgesic requirement and prevention of postoperative nausea and vomiting in patients scheduled for total abdominal hysterectomy with or without bilateral salphingo oophorectomy. The study was conducted in Hospital Raja Permaisuri Bainun, Ipoh.

Methodology: Sixty four (64) women were randomly allocated to receive or not electroacupuncture. Electroacupuncture was started as a single continuous session started intraoperatively till the end of surgery. All patients received similar general anaesthesia and postoperative patient controlled analgesia morphine. Postoperative Numerical Rating Scale, incidence of nausea, vomiting and usage of rescue antiemetics at 30 minutes, 2 hours, 4 hours and 24 hours were recorded. Total morphine demand and usage were also recorded in first 24 hours. Assessment was by a blinded nursing staff. Data entry and analysis was conducted with PASW Statistics Data Editor (Statistical Package for Social Science SPSS Version 21)

Results: Postoperative pain score was numerically lower in the electroacupuncture group with a significant reduction in the mean pain score at 30 minutes and 2 hours postoperation, showing a mean pain score of $2.75 \pm (2.34)$ and $2.25 \pm (1.80)$ (*p value* < 0.05) respectively. In comparison, the mean pain score for the control group were $4.50 \pm (2.37)$ and $3.88 \pm (2.21)$ (*p value* < 0.05) respectively. The mean PCA morphine demand within 24 hours was significantly lower in electroacupuncture group showing $27.28 \pm (21.61)$ times pressed as compared to the control group which recorded $55.25 \pm$

(46.85) times pressed (*p value* < 0.05). The mean morphine dosage requirement within 24 hours showed a significant reduction in usage in electroacupuncture group showing a mean of $21.38 \pm (14.38)$ mg as compared to the control group which recorded a usage of $33.94 \pm (20.34)$ mg (*p value* < 0.05). Incidence of postoperative nausea was significantly reduced in electroacupuncture group at 30 minutes with a rate of 15.6 % versus 46.9 % in control group (*p value* < 0.05).

Conclusion: This study concludes that in subjects receiving electroacupuncture intraoperatively, there was a significant reduction in postoperative pain score up to the first 2 hours, decrease in morphine demand and requirement in the first 24 hours and reduction in incidence of postoperative nausea at 30 minutes postoperatively.

Keywords: Electroacupuncture, postoperative pain, postoperative nausea, postoperative vomiting, opioid usage, gynaecological surgery

CHAPTER 1

INTRODUCTION

1.1 Postoperative pain and its challenges

Pain is defined by the International Association of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain in the postoperative period is one of the major factors that impede recovery from anaesthesia and surgery.

It is understood that perception of postoperative pain is affected by many factors including the patient's age, sex, personality, knowledge of and confidence in the procedure and the individual's physiological condition. The same procedure can produce different degrees of postoperative pain in different patients.

Poorly managed pain can result in increased sympathetic response like hypertension, overactive metabolism, tachycardia, diaphoresis, mydriasis, pallor, insomnia, and increased myocardial oxygen consumption. In patients with coronary artery disease, postoperative pain may even result in myocardial ischaemia and possible infarction that in turn may delay postoperative recovery (Stone and Wheatley, 2002).

Unfortunately, in our National Audit on Postoperative Pain (2007), 74 % of patients experience moderate to severe pain in the first 24 hours postoperatively. This dismal figures has alerted us to comply with “ Pain As the 5th Vital Sign” guidelines

and have Acute Pain Services (APS) team that review patients 1 hour postoperatively with regards to their pain control.

To add to our challenges, our surgical fraternity are fast embracing the principles of fast track surgery (KK *et al.*, 2010). Fast track is a concept that systematically uses multimodal strategies perioperatively to reduce postoperative organ dysfunction and complications following elective surgery. It has four strands that mainly involves improving preoperative care, reducing the physical stress of the operation, decreasing postoperative discomfort, thereby leading to improved postoperative mobility and earlier supported discharge (Place and Scott, 2014). The perioperative factors include pain, postoperative nausea and vomiting (PONV), paralytic ileus and fatigue. Today, the concept “fast track” is used synonymously with “enhanced recovery after surgery” (ERAS) which consists of a team of surgeons, anaesthetists, nurses and physiotherapists (KK *et al.*, 2010).

In our local settings, most post laparotomy patients are put on a patient controlled analgesia (PCA) that administers intravenous opioids like morphine. The patient receives immediate delivery of pain medication without the need for a nurse to administer it. The patient controls when the medication is given. Among adverse effects from opioid use are respiratory depression, constipation, vomiting, gastroparesis, and central nervous system depression including somnolence and consciousness disturbance. Opioid-related side effects often occur post-operatively, and are related to the total dosage of opioid medication (Stone and Wheatley, 2002).

Hence, we are exploring non pharmaceutical methods of reducing opioids use while having better pain management and reduction of postoperative nausea and vomiting (PONV). We hope to study the use of electroacupuncture intraoperatively to reduce total opioid dosage postoperatively.

1.2 Acupuncture

Acupuncture is a form of complementary medicine that is finding its place in modern medicine. It consist of inserting fine needles (32 to 36 gauge size) into body locations referred to as acupoints. In acupuncture, there are 12 major meridian lines, 8 secondary meridian lines with 356 acupoints on these meridian lines (Chapple, 2013). These are complete mappings of body structures and functions by points along the outer ears, on the nose, in the scalp, on the hands, on the feet, and at the wrists and ankles (Figure 1.1).

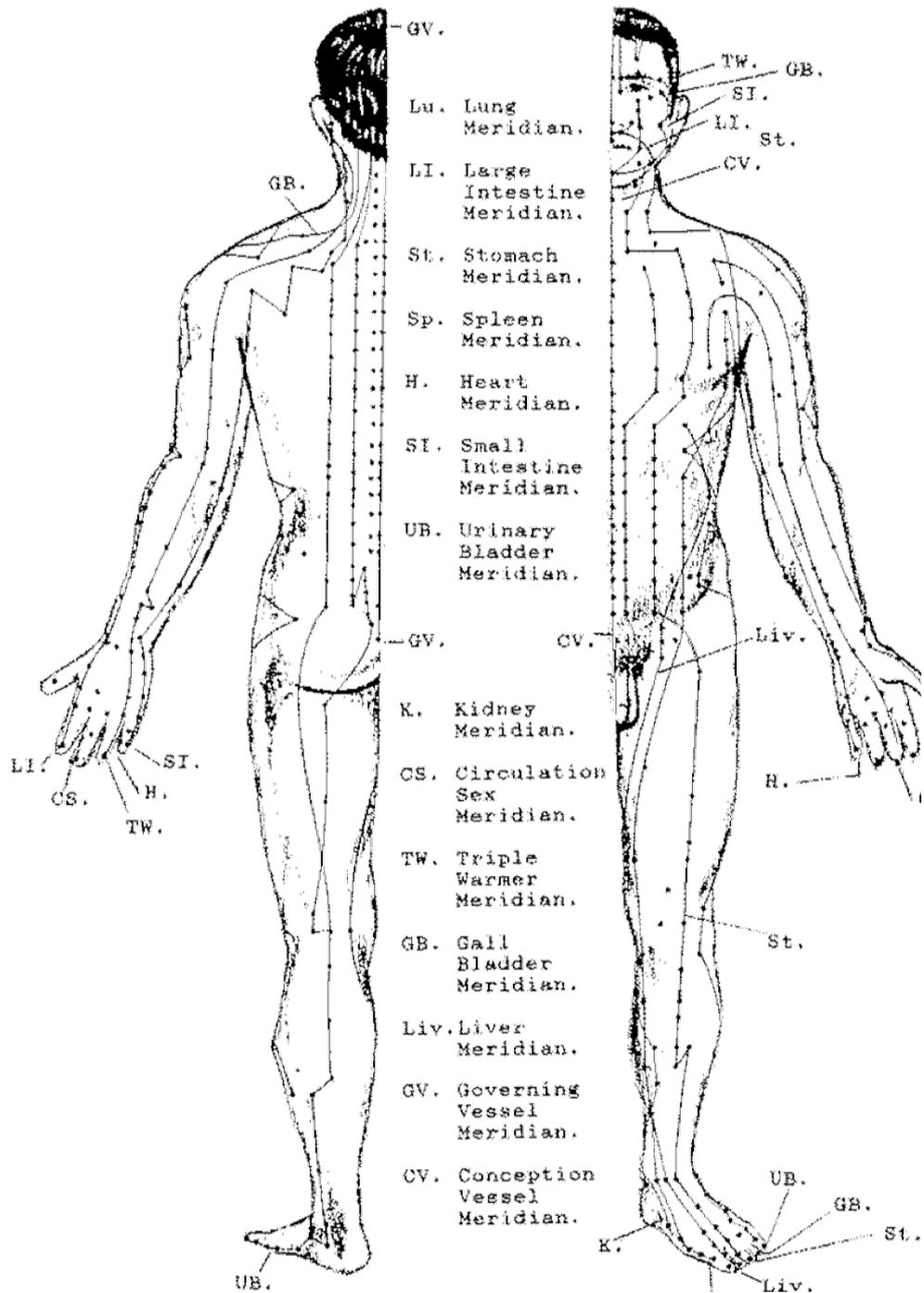


Figure 1.1: Mappings of body structures and functions by points along the outer ears, on the nose, in the scalp, on the hands, on the feet, at the wrists and ankles (Chapple, 2013)

In Traditional Chinese Medicine (TCM) system, the body is seen as a delicate system of two opposing and inseparable forces known as yin and yang. It is believed that the body is maintained in a healthy state by having good flow of energy which is the yin and yang. A major assumption is that anything that blocks the flow of energy, known as Qi along its pathways or meridians will leave the body in a state of imbalance or poor health. In this study, both the Pericardium Meridian point 6 (p6) (Figure 1.2) and Large Intestine Meridian point 4 (p4) (Figure 1.3) are stimulated.

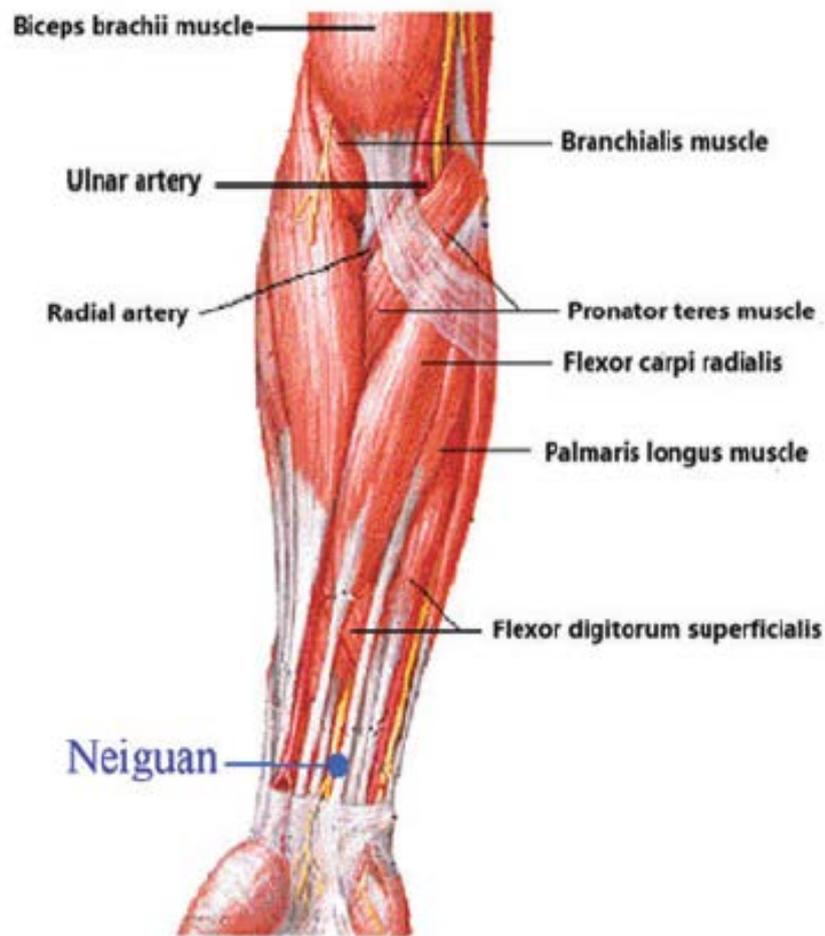


Figure 1.2: Pericardium Meridian point 6 (p6) (Chapple,2013)

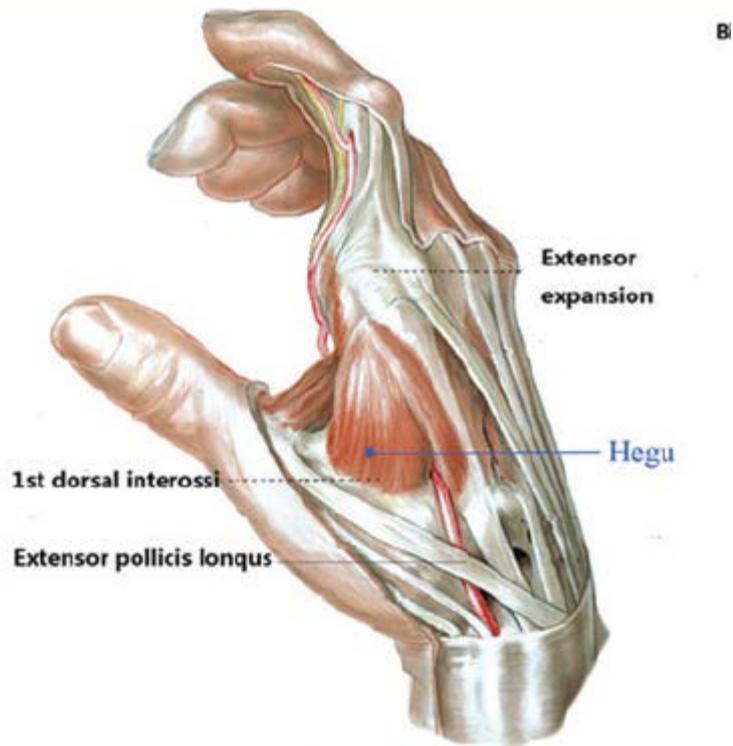


Figure 1.3: Large Intestine Meridian point 4 (p4) (Chapple,2013)

The National Institute Health (NIH), World Health Organization (WHO) and British Medical Association (BMA) have supported the use of acupuncture in the treatment of a wide range of pain conditions, such as post-operative pain, obstetric pain, dental pain, chronic lower back pain, osteoarthritic pain, headache and fibromyalgia (Silvert, 2000).

In acupuncture studies, it was reported that two such transmitters, substance P and calcitonin gene-related peptide, were released from primary sensory neurons. Acupuncture analgesia appears to be mediated by release of enkephalin and beta-endorphins, with regulation of prostaglandin synthesis: all these have an effect on pain perception. One of the dominant areas of research into acupuncture mechanisms has

been its effect on endorphins. Endorphins are one of several neuropeptides that have been shown to alleviate pain, and have been described as the body's own "opiates" (Tobaldini *et al.*, 2014).

1.3 Electroacupuncture

Electroacupuncture (EA) is different from acupuncture in that it applies needling stimulation and electric pulses to acupuncture meridians and points in order to strengthen the stimulating effect of treatment. However, as with traditional acupuncture, needles are inserted on specific acupuncture points along the body. The needles are then attached to a device that generates continuous electric pulses using small clips. These devices are used to adjust the frequency and intensity of the impulse being delivered, depending on the condition being treated. Electroacupuncture uses two needles at time so that the impulses can pass from one needle to the other (Chen and Wang, 2013).

Using different frequencies via electroacupuncture specific endogenous opioid responses have been reported (Wilkinson and Faleiro, 2007). In low frequency stimulation (1 to 2 Hertz) there are release of endorphins and enkephalins (A δ fibers). In mid range frequencies (12 to 15 Hertz) stimulation results in the production of all three opioid classes. In high frequencies (100 Hertz) results in dynorphins release and has no effect of endorphins or enkephalins (A β fibers). There is no further gain in opioid peptide release beyond 200 Hertz (Wilkinson and Faleiro, 2007).

As such, this study utilises electroacupuncture 2 Hertz (Hz) on bilateral Pericardium Meridian point 6 (p6) and Large Intestine Meridian point 4 (p4) intraoperatively in addition to standard opioid analgesia to capture the release of endorphins and enkephalins to improve pain relief postoperatively.

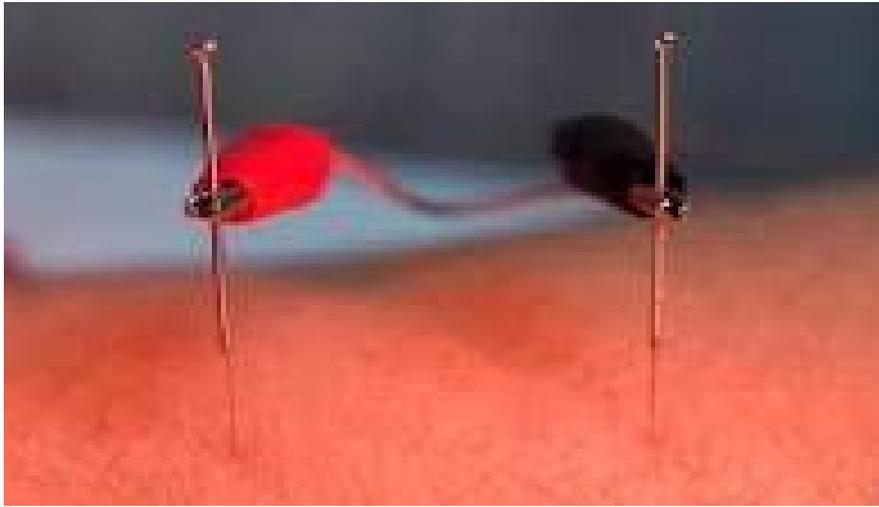


Figure 1.4: Acupuncture needles attached to small clips to deliver the electric pulses (model No SDZ-V, Suzhou Medical Appliances Co., Ltd, Suzhou, China)



Figure 1.5: Hwato electronic acupuncture treatment instrument (model No SDZ-V, Suzhou Medical Appliances Co., Ltd, Suzhou, China)

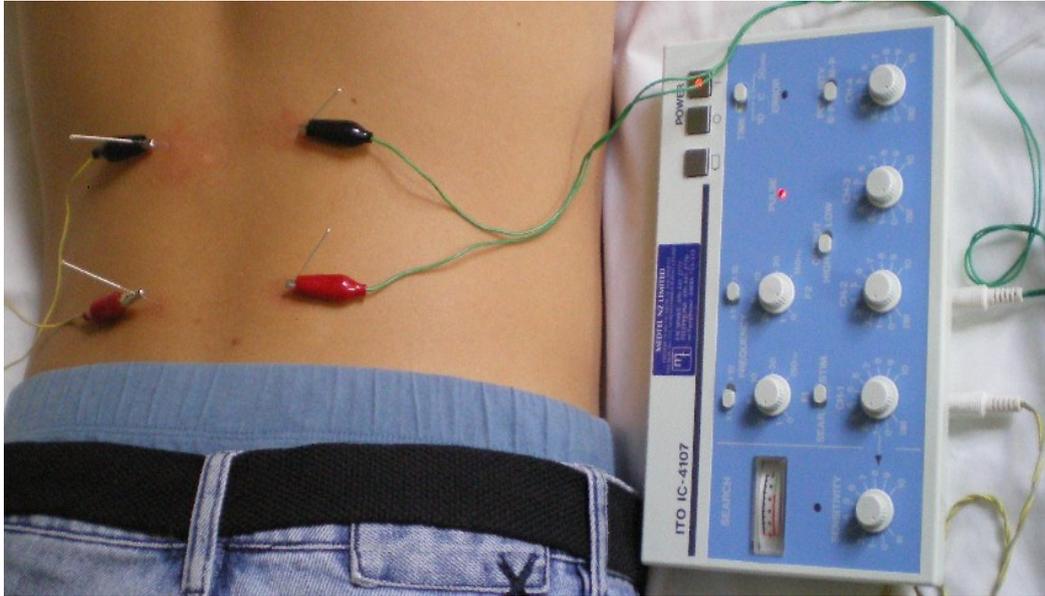


Figure 1.6: An electroacupuncture procedure (model No SDZ-IV, Suzhou Medical Appliances Co., Ltd, Suzhou, China)

1.4 Use of Electroacupuncture in this study

In this study, we enrolled 64 consented elective abdominal hysterectomy patients to study the effects of addition of electroacupuncture to standard opioid analgesia with relation to postoperative pain and opioid related side effects. This is a randomised single blinded study and subjects are randomised into 2 groups. This research analysed the analgesic and antiemetic effect patients post hysterectomy within the first 24 hours.

Consented subjects were randomised into 2 groups.

Group A (electroacupuncture group): Received electroacupuncture of 2 Hertz at continuous wave in addition to standard care.

Group B (control group): Received standard care and we did not attach any electroacupuncture needles on the patient. Standard care was defined as general anaesthesia for surgery like all other patients undergoing the same surgery and also receiving standard pain relief medications as well.

We analysed postoperative analgesia via Numerical Rating Scale that is already in use in all Ministry of Health hospitals at 30 minutes, 2 hours, 4 hours and 24 hours. Data on the total Patient Controlled Analgesia (PCA) demand and total PCA doses in the first 24 hours were collected. We also analysed incidence of nausea and

postoperative antiemesis use by looking at incidences of need of rescue pharmacologic antiemetic in the first 30 minutes and 24 hours.

The aim of this study is to examine the effects of electroacupuncture (EA) on reducing postoperative pain, analgesic requirement & nausea and vomiting on subjects recovering from elective hysterectomies. The hypothesis is that patients receiving addition of electroacupuncture would demonstrate increased analgesic and antiemetic relief over a duration of time and reduced opioid related side effects compared to control group.

CHAPTER 2

LITERATURE REVIEW

2.1 Pain

2.1.1 Pain perception

Pain is subjective and difficult to quantify. It is recognised by its international definition to have an affective and sensory component. Although neuroanatomical basis for pain reception develops before birth, individual pain responses are learned in early childhood. Again, these responses are modulated based on the individuals, social, cultural, psychological, cognitive and genetic factors (KK *et al.*, 2010).

As such, it is not surprising that in ancient times, humankind had even viewed pain as a form of punishment inflicted by gods or demons on humans. Early medical beliefs of perception had often been conflicting. The great ancient Greek physician Hippocrates believed that pain is associated with too much of blood, phlegm, yellow bile or black bile. Some reports also say that the ancient Muslims physician Avicenna associated pain with a change in physical condition of the body (2014).

In modern medicine, we have more understanding of pain pathways and are able to classify it (Jessel, 1982). Pain may be classified in many ways, that is:

1. Duration: acute, chronic

2. Pathophysiology: nociceptive, neuropathic
3. Aetiology: arthritic, cancer pain
4. Affected area: headache, low back pain

2.1.2 Pain pathway

Pain is conducted along neuronal pathways from the periphery to the cerebral cortex. This neuronal pathway is commonly known as the pain pathway. The pain pathway starts with the first order neuron, has one end at the peripheral tissue and the other at the dorsal horn of the spinal column. Once in the dorsal horn, it would synapse with second order neurons, interneurons, sympathetic neurons and ventral horn motor neurons. The second order neurons, synapses at the ipsilateral side of the dorsal column and crosses the midline to ascend via the contralateral spinothalamic tract to reach the thalamic nuclei (Jessel, 1982).

The spinal cord grey matter is divided into ten laminae. The first six laminae make up the dorsal horn. Nociceptive sensory neuron are small diameter cell bodies that responds to cutaneous stimulus and ends in the two most superficial layers of the dorsal horn of the spinal cord. The outer layer (lamina 1) appears to contain the central terminal of the thinly myelinated sensory fibers that respond to the high threshold mechanical and noxious thermal stimuli (Jessel, 1982).

The lamina 2 (substantia gelatinosa) contains the terminals of unmyelinated fibers, many of which can be equally activated by noxious mechanical, thermal, and chemical stimuli (termed polymodal nociceptive afferents). Sensory terminals in the deeper layers of the dorsal horn convey information from cutaneous sensory endings that are associated with hair follicle afferents and those that respond to light pressure. The dorsal horn represents the principle site of pain modulation. This is a major site that

opioid process and modulates nociceptive input from cutaneous nociceptors (Jessel, 1982).

Finally the third order neurons are located in the thalamus and sends fibres to the postcentral gyrus of the parietal cortex. Perception and discrete localization of pain takes place in this cortex. Some fibres project to the anterior cingulate gyrus and mediate the suffering and emotional components of pain (Jessel, 1982).

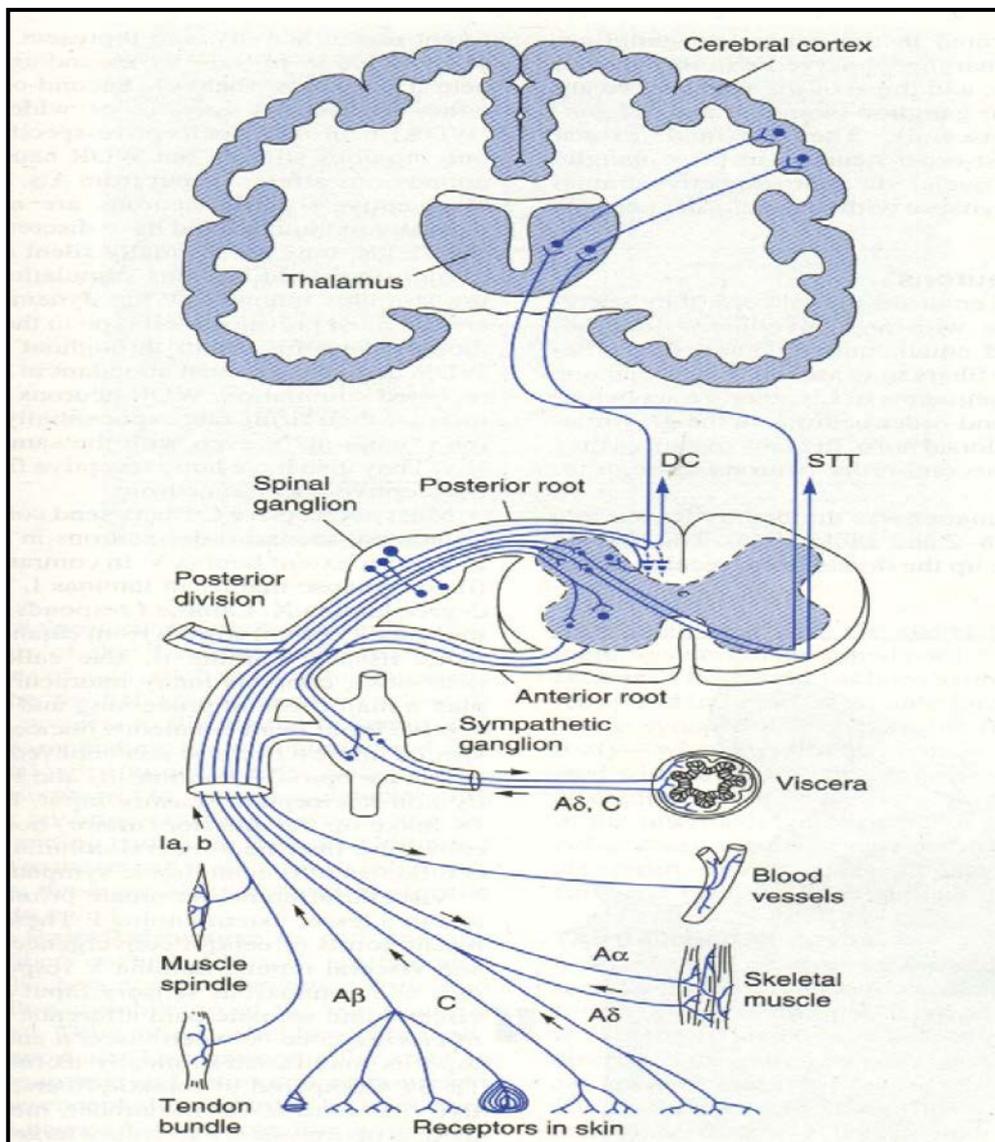


Figure 2.1: Pain pathway (Jessel, 1982)

2.1.3 Gate Control Theory

In 1965, Ronald Melzack and Patrick Wall published their paper in *Science* proposing that a gating mechanism exists within the dorsal horn of the spinal cord. It became famously known as “New Gate Control Theory of Pain”. It was succinctly stated that the transmission of pain from the peripheral nerve through the spinal cord was subject to modulation by both intrinsic neurons and controls emanating from the brain.

The Gate Theory proposed that small (C) fibers activated excitatory system that excited output cells. These latter cells have their activity controlled by the balance of large fibers (A beta) mediated inhibitions and are under the control of descending systems (Dickenson, 2002).

The interplay among these connections determines when painful stimuli go to the brain:

1. Without any input, the inhibitory neuron prevents the projection neuron from sending signals to the brain (gate is closed).
2. Normal somatosensory input happens when there is more large-fiber (A beta) stimulation (or only large-fiber stimulation). Both the inhibitory neuron and the

projection neuron are stimulated, but the inhibitory neuron prevents the projection neuron from sending signals to the brain (gate is closed).

3. Nociception (pain reception) happens when there is more small (C) fiber stimulation or only small (C) fiber stimulation. This inactivates the inhibitory neuron, and the projection neuron sends signals to the brain informing it of pain (gate is open).

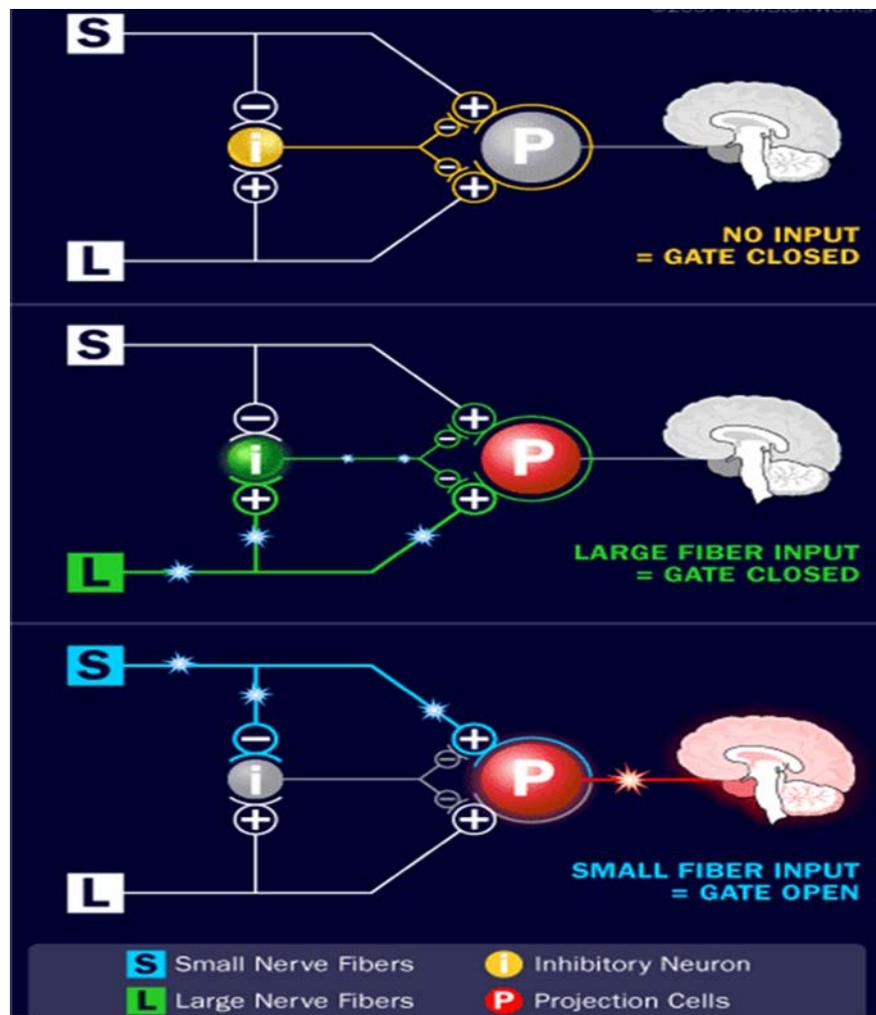


Figure 2.2: Descending pathways from the brain close the gate by inhibiting the projector neurons and diminishing pain perception (Dickenson, 2002)

2.1.4 Neurotransmitters and Pain

Nociceptors are free nerve endings that responds to multiple stimulus like heat, mechanical, chemical, pressure. In contrast to the well-established cholinergic and adrenergic properties of the principal parasympathetic and sympathetic neurons there is still considerable uncertainty over the nature of the transmitters used by primary sensory neurons (Jessel, 1982).

Alogens or pain producing transmitters identified includes bradykinin, histamine, serotonin, prostaglandin, capsaicin, adenosine triphosphate. Several neuropeptides and excitatory amino acids function as neurotransmitters for afferent neuron subserving pain. Most important peptides are Substance P and calcitonin gene related peptide (CGRP). Most important excitatory amino acid is Glutamate (Jessel, 1982).

Substance P is a transmitter synthesized and released by the first order neuron both peripherally and in the dorsal horn. Substance P is present in 10 % to 20 % of spinal sensory neurons in all mammalian species examined, including man, and is found within synaptic vesicles in the central terminals of sensory neurons located in laminae I and II of the dorsal horn (Jessel, 1982).

As for neurotransmitters in the dorsal horn involved in pain processing, they are opioid peptides. And this is the major site for opiate-induced analgesia. Leucine and

methionine enkephalins, the first opioid peptides to be discovered, represent only a small subset of the family of opioid peptides. Although there is still no direct proof that opiate receptors located on sensory neurons contain substance P, biochemical evidence for an interaction between opiates and substance P has now emerged in several different systems. The specificity of these opiate effects is demonstrated by the resumption of substance P release after administration of the opiate antagonist naloxone (Jessell, 1982).

Pain perception is also modulated by neurotransmitters from the supraspinal level in the descending pathway. The periaqueductal grey (PAG) region and the nucleus raphe magnus (NRM), which lies more caudally in the medulla, are among the most effective sites in eliciting analgesia. These nuclei are also sites at which focal microinjection of opiates has been shown to elicit analgesia, raising the possibility of release of endogenous opioids. This association is strengthened by the finding that opiate antagonists are often effective in abolishing analgesia elicited by brainstem stimulation (Yu *et al.*, 2013).

2.1.5 Acute Pain post Hysterectomy

Hysterectomy is the surgery to remove a woman's uterus. Depending on the reason of the hysterectomy, their surgeon may opt to remove all or only part of the uterus. For example, in subtotal hysterectomy, the surgeon removes only the upper part of the uterus, keeping the cervix in place. A total hysterectomy removes the whole uterus and cervix. In this study we have chosen to include total abdominal hysterectomy. In this type of surgery the surgeon opts for a midline or Pfannansteil incision to remove the uterus (Tay and Bromwich, 1998).

There are many causes that lead the patient to opt for a surgical intervention. Among those are uterine fibroids, endometriosis, uterine leiomyoma, uterine adenomyosis, uterine prolapse, uterine cancer, cervical cancer or ovarian cancer. In some of the aetiologies, the patient may have been subjected to years of some form of abdominal pain (Tay and Bromwich, 1998).

Chronic postoperative pain can generally occur after any surgery. Interestingly, the incidence of chronic pain post hysterectomy is up by 30 %, although the relative role of the different pathogenic factors has not been defined. It was found in one study involving 90 women undergoing elective hysterectomy, preoperative increased superficial and vaginal mechanosensitivity was related to the intensity of early pain after hysterectomy. It was correlated that poor control of acute pain in this patient population reflected in chronic pain later during their follow up (Brandsborg *et al.*, 2011).

2.1.6 Validation of Numerical Rating Scale (NRS)

Current guidelines on good management of pain practice includes the ability of pain to be assessed regularly and documented. There are multiple unidimensional measurements tools that may be used for the assessment of pain. Amongst those available are Visual Analogue Score (VAS), Numerical Rating Scale (NRS) and Verbal Rating Scale (VRS). All these tools are essentially used to measure the pain intensity experienced by the patient (Huskisson, 1974).

The VAS is a 10-cm line, anchored by verbal descriptors, usually ‘no pain’ and ‘worst imaginable pain’. The patient is asked to mark a 100 mm line to indicate pain intensity. The score is measured from the zero anchor to the patient’s mark (Figure 2.3)



Figure 2.3: Visual Analog Score (Huskisson, 1974)

One of the limitations of the VAS is that it must be administered on paper or electronically (Carlsson 1983). Interestingly, the graphic orientation of the VAS whether horizontally or vertically can make a difference to the statistical distribution of the data obtained using it. A study by Huskisson, 1974 explored the use of the VAS by English language speakers found that there was a 7% failure rate for the VAS when it was presented vertically but less when presented horizontally. They postulated that the graphic orientation of the VAS should be decided according to the normal reading tradition of the population on which it is being used.

The NRS is a 11 point scale where the end points are the extremes of no pain and pain as bad as it could be, or worst pain (Figure 2.4). The NRS can be graphically or verbally delivered. When presented graphically the numbers are often enclosed in boxes and the scale is referred to as an 11 point box scale depending on the number of levels of discrimination offered to the patient. The scale is interval level and can provide data for parametric analysis.

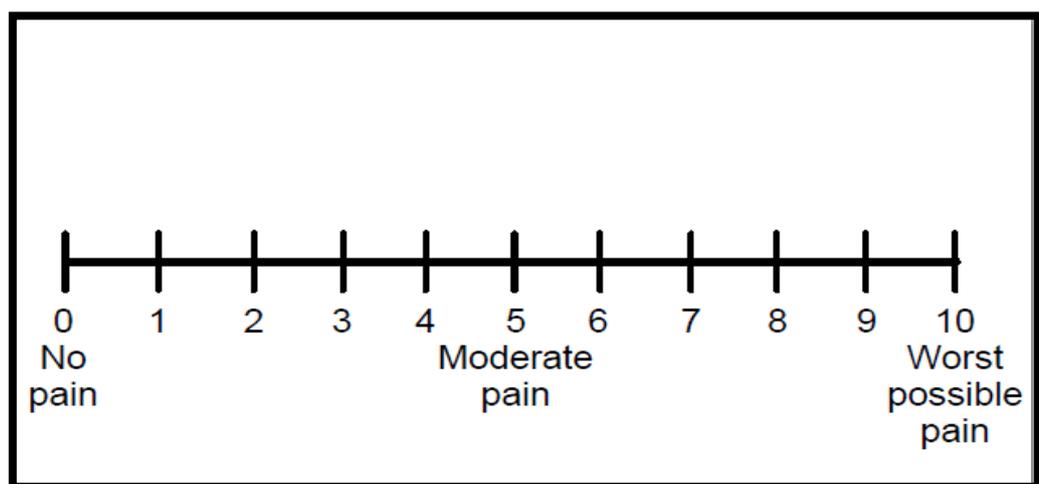


Figure 2.4: Numerical Rating Scale (Huskisson 1974)