THE PREVALENCE OF CHRONIC POSTMASTECTOMY PAIN SYNDROME IN FEMALE BREAST CANCER SURVIVORS

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine in Anaesthesia

Johannesburg, 2013
DECLARATION

I, Muhammed Luqmaan Variawa declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature

Signed at: University of the Witwatersrand, Johannesburg

On this date: 18 June 2013
PRESENTATIONS ARISING FROM THIS STUDY

• Research presentation at the Pain SA Congress, Pretoria, South Africa, June 2012. Won third place prize.
ABSTRACT

BACKGROUND: Breast cancer is one of the most common cancer diagnoses in women and is a significant cause of mortality and morbidity worldwide. Surgical treatment is indicated in most patients. Postmastectomy pain syndrome (PMPS) is a distinctive, persistent and debilitating neuropathic pain syndrome that develops after breast surgery. A review of the literature revealed no studies determining the prevalence of PMPS conducted in South Africa, specifically at the Chris Hani Baragwanath Academic Hospital (CHBAH). A detailed description of the prevalence of PMPS is needed to understand the problem in this patient group which may enable the development of a more effective pain management strategy.

OBJECTIVES: The objectives of this study were to determine the prevalence of postmastectomy pain syndrome in adult female breast cancer patients following general anaesthesia without regional anaesthesia at the CHBAH, as well as the impact of various clinical and demographic variables (e.g. age, adjuvant therapy) on the prevalence of PMPS.

METHOD: The research design was that of a cross-sectional descriptive survey study assessing chronic pain in breast cancer survivors. The validated DN4 Questionnaire, including demographic and clinical data, was used in this study. A convenience sample of women were recruited and interviewed when returning to the breast surgery follow-up clinic for routine examinations. Further data were obtained by examining the patients` medical records and reviewing the patient database at the breast clinic.

According to the literature, an average prevalence estimation of 35% was used to statistically calculate the sample size using STATCALC.

RESULTS: The study included 92 patients. The prevalence of PMPS in this study was found to be 38.04% (n=35). The median DN4 pain score was six (range 4-8). The average duration that patients experienced neuropathic pain symptoms was 12.22 months (range 3-39 months). The average age of patients interviewed was 58.54 years (range 30-90 years). There was no statistically significant association between
age and PMPS (p=0.47). The study also showed that no statistically significant
association existed between pain experienced and adjuvant therapy administered,
at a 0.05% level of significance. The majority of patients were prescribed simple
and combination analgesic medications for pain relief.

CONCLUSION: Even though surgical procedures are becoming less invasive, the
prevalence of PMPS after treatment for breast cancer remains a clinically
significant problem. This necessitates the development of more effective
prevention and treatment strategies for this syndrome to improve patients` quality
of life.
ACKNOWLEDGEMENTS

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<td>BPI</td>
<td>Brief Pain Inventory</td>
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<td>CEO</td>
<td>Chief Executive Officer</td>
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<td>CHBAH</td>
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<td>CI</td>
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<td>CPSP</td>
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<td>Douleur Neuropathique 4</td>
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<td>Eutectic mixture of local anaesthetic</td>
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<td>GA</td>
<td>General anaesthesia</td>
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<td>IASP</td>
<td>International Association for the Study of Pain</td>
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CHAPTER ONE

OVERVIEW OF THE STUDY

1.1 INTRODUCTION

In this chapter, a brief overview and summary regarding this research report is presented. Topics covered include introduction and background, problem statement, aims and objectives, research assumptions, demarcation of the study field, ethical considerations, research methodology, significance of the study, validity and reliability summary, potential limitations, and project outline. A more in-depth review of these topics will be presented in subsequent chapters.

1.2 BACKGROUND TO THE STUDY

Breast cancer is one of the most common cancer diagnoses in women and is a significant cause of mortality and morbidity worldwide (1). In South Africa, a crude incidence rate of 18.5/100 000 women was recorded between the years 1993 and 1995 (2). Surgical treatment is indicated in most patients, according to the clinical staging, to remove the primary tumour and axillary staging or dissection (3). These surgical procedures are typically performed using general anaesthesia with intravenous analgesia or regional anaesthesia (4). However, more patients are surviving breast cancer as a result of progress in the development of diagnostic and treatment strategies (5). Therefore, the population at risk for late post-surgical complications such as chronic pain can be expected to increase in the future, even though most surgical advances are less invasive (5).

Postmastectomy pain syndrome (PMPS) is a distinctive, persistent and debilitating neuropathic pain syndrome that develops after breast surgery and is regarded in many surgical texts as a complication of breast surgery (6). The description is somewhat misleading, as the syndrome also includes chronic pain after breast conserving surgery (7). PMPS can develop shortly after, or up to several months after surgery and can persist for years. The pain is often described as neuropathic in nature and is characterised by sensations of burning pain, shooting pain, electric shock-like pain,
stabbing pain, pain evoked by pressure and deep blunt pain. The pain is usually felt in the region innervated by the affected nerves (6). The exact mechanism is uncertain, but is thought to be the result of damage to nerve pathways, particularly the intercostobrachial nerve, during operative procedures on the breast and/or axilla (7).

Long-term disease and treatment-related symptoms, such as chronic pain, can have wide-ranging effects on health, functioning and quality of life. Burckhardt and Jones (8) state that studies conducted previously show a significant number of postmastectomy breast cancer survivors experience chronic pain that interferes with physical functioning, work, mood, sleep, relationships and enjoyment of life (8). Furthermore, chronic pain syndromes are often underestimated and poorly managed by health care providers. In addition, PMPS can often be difficult to treat, like other neuropathic pain conditions (9).

According to the literature, there is a wide variability in the prevalence of PMPS. Vilholm et al. (9) indicate that estimates in various studies range between 20-68%. A 20% prevalence rate of PMPS was found by Stevens et al. in 1995 (9). A study conducted by Vilholm et al. (9) showed the prevalence to be 23.9%. Another study conducted by Cairns et al. (6) in 1999, concluded that their survey revealed a 43% prevalence of PMPS. In 2009, Gartner et al. (10) reported a 47% incidence of chronic pain in postmastectomy patients.

Doss et al. (11) state that a number of studies have been conducted, comparing the effectiveness of regional anaesthesia with general anaesthesia for pain relief, side effects, post-anaesthesia recovery and hospital discharge after breast surgery (11). Various regional anaesthetic techniques for breast surgery have been suggested, including local anaesthetic infiltration, field block, intercostal nerve block, paravertebral block, thoracic epidural anaesthesia, and brachial plexus block (11). Advantages of regional anaesthesia appear to include: decreased nausea and vomiting, prolonged postoperative pain relief and the potential for earlier hospital discharge (4). However, because of technical difficulties, lack of experience, limitations of anaesthetic and analgesic effects and the possibilities of complications (e.g.
pneumothorax), the application of some of these approaches is not entirely suitable (11). Hence, general anaesthesia may be the preferred choice.

The review of the literature revealed no studies determining the prevalence of PMPS conducted in South Africa, specifically at the Chris Hani Baragwanath Academic Hospital (CHBAH). The majority of breast surgery at CHBAH is performed using general anaesthesia with intravenous analgesia. The reason for this is two-fold. Firstly, the theatre lists are long and there is a perception that performing a regional block would take more time. Secondly, there is a lack of co-operation from the surgeons with regard to performing regional blocks. The current anecdotal perception is that the prevalence of PMPS at the CHBAH breast surgery follow-up clinic is low. A detailed description of the prevalence of PMPS is needed to understand the problem in this patient group which may enable the development of a more effective pain management strategy.

1.3 PROBLEM STATEMENT

Postmastectomy pain syndrome (PMPS) is a distinctive postsurgical neuropathic pain syndrome and a recognised complication of breast surgery (6). The prevalence of PMPS has not been extensively established in the literature, specifically in the South African setting. At CHBAH, female breast surgery patients who underwent general anaesthesia without any regional anaesthesia are perceived to have a low prevalence of PMPS, contrary to international evidence. Currently, the prevalence of PMPS in patients following breast surgery under general anaesthesia without regional anaesthesia at the CHBAH is not known.

1.4 THE AIM OF THE STUDY

The aim of this study was to determine the prevalence of PMPS in adult female breast cancer patients following general anaesthesia without regional anaesthesia at the CHBAH surgical follow-up breast clinic.

1.5 OBJECTIVES OF THE STUDY

The primary objective of this study was:
• to describe the prevalence of PMPS at the CHBAH breast surgery follow-up clinic in adult female patients by administering the DN4 Questionnaire to these patients.

Secondary objectives were:

• to describe the duration of time that the patients have experienced neuropathic pain symptoms
• to describe the age of all participants
• to describe the number of patients who had adjuvant therapy (chemotherapy, radiation therapy or combination chemo-radiation therapy)
• to describe the number of patients who had adjuvant therapy presenting with and without PMPS
• to describe the prescribed analgesic medications that patients were receiving.

1.6 RESEARCH ASSUMPTIONS USED IN THE STUDY

In this study the following shall be the accepted definitions:

**Adult** - an individual who is 18 years or older.

**Prevalence** - the number of existing cases of PMPS reported during a specified period in a defined population (12).

**Chronic pain** – the International Association for the Study of Pain (IASP) has defined chronic pain as that persisting beyond the normal healing time of three months (13).

**Chronic postsurgical pain** – includes the following definitions: pain developing after a surgical procedure; pain of at least two months duration; other causes of pain excluded (e.g. malignancy, infection); pain continuing from pre-existing pain problem excluded (14).

**Neuropathic pain** – initiated or caused by a primary lesion or dysfunction in the nervous system (5), which is characterised by hyperalgesia, alldynia, and
spontaneous pain (15). Often described as sensations of burning, lancinating, electric shock like, or stabbing. Usually felt in the region innervated by damaged nerves (6).

**Hyperalgesia** – an increased response to a stimulus that is normally painful (16).

**Allodynia** – perception of a non-noxious stimulus as pain, such as light touch (16).

**Postmastectomy pain syndrome** – the definition used for the purposes of this study is based on three criteria: timing of the pain, character of the pain, and pain location. The pain should persist, either continuously or intermittently, beyond the normal healing time of three months. It should be typical of neuropathic pain, described in terms of numbness, pins and needles, burning, tingling etc. The pain should be located in the axilla, arm, shoulder, or chest wall on the side of surgery (6).

**Adjuvant Therapy** – refers to chemotherapy, radiotherapy or combination chemoradiation therapy administered to patients before or after breast cancer surgery.

**Mastectomy** – surgical procedure for breast cancer involving the removal of breast tissue. Two subtypes exist, namely, radical mastectomy and modified radical mastectomy. In this study, breast conserving surgery with axillary lymph node dissection (ALND) was also included.

1.7 DEMARCATION OF THE STUDY FIELD

The research was conducted at the CHBAH breast surgery follow-up clinic. This clinic operates on a weekly basis. Between four and eight mastectomies are performed in theatre per week. Approximately 120 to 150 women are consulted at the clinic per month and, of these, about 100 to 110 are postmastectomy patients.

CHBAH is a tertiary level hospital in Johannesburg, Gauteng, and is a referral centre for a number of smaller regional hospitals. The hospital is affiliated to the University of the Witwatersrand.
1.8 ETHICAL CONSIDERATIONS

Approval to conduct this study was obtained from the Postgraduate Committee (Appendix A) and the Human Ethics Committee of the University of the Witwatersrand (Appendix B), as well as the Chief Executive Officer (CEO) of the CHBAH (Appendices C and D).

The Head of the CHBAH surgical breast follow-up clinic, the Matron in charge of the clinic and the Head of the Department of Anaesthesia were approached for permission to conduct this study.

Informed written consent was obtained from all the participants enrolled in this study. An introduction and detailed explanation was delivered beforehand regarding the purpose of the study, participant selection, voluntary participation, information about data collection procedures, and confidentiality. The participant information letter (Appendix E) and informed consent form (Appendix F) were written in terms comprehensible to the intended subjects.

This study did not involve any drug or therapeutic management, and was conducted by adhering to good clinical research practice and the Declaration of Helsinki (17).

1.9 RESEARCH METHODOLOGY

1.9.1 Study design

The research design was that of a cross-sectional descriptive survey study assessing chronic pain in breast cancer survivors at the CHBAH. A validated pain questionnaire, including demographic and clinical data, was used in this study during the patient interview to collect the necessary information from the patient.

1.9.2 Study population and study sample

The CHBAH breast surgery follow-up clinic operates on a weekly basis. Between four to eight mastectomies are performed per week in theatre. Approximately 120 to 150 women are consulted at the follow-up clinic per month. Among these, about 100 to 110 are postmastectomy patients seen monthly.
1.9.3 Sample size

According to the literature review of international studies, the estimated average prevalence of PMPS was 35%. This prevalence estimation was used, along with a 10% precision level (power 90%) and 95% confidence interval (CI) in consultation with a biostatistician, to statistically calculate the sample size using STATCALC, a statistical programme under Epi Info, in order to obtain a good estimate of the prevalence of PMPS in this population. This revealed a sample size of 80 patients. A 25% safety margin was added for patients whose information may not be eligible for data analysis. A total sample size of 100 patients was used in this study.

Following a discussion with a senior colleague, a low prevalence rate was decided upon at one third of the international prevalence rate i.e. 11%. During the course of the data collection, if the prevalence of PMPS was below 11%, the sample size would need to be increased accordingly. This would be accomplished in consultation with a biostatistician to determine the exact number that the sample size needed to be increased to, within the scope of the study.

1.9.4 Sampling method

A convenience sample of women (n=100) who had undergone mastectomy for breast cancer at the CHBAH would be recruited and interviewed, using consecutive sampling, when returning to the breast surgery clinic for routine follow-up examinations.

1.9.5 Inclusion and exclusion criteria

For the purposes of this study, the inclusion criteria were:

- female adult patients 18 years and older
- radical or modified radical mastectomy, as well as breast conserving surgery with ALND, for breast cancer under general anaesthesia with intravenous analgesia and no regional anaesthesia
- at least three months post-surgery
- attending routine follow-up at the breast clinic
- no recurrence of breast cancer
• patients who may have received adjuvant therapy pre- or post-surgery
• able to communicate effectively with or without a translator.

Exclusion criteria were:

• conservative (without ALND), reconstructive or corrective breast surgery
• regional anaesthesia as part of the anaesthetic management
• chronic pain caused by anything other than PMPS, for example, cancer relapse, new breast cancer, other metastatic disease, post-surgical wound infection, lymphoedema etc.
• patients whose medical records were incomplete.

1.9.6 Data collection procedures

The prevalence of chronic pain after mastectomy was assessed using the definition of PMPS provided under the Research Assumptions in Chapter one. This definition, which is based on three criteria, excludes non-neuropathic pain, pain outside the distribution of the nerves affected and pain directly related to the surgery or wound healing process. Thus, this definition is specific to PMPS (25). All patients who satisfied both the inclusion and exclusion criteria were counselled and were required to give their written informed consent before entering the study. The participants were then asked the following initial question: “Have you experienced pain in the region of the operation lasting more than three months?” The DN4 Questionnaire was then administered to those individuals who answered in the affirmative during the interview, in order to differentiate nociceptive from neuropathic (PMPS) pain.

Various demographic and clinical variables were also obtained by examining the patients` medical records and reviewing the patient database at the breast clinic. These included age, date of surgery, whether the patient received any adjuvant therapy (chemotherapy and/or radiotherapy), and which analgesic medications were prescribed. Furthermore, the anaesthetic record was reviewed to ensure that the procedure was performed with general anaesthesia and intravenous analgesia alone, and no regional block.
All patients who were assessed as having confirmed chronic pain were referred back to the surgical team at the CHBAH breast clinic for further assessment, treatment and, if necessary, referral to a pain clinic for chronic pain management.

1.9.7 Study Questionnaire

The study questionnaire used for the purposes of this study was the DN4 Questionnaire (Appendix G). Key factors that contributed to the use of the DN4 Questionnaire in this study include the following: the integration of self-reported symptoms and physical examination, leading to improved precision than self-report alone; high discriminatory value for the identification of neuropathic pain; brevity and ease of scoring.

The DN4 Questionnaire presented by Bouhassira et al. (44) in Appendix G was adapted by Arnstein (38) in 2010. For the purposes of this study, the adapted questionnaire was further modified to include demographic and clinical information in order to facilitate data collection. All the information regarding pain characteristics and examination from the original questionnaire remained unchanged on the modified version (Appendix H).

1.9.8 Statistical Analysis

Raw data was captured using an Excel data spreadsheet and analyzed using the software programme STATA/IC (version 12), with the aid of a biostatistician. Individuals with missing information from the questionnaire were excluded from the specific analysis.

1.10 SIGNIFICANCE OF THE STUDY

PMPS is a common and serious complication of breast surgery. It is associated with restriction of activities of daily living, significant effects on quality of life, greater psychological or psychiatric morbidity, increased analgesic use, and increased health-care utilisation, posing a considerable economic and health-care burden (14). The numbers of breast cancer survivors are expected to increase due to improved diagnostic and treatment strategies, and therefore the number of women at risk for PMPS would also be expected to increase with time (5). Women suffering with PMPS
are often undertreated and generally achieve poor pain relief from their symptoms (45). In addition, a confirmed diagnosis of PMPS can be difficult to treat.

Knowledge of PMPS among breast cancer survivors is limited, specifically in South Africa at the CHBAH. A review of the literature revealed no studies of this nature having been carried out at this institution, or in South Africa. Current anaesthetic management at CHBAH involves general anaesthesia with intravenous analgesia. Anecdotal perception is that of a low prevalence of PMPS in this patient group at the CHBAH breast surgery follow-up clinic. An accurate, detailed description of PMPS is needed at this institution in order to understand the magnitude of the problem in this population group. This would facilitate accurate identification and treatment of PMPS patients. Furthermore, it would also enable the development of more effective prevention strategies, such as nerve-sparing surgery, relief of severe acute pain with regional anaesthesia, and medical analgesic therapies.

Hence it was decided, following the understanding of senior colleagues in the Department of Anaesthesia at CHBAH, that a study should be undertaken to document the prevalence of PMPS and attempt to identify certain factors which may be associated with its occurrence, with a view to changing local practice at this institution.

1.11 VALIDITY AND RELIABILITY OF THE STUDY

Formal evaluation of measurement error is an important consideration when developing a research study design. These measures are usually considered in terms of their reliability and validity (12). Reliability refers to the degree of similarity of the information obtained when the measurement is repeated on the same subject or the same group (12). Validity refers to the degree to which a measure actually quantifies what it is meant to measure (12).

The reliability and validity of this study was ensured by the following: use of a standardised patient interview process conducted by one researcher; use of the DN4 Questionnaire which has been validated and standardised in several languages with a high sensitivity (83%) and specificity (90%) in discriminating neuropathic pain (PMPS);
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and stringent application of recruitment strategies and the inclusion and exclusion criteria to avoid the same patients being enrolled more than once.

1.12 POTENTIAL LIMITATIONS OF THE STUDY

The following limitations have been identified:

A contextual limitation applies to this study and, thus, may not be representative of the post-breast cancer surgery population. Limited generalisability to the target population was further compounded by the relatively small, non-random convenience sample of patients from one geographic location, who had undergone treatment for breast cancer at one centre. However, this study does have the potential to change local practice at the current academic institution (CHBAH).

A cross-sectional study design provides only one estimate of pain prevalence and does not follow patients over time. Therefore, it cannot provide information on pain development after breast cancer treatment. Also, the cross-sectional design does not allow drawing conclusions regarding causality, but merely describes factors associated with PMPS occurrence.

The prevalence of PMPS in this study would only reflect those patients who chose to participate in the study. Therefore, the results may overestimate the problem of PMPS if women who chose to participate were those most likely to be experiencing pain. It could also lead to an underestimation of the problem if patients experiencing pain lacked the energy necessary for participating. Probable biases in sampling will be reduced by meticulous recruitment strategies that will minimise the likelihood of excluding some people from the sample or over representing others.

The DN4 Questionnaire used in this study has not yet been validated in any African language. This may pose a problem with non-English speaking patients understanding certain questions asked. This predicament was overcome with the aid of a translator who helped explain questions that the patients may not have understood.

Other factors which may have had an impact on the prevalence of PMPS, such as preoperative quality of life, pain intensity and analgesic consumption in the acute postoperative period, and HIV status, were not be taken into consideration in this
study. Additionally, the type, dose and duration of adjuvant therapy (chemotherapy/radiotherapy) administered to patients was beyond the scope of this study. Another potential bias that may be reflected in the results was the possibility that patients experiencing PMPS for a prolonged period of time could have adapted their response to the chronic pain that they were experiencing. This could have resulted in over-reporting or under-reporting of pain symptoms.

1.13 PROJECT OUTLINE

Chapter one represents an overview of this research report. Chapter two includes an in-depth literature review of various concepts regarding chronic pain and PMPS. In chapter three, a comprehensive discussion of the research methodology is offered. Chapter four includes the presentation of the results and the discussion thereof. The final chapter provides the conclusion of the study as well as further recommendations.

1.14 SUMMARY

This chapter provided a brief overview and summary regarding this research report. Topics covered included introduction and background, problem statement, aims and objectives, research assumptions, demarcation of the study field, ethical considerations, research methodology, significance of the study, validity and reliability summary, potential limitations, and project outline. A more comprehensive review of these topics are presented in subsequent chapters.
CHAPTER TWO
LITERATURE REVIEW AND BACKGROUND

2.1 INTRODUCTION

In this chapter, various concepts regarding pain and PMPS are reviewed in the literature. Firstly, a brief anatomy of pain signal transmission and nerve supply of the breast is provided. Secondly, various types of pain mechanisms, including nociceptive and neuropathic pain, are discussed. Mechanisms of chronic pain following breast cancer surgery in particular are reviewed thereafter.

PMPS will then be discussed in detail. The prevalence of PMPS according to various international studies will be considered. Risk factors for the development of PMPS are examined next. Following this, the consequences of PMPS on patient’s quality of life and functioning will be addressed. Important principles regarding the prevention and treatment of PMPS will then be evaluated. Lastly, various instruments for assessing neuropathic pain, including the rationale for the choice of questionnaire in this study, are reviewed.

2.2 BRIEF ANATOMY OF PAIN PATHWAYS

The innervation of the cutaneous and subcutaneous structures of the breast includes somatic and preganglionic sympathetic innervation that is supplied through the medial and lateral cutaneous branches of the ventral rami of the third through sixth intercostal nerves (5). The lateral cutaneous branch of T2 (intercostobrachial nerve) crosses the axilla to supply the upper medial portion of the arm, while the lateral and anterior branches innervate the upper back and anterior chest (5). T3 supplies the skin of the axilla as well as the anterior and posterior torso. The nipple is innervated primarily by T4 (5).

Specific sensory receptors called nociceptors respond selectively to different noxious modalities such as thermal, mechanical or chemical stimuli. These nociceptors are free nerve endings with cell bodies in the dorsal root ganglion and terminate in the dorsal horn of the spinal cord. Nociceptors do not adapt i.e. continued stimulation results in
repetitive firing. Noxious information is relayed mainly via two different types of primary afferent nociceptive neurons that conduct at different velocities. C-fibres are nonmyelinated and conduct in the range of 0.5-2m/sec, whereas A-delta fibres are thinly myelinated and conduct in the range of 2-20m/sec (18). In the spinal cord these neurons release neurotransmitters such as glutamate, substance P and calcitonin gene related peptide. These neurotransmitters will result in activation of the second-order neurons which cross to the contralateral side of the spinal cord and ascend the spinothalamic tract until it reaches the thalamus (18). From there the third-order neuron is activated, travelling to the somatosensory cortex (allows for the perception of pain), insular cortex (distinguishes pain from other homeostatic emotions) and the anterior cingulate cortex (embodies the motivational element of pain) (18).

Pain modulation represents changes that occur in the nervous system in response to noxious stimuli and allows noxious signals received at the spinal cord to be selectively inhibited so that the transmission of the signal to higher centres is modified. This system consists of intermediate neurons in the spinal cord and descending neural tracts that can inhibit the transmission of pain signals (18).

2.3 OVERVIEW OF PAIN MECHANISMS

Pain remains one of the most common reasons for medical consultation worldwide (19). It is often described as an unpleasant emotional and sensory experience that usually results from activation of nociceptive afferents by actual or potential tissue damaging stimuli, or described in terms of such damage (20). The ability to experience pain is essential for recognition of the presence of injury and for protection from injury. It enables us to withdraw from potentially damaging situations, protect the body while it heals and avoid those situations in the future.

Nociceptive pain is usually transitory, lasting only until the noxious stimulus is removed or the underlying damage or pathology has healed, and is called acute pain. However, pain may also arise by activity generated within the nervous system without sufficient stimulation of its peripheral sensory endings, and often results in chronic pain (20). The IASP has introduced the term neuropathic pain for this type of pain and defined it as, “pain initiated or caused by a primary lesion or dysfunction in the nervous system”
Treede et al. (20) felt that this definition lacked defined boundaries and presented a more precise definition developed by a group of experts from the neurologic and pain community i.e. “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” (20). The distinction between acute and chronic pain relies upon the time interval from onset. Chronic pain is defined by the IASP as that extending beyond the expected healing period of three months (13).

Chronic post-surgical pain (CPSP) is one of the most common and serious complications after surgery. A commonly used, working definition of CPSP proposed by Macrae (21) is as follows:

- pain developing after a surgical procedure
- pain of at least two months duration
- other causes of pain excluded (e.g. malignancy, infection)
- pain continuing from a pre-existing pain problem excluded (21).

CPSP is associated with restriction of activities of daily living, increased analgesic use, deleterious effects on quality of life, and increased health-care utilisation with significant economic and health-care system burden (14).

Nerve injury during surgery has been implicated in the development of chronic pain syndromes. Inflammatory and immune reactions, after damage to axons, results in the release of neurotransmitters that act locally (peripheral sensitisation) and in the spinal cord to produce ectopic neural activity and hypersensitivity. This leads to central sensitisation (11). Central sensitisation occurs when repetitive nociceptive stimuli result in altered dorsal horn activity and amplification of sensory flow. This can result in persistent nervous system changes, for example, microglial activation, death of inhibitory neurons and their replacement with excitatory afferent neurons (14). These changes lead to spontaneous and evoked symptoms associated with neuropathic pain, for example, hyperalgesia and allodynia (14).
2.4  CHRONIC PAIN AFTER BREAST CANCER SURGERY

Persistent pain in a patient with a prior surgical procedure for breast cancer can occur for many reasons, including tumour recurrence, paraneoplastic processes, chemotherapy-associated neuropathy, radiation plexitis and plexopathy, or surgical injury (5). Chemotherapy is often initiated after surgery and before radiation therapy when disease is found in axillary nodes. It can also be used in selected patients as an initial treatment to reduce tumour size in preparation for later surgical removal (5). Patients undergoing breast-conserving surgery (see later) are routinely administered post-operative radiotherapy targeting the breast, tumour bed and the axillary area (5).

Chronic pain that occurs as a direct consequence of surgery can be either nociceptive (e.g. injury to muscle or ligament) or neuropathic. Nociceptive pain usually resolves as the damaged tissue heals, whereas neuropathic pain can persist indefinitely (5).

Surgical treatment of breast cancer encompasses conservative and non-conservative procedures. Conservative surgical treatment includes lumpectomy, lumpectomy with axillary node dissection and lumpectomy with sentinel node biopsy. Radical mastectomy is a non-conservative procedure involving removal of the skin and breast tissue, all axillary lymph nodes, and the pectoralis major and minor muscles. A modified radical mastectomy preserves the pectoralis muscles (5). Despite the efficiency of the surgical treatment of breast cancer, several complications have been reported, among these are lymphoedema, infection of the surgical wound, and chronic postoperative pain (22).

Jung et al. (5) proposed a classification system of chronic neuropathic pain following breast cancer surgery that occurs as a direct consequence of the surgical procedure (5). They distinguish four subtypes of neuropathic pain following breast cancer surgery, namely:

• phantom breast pain – a sensory experience of a removed breast that is still present and is painfull

• neuroma pain – pain in the region of a scar on the breast, chest, or arm that is triggered by percussion
• **other nerve injury pain** – pain outside the distribution of the intercostobrachial nerve consistent with damage to other nerves during breast cancer surgery (e.g. long thoracic, thoracodorsal, medial and lateral pectoral, and other intercostal nerves)

• **intercostobrachial neuralgia** – pain, typically accompanied by sensory changes, in the distribution of the intercostobrachial nerve following breast cancer surgery with or without axillary dissection (5).

PMPS is included in the last subtype of post-mastectomy chronic pain (22). Damage to the intercostobrachial nerve has been considered the most common cause of PMPS (5). The risk of nerve damage during surgery can be similar for radical and conservative surgeries and depends on the anatomical variations of this nerve (22). Axillary dissection poses risks to the intercostobrachial nerve, from stretch during retraction as well as from complete transection (5). Indeed, recent studies have demonstrated that a higher rate of pain is not related to the type of surgery, but to the approach to the axilla where the intercostobrachial nerve can be damaged. However, other studies have shown that this syndrome is commonly associated with radical mastectomy and axillary lymphadenectomy (22).

### 2.5 POSTMASTECTOMY PAIN SYNDROME

Persistent pain after mastectomy was first reported in the 1970’s. It was characterised as a dull, burning and aching sensation in the anterior chest, arm and axilla, aggravated by movement of the shoulder girdle (23). The IASP has defined persistent pain after mastectomy as chronic pain in the anterior aspect of the thorax, axilla, and/or upper half of the arm beginning after mastectomy or quadrantectomy and persisting for more than three months after the surgery (13). The literature is not precise when defining chronic pain after the surgical treatment of breast cancer, because chronic pain has also been reported after other breast procedures, including breast reconstruction, augmentation and reduction (24). Therefore, the classification proposed by Jung et al. (5) that emphasises chronic pain syndromes as a direct consequence of breast cancer surgery, may be more applicable.
2.5.1 Prevalence of PMPS

A literature review revealed that there is a wide variability in the reported prevalence of PMPS. The variability in estimates of the prevalence of chronic pain following breast cancer surgery can be due to multiple factors, including duration of time since surgery, type of surgery, research method (prospective versus retrospective), diagnostic criteria, pain assessment methods, and various demographic and clinical characteristics (e.g. age, acute postoperative pain, use of adjuvant therapy, tumour recurrence etc.) (4).

In 2009, Gartner et al. (10) conducted a nationwide cross-sectional questionnaire study of 3754 women between the ages of 18 to 70 years who received surgery and adjuvant therapy (if indicated) for primary breast cancer in Denmark over a period of two years. They examined the prevalence, associated factors and severity of persistent pain following surgery. A detailed questionnaire was designed based on topics identified in the literature and open interviews.

The overall response rate was 87% (n=3253). The mean time from surgery to questionnaire was 26 months. A total of 1543 patients (47%) reported pain in one or more areas. The most frequently reported area of pain was the breast (86%), followed by the axilla (63%), arm (57%) and side of the body (56%). Young age (18 to 39 years) was associated with a higher risk, especially for patients receiving breast-conserving surgery (OR 3.62; 95% CI 2.25-5.82; P<0.001). Adjuvant radiotherapy was an independent and significant risk factor for reporting pain, but without relation to the extension of the radiation field on pain severity. Use of adjuvant chemotherapy had no independent association for pain.

The strengths of this study were that it was based on a large proportion of the Danish population, had a high response rate, lack of recall bias, and standardised treatment. Therefore, reasonably precise estimates of all treatment modalities can be provided. A cross-sectional study design is probably the main limitation of the study, in that it provided only one estimate of pain prevalence. Also, this study design does not allow drawing conclusions regarding causality. The Danish population was studied, thus limiting the ability to generalize the results to other populations. The questionnaire
that they used was designed specifically for this study, and not validated. Gartner et al. (10) concluded that persistent pain after breast cancer surgical treatment is a clinically significant problem and future strategies for improvement should include nerve-sparing axillary dissection and attention to patients with other chronic pain symptoms.

Vilholm et al. (9) assessed the prevalence of PMPS and its clinical characteristics in a group of patients who underwent breast cancer surgery, also in Denmark, within a period of one year from May 2003 to April 2004. They conducted a postal survey one and a half years after surgery for breast cancer. PMPS was defined as pain located in the area of the surgery or the ipsilateral arm, present at least four days a week and with an intensity of three or more on a numeric rating scale from zero (no pain) to ten (worst pain possible) (9). A control group was randomly selected from the same general population as the breast cancer group. Questionnaires were mailed to 258 breast cancer patients and 219 (84.9%) responded. Out of the 774 control subjects, 563 (72.7%) responded.

The prevalence of PMPS in the breast cancer patients was 24% compared to the control group, which was 10%. The odds ratio for developing PMPS after breast cancer surgery was 2.88 (95% CI 1.84-4.51). Three risk factors for developing PMPS were identified in this study: having undergone earlier breast surgery, tumour located in the upper lateral quarter and young age. Tumours located close to the axilla have a higher risk of damaging nerves in the area, and may increase the risk of subsequent chronic pain. It has been suggested that young patients have more aggressive disease requiring more invasive surgery and chemotherapy; however, these factors were included in the multiple regression analysis, indicating that other factors may account for the higher incidence of PMPS in young patients. Only 22% of the breast cancer patients reported that the pain had an impact on daily life and use of analgesics was low. These findings suggest that the severity of PMPS, in general, is moderate (9).

There are some methodological limitations to this study. The study group consisted of 219 Caucasian women who had undergone treatment at one centre. Therefore, the analysis of risk factors may have been hampered by the low number of patients, and the ability to generalize the results is not known. Also, the questionnaire used was
specifically designed for this study and there is no data to support its validity. The study concluded that there is still considerable risk of developing PMPS after treatment for breast cancer, and that the development of preventative measures as well as treatments of the syndrome are highly relevant (9).

A retrospective cohort study of PMPS conducted by Cairns et al. (25) in 1999, revealed that 43% of patients had ever suffered from PMPS and 29% reported current symptoms although the majority were decreasing in intensity. The study was conducted in Scotland and included consecutive mastectomy cases over a six year period, of which 511 survivors were traced and eligible for survey. A total of 408 completed the questionnaire survey. PMPS was defined as typical neuropathic pain located in the axilla, arm, shoulder, or chest wall of the affected side; and should persist beyond three months. The study questionnaire used included questions on demography, breast surgery and adjuvant treatments, part of the Cancer-Related Pain Questionnaire, and the Short-Form 36 (SF-36) (25).

The age of the responders ranged from 32-93 years with a mean of 60.1 years. A significant finding was the very high cumulative prevalence of PMPS in younger women aged 30-49 years (65%) compared to 26% in older women (70 years and over). The age difference was statistically significant (P<0.001), and accounted for most of the differences in marital status, employment status and housing. The authors surmised that the age effect could be due to a greater sensitivity to nerve damage in younger patients, or more extensive axillary dissection and clearance. It could also be a reflection of the more aggressive nature of breast cancer in pre-menopausal women. Patients reporting PMPS were more likely to have received pre-operative chemotherapy and post-operative radiotherapy and tamoxifen, however, there were no clear associations observed with chemotherapy, radiotherapy or tamoxifen. There was also a trend of increasing frequency of PMPS with increasing body mass index (BMI) (25). This study demonstrated that PMPS is common, and that the variability of onset and natural history is a challenge to developing and evaluating therapeutic measures to control symptoms (25).
Macdonald et al. (24) undertook a long-term follow-up to assess the outcome of PMPS at 7-12 years postoperatively in the same cohort of women studied by Cairns et al (25). Chronic pain and quality of life were assessed using the McGill Pain Questionnaire (MPQ) and SF-36. Of 175 women reporting PMPS in 1996, 138 were eligible for follow-up in this study. Mean time since surgery was nine years. A response rate of 82% was achieved (24).

The cumulative prevalence of PMPS at a mean of nine years postoperatively was 52% for the follow-up sample, while 48% of women reported that their PMPS had resolved since the previous survey. Quality of life scores were significantly lower in women with persistent PMPS compared to those women whose pain had resolved. However, there was a statistically significant improvement in physical functioning since 1996 in patients with persistent PMPS. Risk factors for PMPS elucidated in this study include younger age and heavier weight. The frequency of PMPS decreased with age from 91% in women aged 30-49, to 29% in women aged 70 years and older. No significant differences in BMI were found between those with persistent and resolved chronic pain (24). Limitations of the study, acknowledged by the authors, include small sample size, the absence of data on preoperative quality of life, pain intensity and analgesic use in the acute postoperative period (24).

Conclusions drawn by the authors suggest a decrease in pain intensity over time, although the neuropathic characteristics of PMPS remained constant. They also commented that all women undergoing breast cancer surgery should be informed of the possibility of developing chronic neuropathic pain syndromes (24).

Carpenter et al. (26) focused on postmastectomy or postlumpectomy pain in breast cancer survivors. Their aim was to determine the prevalence of postmastectomy pain (PMP), describe the subjective and objective characteristics of PMP, and examine the effect of PMP on quality of life (QOL). The Brief Pain Inventory (long form) was used to obtain a comprehensive description of pain and the SF-12 Health Survey was used to assess QOL. There were 123 participants who had complete staging data with a mean age of 56.5 years (SD=11.0, range 36-83) and the mean time post-treatment was 35 months (SD=21.8, range 4-116) (26).
The prevalence of PMP was reported to be 27%. The total sample was classified according to type of treatment received: lumpectomy and radiation, 27%; lumpectomy, radiation and chemotherapy, 33%; mastectomy alone, 23%; and mastectomy with chemotherapy, 15%. The high prevalence of PMP among women who underwent lumpectomy and radiation in this study shows that the term PMP is misleading (26).

Certain limitations of this study include the following. Findings are based on a relatively small, cross-sectional sample from one location. Secondly, the prevalence rate found in this study reflects only those patients who chose to participate in the study. This could lead to over- or underestimation of the results. In summary, this study showed that PMP is a relatively common problem in outpatient breast cancer survivors and was associated with a poorer QOL (26).

A questionnaire-based study conducted by Wallace et al. (27) included 479 women who underwent breast surgery at the San Diego Medical Centre between January 1988 and December 1992. Only women who had a lumpectomy with axillary dissection, a modified radical mastectomy, or a radical mastectomy were included in the study. A 59% response was achieved. The incidence of pain occurring at least one year postoperatively was 31% in the mastectomy group and 49% in the mastectomy and reconstruction group (27).

2.5.2 Risk factors for PMPS

Studies in the literature that have assessed risk factors for chronic pain following breast cancer surgery will now be discussed. Understanding the risk factors for chronic pain provides a basis for developing preventative measures. A paper published by Searle and Simpson (14) on chronic post-surgical pain (CPSP) identifies preoperative, intraoperative, and postoperative risk factors. The presence of preoperative pain is a risk factor for CPSP, as well as the age of the patient. The probability of developing CPSP after breast cancer surgery decreases by 5% for each yearly increase in the patient’s age (14). Genetic susceptibility and psychosocial factors (e.g. fear of surgery) also play a role in the development of CPSP. Intraoperative factors include longer and
more complicated operations. Acute postoperative pain and adjuvant interventions, such as radiotherapy, also increase the risk of developing CPSP (14).

A prospective study conducted by Poleshuck et al. (28) identified younger age as a significant risk factor for developing chronic pain three months after surgery. However, radiotherapy after surgery, more invasive surgery, and acute postoperative pain were independent predictors of more intense chronic pain three months after surgery, suggesting that the aggressive treatment of acute postoperative pain may reduce the prevalence of chronic pain. Psychosocial distress did not independently predict the prevalence or intensity of chronic pain.

However, Carpenter et al. (29) found that women with PMPS were not significantly different from women without PMPS, based on surgical, demographic, treatment or disease variables. They included 134 breast cancer survivors with a mean age of 55 years (SD=9) and a mean of 35 months post-surgery (SD=19). Pain was assessed using the Brief Pain Inventory (BPI). In addition, pain intensity was not significantly associated with time post-surgery, age at diagnosis, or time post-treatment. Their findings suggest that cases of PMPS cannot be consistently recognized based on the presence or absence of certain factors (29).

### 2.5.3 Impact of PMPS on quality of life

Long-term disease and treatment-related symptoms, such as chronic pain, can have wide-ranging consequences for health, functioning and quality of life (QOL), including mood, work, relationships and sleep (30). Compared to the general population, these patients have been found to have significantly greater psychological distress and morbidity, including depression and anxiety (5).

In 2003, Caffo et al. (31) used the MPQ-SF to identify four subscales exploring physical well-being, physical autonomy, relational life and psychological well-being in 757 disease-free patients treated for breast cancer between the years 1995 and 1998. A final analysis of 529 patients revealed that 39.7% of these women reported pain, and that the women with pain had significantly worse QOL scores on all of the subscales than those without pain.
In the study conducted by Carpenter et al. (26), they also assessed PMPS in relation to QOL using the BPI and SF-12 scores. The variables examined included, amongst others, general activity, mood, work, sleep, mental health, and physical health. In comparison to breast cancer survivors without pain, the PMPS group reported significantly poorer mental (P<0.05) and physical (P<0.001) health.

Many breast cancer patients suffer from chronic, widespread, diffuse pain in addition to the localised or regional pain after surgery. These patients have a significant risk for the development of fibromyalgia, a specific syndrome of widespread chronic pain (30). Burckhardt et al. (30) undertook a cross-sectional, descriptive pilot study, published in 2005, to compare and contrast the effects of chronic widespread pain with regional chronic pain in terms of pain characteristics, syndrome impact, health status, and QOL.

Women with chronic pain that began after surgery were divided into two groups, namely, regional pain (n=11) and widespread pain (n=12). Various validated instruments were used for measuring pain characteristics and impact on health status and QOL. In the widespread pain group, the interference of pain with activities and enjoyment of life measured by the BPI was 3-4 times greater than the regional pain group (30). Also, the widespread pain group had significantly more psychological distress identified on the instruments used (30).

There are, however, a few limitations to this study. The sample size was small and was one of convenience, with a large number of variables. Thus, these findings must be viewed with caution and cannot be construed as representative of the post-breast cancer surgery population (30).

2.5.4 Prevention and treatment of PMPS

The risk of developing chronic pain following breast cancer surgery can be attenuated by the type of surgical procedure employed (5). Careful dissection or preservation of the intercostobrachial nerve during surgery reduces the risk of sensory deficits and may reduce the risk of PMPS. Increasing use of sentinel lymph node biopsy may also reduce the prevalence of PMPS (5).
As discussed previously, acute postoperative pain is an important risk factor for the development of chronic postoperative pain in women after breast surgery (3). Preventative regional analgesia, given in the perioperative period, has an effect that extends beyond the duration of drugs used (14). Establishing adequate afferent block before the surgical incision and continuing this well into the postoperative period reduces the nociceptive bombardment that results in central sensitisation (14). Thoracic paravertebral block initiated before the surgical incision and continued into the postoperative period decreases the incidence of chronic pain in breast cancer surgery patients (14).

A meta-analysis of fifteen randomized controlled trials, published between 1999 and 2009, was conducted by Schnabel et al. (3) to assess the efficacy and safety of paravertebral block (PVB) to provide anaesthesia and post-operative analgesia during breast surgery, compared with general anaesthesia (GA). A systematic search, critical appraisal, data extraction, and pooled analysis were performed, and the relative risk (RR), mean difference (MD) and 95% confidence intervals (CI) were calculated. Included in the study were 877 patients who met the criteria.

A significant difference was found in postoperative pain scores between PVB alone and combined with GA, compared to GA alone, at various time intervals postoperatively. The study also revealed that the relative risk for chronic pain was slightly lower in the PVB group six months after surgery (3). Two studies in this meta-analysis showed a lower incidence of chronic pain twelve months after surgery, when patients had a PVB in addition to GA (RR: 0.61; 95% CI: 0.08-4.90; P=0.64) (3). The relative risk for reported adverse events (e.g. pneumothorax) was low. This study found evidence that PVB in addition to GA or alone provides better pain control with little adverse effects compared with other treatment strategies (3).

Limitations of this study are mainly due to clinical heterogeneity of several studies with respect to pain rating scores, extent of breast surgery, type of local anaesthetic and additives used, and positive publication bias (3).

Two other studies conducted by Coveney et al. (4) and Greengrass et al. (32), assessing the efficacy of PVB for the operative treatment of breast cancer, both concluded that
PVB can be successfully performed in the majority of patients with few adverse effects. There is an improvement in quality of recovery after surgery and it provides the patient with an option of ambulatory discharge. The side-effects of GA and narcotic analgesia are also minimised with PVB, for example, nausea and vomiting.

Exadaktylos et al. (48) conducted a retrospective analysis suggesting that paravertebral anaesthesia and analgesia for breast cancer surgery reduces the risk of recurrence or metastasis fourfold during a 2.5 to 4 year follow-up period by helping to maintain perioperative immune function. Munoz et al. (49) also suggest that PVB reduces mitogenesis in tumour cells by inhibiting the substance P/neurokinin-1 receptor system, which is over-expressed in breast cancer cells.

Several other regional techniques have also shown efficacy for postoperative analgesia after breast surgery, used with or without GA or sedation. These include, amongst others, thoracic epidural anaesthesia, stellate ganglion block, and field block (33-35). However, due to certain limitations of regional anaesthesia, such as technical difficulties, lack of experience, lack of cooperation from surgeons, and the possibility of complications, a GA with intravenous analgesia may be a more suitable option (11).

The treatment of established chronic pain following breast cancer surgery can be difficult. Satisfactory and persistent pain remission is seldom observed (36). In 1986, the World Health Organisation (WHO) presented the analgesic ladder for the treatment of cancer pain (37). This proposed that treatment of pain should begin with a non-opioid medication, and if the pain is not controlled, one should introduce a weak opioid. If this was still insufficient, one could then begin a more powerful opioid (37). The analgesic ladder also includes the possibility of adding adjuvant treatments (e.g. antidepressants, antiepileptics etc.) for neuropathic pain, however, the treatment algorithm is completely different for neuropathic pain, and opioids should be considered adjuvant medications and not the principal drugs for such pain (37).

Several therapies have had variable success in treating chronic neuropathic pain. These include Gabapentin, Ketamine, Clonidine (as a regional anaesthetic adjunct), Amitriptyline and Nortryptiline, Tramadol, EMLA cream, etc. In Italy, Dini et al. (36) demonstrated the usefulness of topical capsaicin in the treatment of PMPS. Capsaicin
is found in red peppers and other similar plants and supposedly produces an interruption of nociceptive transmission by depletion of substance P in unmyelinated sensory neurons (36). Treatment was well tolerated with no apparent side-effects.

A multidisciplinary treatment approach, which includes psychological interventions, physical therapy, as well as medical and interventional treatments, would provide a significant benefit in treating PMPS, as it has well established efficacy in the treatment of other chronic pain syndromes (5).

2.6 ASSESSMENT OF NEUROPATHIC PAIN

As mentioned previously, PMPS is classified as a chronic neuropathic pain syndrome. Therefore, distinguishing whether chronic pain after breast cancer surgery is nociceptive or neuropathic has important implications for diagnostic, lifestyle and treatment decisions for these patients (38). Traditionally, the diagnosis of neuropathic pain has been based on identification of the neurological lesion through the medical history, neurological examination, and electrophysiological or imaging investigations (39). Recent studies have shown that chronic neuropathic pain has specific symptoms and signs that have a very high discriminant value (39). This was the basis for the development of screening tools in the form of simple questionnaires that could aid in daily practise and clinical research (39).

Several tools are available to distinguish nociceptive from neuropathic pain. They were developed in different languages, but despite the specificities associated with the description of chronic pain in different cultures, the symptom-based approach for diagnosis of neuropathic pain appears to have transcultural validity (39). Tools that combine self-report and physical examination are more accurate than self-report alone (38).

Examples of various screening tools include, Neuropathic Pain Scale, Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Neuropathic Pain Questionnaire (NPQ), Neuropathic Pain Symptom Inventory, and the Douleur Neuropathique 4 (DN4) Questionnaire, amongst others (1). Arnstein (38) described three tools, namely, the LANSS, DN4, and NPQ, that have demonstrated good validity and reliability. The LANSS
Pain Scale was the first of the tools to be developed (38). It has seven items (five symptoms and two examination findings) to determine if pain is nociceptive or neuropathic (38). It is a validated, self-completed epidemiological tool with a sensitivity of 85% and specificity of 80% (38). The NPQ asks about pain (ten sensations and two emotions) and rates it on a scale of 0-100, but does not include physical examination methods, and therefore, is not highly recommended. It has 66% sensitivity and a specificity of 74% (38). In addition, this tool is long with complex mathematics involved (38).

The DN4 Questionnaire was originally developed and validated in France in 2005 (40) and, thereafter, translated into various languages, including English (called the Neuropathic Pain Diagnostic Questionnaire), using appropriate procedures. It consists of ten items (seven symptoms and three clinical examinations) that are easy to score, with a total of four or more classifying the pain as neuropathic (38). The sensitivity of this questionnaire is 83% and the specificity 90% (39). Arnstein (38) concluded that the LANSS and DN4 are preferred because of their conciseness and the integration of self-reported symptoms and physical examination. Furthermore, the DN4 is easiest to score and possibly the best tool to use (38).

Perez et al. (39) assessed the validity and reliability of the Spanish version of the DN4 Questionnaire for differentiating neuropathic pain and non-neuropathic pain. The two phases of the study included cultural adaptation into the Spanish language by means of conceptual equivalence, and analysis of psychometric properties using reliability and validity indices. A sample of 94 patients with neuropathic pain and 70 patients with non-neuropathic pain were enrolled (39).

The DN4 Questionnaire was found to be reliable [Cronbach’s alpha coefficient: 0.71, inter-rater agreement coefficient: 0.80 (95% CI 0.71-0.89), and test-retest intra-class correlation coefficient: 0.95 (95% CI 0.92-0.97)] and valid for a cut-off value of four or more points, which was the best value to differentiate between neuropathic and non-neuropathic pain (39). This study supported the high discriminatory value of the DN4 Questionnaire for the detection of neuropathic pain (39).
The study conducted by Harifi et al. (40), published in 2011, represented the second validation of the DN4 in a language different from the original, namely, Arabic. The sample consisted of 170 subjects, and a cut-off value of three or more points was used. The study results also supported the high discriminatory value of the DN4 Questionnaire (40).

Santos et al. (41) translated the DN4 Questionnaire into Portuguese to allow its use in clinical and research settings, and conducted a double-blind, accuracy study to analyze the reproducibility, reliability and validity of the instrument. The DN4 Questionnaire was applied to a sample of 101 patients with neuropathic (n=42) or nociceptive pain (n=59). This version of the questionnaire showed a high diagnostic power with good validity and reliability, allowing it to identify neuropathic pain (41).

For the purposes of this study, the English version of the DN4 Questionnaire was chosen to assess the incidence of PMPS in breast cancer surgery patients with chronic pain. The sensible and quick format of this instrument, which allows true recognition of patients with neuropathic pain, were key factors that contributed to its use in this study (41).

2.7 SUMMARY

An in-depth discussion on various subjects has been presented in the literature review regarding pain and PMPS. Firstly, a brief anatomy of pain signal transmission and nerve supply of the breast was provided. Secondly, various types of pain mechanisms, including nociceptive and neuropathic pain, were discussed. Mechanisms of chronic pain following breast cancer surgery in particular were reviewed.

Thereafter, PMPS was discussed in detail. The prevalence of PMPS according to various international studies was considered. Risk factors for the development of PMPS were examined next. The consequences of PMPS on patient`s quality of life and functioning was addressed. Important principles regarding the prevention and treatment of PMPS were then evaluated. Lastly, various instruments for assessing neuropathic pain, including the rationale for the choice of questionnaire in this study, were reviewed. The following chapter deals with the research methodology of this study.
CHAPTER THREE
RESEARCH DESIGN AND METHODOLOGY

3.1 INTRODUCTION

A detailed explanation of the research methodology is discussed under the headings of study design, study population and study sample (including sample size, sampling method, inclusion and exclusion criteria), description of data collection procedures including the DN4 Questionnaire, and the planned statistical analysis of the data.

3.2 PROBLEM STATEMENT

PMPS is a distinctive postsurgical neuropathic pain syndrome and a recognised complication of breast surgery (6). The prevalence of PMPS has not been extensively established in the literature, specifically in the South African setting. At CHBAH, female breast surgery patients who underwent general anaesthesia without any regional anaesthesia are perceived to have a low prevalence of PMPS, contrary to international evidence. Currently, the prevalence of PMPS in patients following breast surgery under general anaesthesia without regional anaesthesia at CHBAH is not known.

3.3 THE AIM OF THE STUDY

The aim of this study was to determine the prevalence of postmastectomy chronic pain in adult female breast cancer patients following general anaesthesia without regional anaesthesia at the CHBAH breast surgery follow-up clinic.

3.4 OBJECTIVES OF THE STUDY

The primary objective of this study was:

- to describe the prevalence of PMPS at the CHBAH breast surgery follow-up clinic in adult female patients by administering the DN4 Questionnaire to these patients.
Secondary objectives were:

- to describe the duration of time that the patients have experienced neuropathic pain symptoms
- to describe the age of all participants
- to describe the number of patients who had adjuvant therapy (chemotherapy, radiation therapy or combination chemo-radiation therapy)
- to describe the number of patients who had adjuvant therapy and presented with and without PMPS
- to describe the prescribed analgesic medications that patients were receiving.

3.5 DEMARCATION OF STUDY FIELD

The research was conducted at the CHBAH breast surgery follow-up clinic. This clinic operates on a weekly basis. Between four and eight mastectomies are performed in theatre per week. Approximately 120 to 150 women are consulted at the clinic per month and, of these, about 100 to 110 are postmastectomy patients.

CHBAH is a tertiary level hospital in Johannesburg, Gauteng, and is a referral centre for a number of smaller regional hospitals. The hospital is affiliated to the University of the Witwatersrand.

3.6 ETHICAL CONSIDERATIONS

Approval to conduct this study was obtained from the Postgraduate Committee (Appendix A) and the Human Ethics Committee of the University of the Witwatersrand (Appendix B), as well as, the Chief Executive Officer (CEO) of the CHBAH (Appendices C and D).

The Head of the CHBAH breast surgery follow-up clinic, the Matron in charge of the clinic, and the Head of the Department of Anaesthesia were approached for permission to conduct this study.
Informed written consent was obtained from all the participants enrolled in this study. An introduction and detailed explanation was delivered beforehand regarding the purpose of the study, participant selection, voluntary participation, information about data collection procedures and confidentiality. The participant information letter (Appendix E) and informed consent form (Appendix F) was written in terms comprehensible to the intended subjects.

This study did not involve any drug or therapeutic management, and was conducted by adhering to good clinical research practice and the Declaration of Helsinki (17).

3.7 RESEARCH METHODOLGY

3.7.1 Study design

The research design was that of a cross-sectional descriptive survey study assessing chronic pain in breast cancer survivors who previously received surgical treatment under general anaesthesia alone with or without adjuvant therapy at the CHBAH.

Descriptive study designs are used to obtain more information about certain characteristics within a particular field of study (42). Their purpose is to clearly delineate a phenomenon (e.g. PMPS) before prediction or causality can be examined. It describes a phenomenon of interest and the variables (e.g. age, adjuvant therapy) within that phenomenon. Variables are not manipulated and there is no treatment or intervention. The relationships among variables present an overall picture of the phenomenon being examined, but assessment of the types and degrees of relationships is not the purpose of a descriptive study. This study design involves no attempt to establish causality (42). This is an important design for acquiring knowledge in an area in which little research has been conducted (42). A study design of this nature was best suited for the purposes of this research project.

Cross-sectional designs study groups of subjects in various stages of development, patterns, trends and changes concurrently with the intent to describe changes in the phenomenon across stages (42). An assumption is made i.e. that the stages are part of a process that will evolve over time. Subjects are categorised by group, and data on the particular variables are collected at a single point in time. Even though the same
subjects are not observed through the entire process, selecting subjects at various points in the process provides important information about the entirety of the process (42). A cross-sectional design best described the research process in this study.

Surveys are used as a data collection technique in which the researcher uses questionnaires (by mail or in person) or personal interviews to gather data about an identified population (42). They can be an important source of data, and can be used within many study designs, including descriptive (42). A validated pain questionnaire, including demographic and clinical data, was used in this study during the patient interview to collect the necessary information from the patient.

Based on the above explanations, the study design chosen for this particular research report was decided upon.

3.7.2 Study population and study sample

The CHBAH breast surgery follow-up clinic operates on a weekly basis. Between four to eight mastectomies are performed per week in theatre. Approximately 120 to 150 women are consulted at the clinic per month. Among these, about 100 to 110 are postmastectomy patients seen monthly.

3.7.3 Sample size

In quantitative research, the calculation of sample size depends on a number of factors. The larger the sample size the greater the likelihood that the findings will accurately reflect the population (lower sampling error) (43). Sampling error refers to the idea of estimating population characteristics from data collected from a sample. In descriptive studies, sample size calculation is based on the level of precision and confidence intervals required of the results (43). These criteria formed the basis for calculating the sample size of this study.

According to the literature review of international studies, the estimated average prevalence of PMPS was 35%. This prevalence estimation was used, along with a 10% precision level (power 90%) and 95% confidence interval (CI) in consultation with a biostatistician, to statistically calculate the sample size using STATCALC, a statistical programme under Epi Info, in order to obtain a good estimate of the prevalence of
PMPS in this population. This revealed a sample size of 80 patients. A 25% safety margin was added for patients whose information may not be eligible for data analysis. A total sample size of 100 patients was used in this study.

Following a discussion with a senior colleague, a low prevalence rate was decided upon at one third of the international prevalence rate i.e. 11%. During the course of the data collection, if the prevalence of PMPS was below 11%, the sample size would have needed to be increased accordingly. This would have been accomplished in consultation with a biostatistician to determine the exact number that the sample size needed to be increased to, within the scope of the study.

### 3.7.4 Sampling method

To ensure a representative sample, there are two main types of sampling methods, namely, random and non-random sampling. In this study, a non-random sampling technique was utilised. Therefore, all members of the population did not have an equal chance of being selected for enrolment into the study (43). Thus, non-random samples cannot be assumed to fully represent the target population and, subsequently, conclusions about the generalisability of results to the intended population should be qualified (43). Although random sampling is the preferred method for quantitative research, it can be difficult to achieve due to time, cost and ethical considerations (43). Therefore, it is often necessary to use non-random sampling techniques, as was the case in this study.

Convenience sampling is a form of non-random sampling. This category of sampling makes use of the most readily accessible individuals or units in a study (43). It is commonly used in exploratory research to attain an estimate of a particular element of interest. Consecutive sampling is a version of convenience sampling where every available individual or event within an accessible population is chosen (43). This type of sampling is regarded as the best choice of non-random sampling in quantitative research (43).
A convenience sample of women (n=100) who had undergone mastectomy for breast cancer at the CHBAH were recruited and interviewed, using consecutive sampling, when returning to the breast surgery follow-up clinic for routine examinations.

### 3.7.5 Inclusion and exclusion criteria

Inclusion criteria are generally based on the research question and the research plan (43). They are applied to enable selection of a homogenous sample and improve the feasibility of conducting the study. Exclusion criteria are applied to exclude unique characteristics that may confound the results or to deal with ethical considerations relating to research (43).

For the purposes of this study, the inclusion criteria were:

- female adult patients 18 years and older
- radical or modified radical mastectomy, as well as breast conserving surgery with ALND, for breast cancer under general anaesthesia with intravenous analgesia and no regional anaesthesia
- at least three months post-surgery
- attending routine follow-up at the breast clinic
- no recurrence of breast cancer
- patients who may have received adjuvant therapy pre- or post-surgery
- able to communicate effectively with or without a translator.

Exclusion criteria were:

- conservative (without ALND), reconstructive or corrective breast surgery
- regional anaesthesia as part of the anaesthetic management
- chronic pain caused by anything other than PMPS, for example, cancer relapse, new breast cancer, other metastatic disease, post-surgical wound infection, lymphoedema etc.
- patients whose medical records were incomplete.
3.7.6 Data collection procedures

The prevalence of chronic pain after mastectomy was assessed using the definition of PMPS provided under the Research Assumptions in Chapter One. This definition, which was based on three criteria, excluded non-neuropathic pain, pain outside the distribution of the nerves affected, and pain directly related to the surgery or wound healing process. Thus, the definition was specific to PMPS (25). All patients who satisfied both the inclusion and exclusion criteria were counselled and required to give their written, informed consent before entering the study. The participants were then asked the following initial question: “Have you experienced pain in the region of the operation lasting more than three months?” The DN4 Questionnaire was then administered to those individuals who answered in the affirmative during the interview, in order to differentiate nociceptive from neuropathic (PMPS) pain.

Various demographic and clinical variables were also obtained by examining the patients’ medical records and reviewing the patient database at the breast clinic. These included age, date of surgery, whether the patient received any adjuvant therapy (chemotherapy and/or radiotherapy) and which analgesic medications were prescribed. Furthermore, the anaesthetic record was reviewed to ensure that the procedure was performed with general anaesthesia and intravenous analgesia alone, and no regional block (see flow diagram below).

All patients who were assessed as having confirmed chronic pain were referred back to the surgical team at the CHBAH breast clinic for further assessment, treatment and, if necessary, referral to a pain clinic for chronic pain management.
Women who satisfied both the inclusion and exclusion criteria attending follow-up at the breast surgery clinic. Counselling and informed consent given.

Collect demographic and clinical data.

“Have you experienced pain in the area of the operation lasting more than three months?”

Chronic pain reported with initial question.
DN4 questionnaire administered.

No chronic pain reported with initial question.

Nociceptive pain according to DN4 questionnaire.

Neuropathic pain according to DN4 Questionnaire.

Review of anaesthetic records.

Figure 3.1 Flow diagram of data collection procedure
### 3.7.7 Study questionnaire

The study questionnaire used for the purposes of this study was the DN4 Questionnaire (Appendix G). The DN4 Questionnaire was developed and validated in France by the French Neuropathic Pain Group and translated into different languages, including English (called the Neuropathic Pain Diagnostic Questionnaire), using appropriate procedures. Various studies in the literature concerning the DN4 Questionnaire have demonstrated good validity and reliability with a higher sensitivity (83%) and specificity (90%) than many other pain questionnaires.

Key factors that contributed to the use of the DN4 Questionnaire in this study included the following: the integration of self-reported symptoms and physical examination, leading to improved precision compared to self-report alone; high discriminatory value for the identification of neuropathic pain; brevity and ease of scoring.

The DN4 Questionnaire consists of a total of ten items that are grouped in four sections. The first seven items are related to pain quality (burning, painful cold, electric shocks) and its relationship to atypical sensations (tingling, pins and needles, numbness, itching). The other three items are related to neurological examination in the painful area (hypoesthesia to touch, hypoesthesia to pinprick, tactile allodynia). A score of one is given to each positive item and a score of zero given to each negative item. The total score is calculated as the sum of all ten items, and the cut-off value for the diagnosis of neuropathic pain is a total score of four out of ten (4/10) (39).

When examining the participants: light touch sensation was assessed using a tissue; pinprick sensation was assessed using a 25-gauge needle, and tactile allodynia was assessed by movement of a tissue over the painful area. Presence or absence of hypoalgesia, hyperalgesia and allodynia was noted.

The DN4 Questionnaire presented by Bouhassira et al. (44) in Appendix G was adapted by Arnstein (38) in 2010. For the purposes of this study, the adapted questionnaire was further modified to include demographic and clinical information in order to facilitate data collection. All the information regarding pain characteristics and
examination from the original questionnaire remained unchanged on the modified version (Appendix H).

### 3.7.8 Statistical analysis

Raw data was captured using an Excel data spreadsheet and analyzed using the software programme STATA/IC (version 12). With the aid of a biostatistician, descriptive statistics (frequencies, means, standard deviations, and percentages) of the prevalence of PMPS, age of patients, duration of time since surgery, and patients who had received adjuvant therapy were used to characterise the sample.

The findings were described and analysed using descriptive and inferential statistics. Cross tabulations with the prevalence of PMPS were carried out. The Students t-test for continuous variables and the Chi Square test for categorical variables were used where appropriate. P-values of < 0.05 were considered statistically significant, and 95% confidence intervals were calculated where indicated. Individuals with missing information from the questionnaire were excluded from the specific analysis.

### 3.8 VALIDITY AND RELIABILITY

Formal evaluation of measurement error is an important consideration when developing a research study design. These measures are usually considered in terms of their reliability and validity (12). Reliability refers to the degree of similarity of the information obtained when the measurement is repeated on the same subject or the same group (12). Instrument, observer, and subject variations can be evaluated, in the case of a questionnaire, by asking related questions which, if in disagreement, will show inconsistencies (12). Variation between measures can be limited by addressing the cause of the variation. The instrument/questionnaire variation can be minimised by standardisation and calibration of the instrument/questionnaire (12). One of the methods available to reduce observer variation is to standardise the measurement or interview process. Repeated measures enable one to assess and adjust for subject variations (12).

Validity refers to the degree of which a measure actually quantifies what it is meant to measure (12). Different levels of validity exist. Content validity requires that the
measure includes all the elements of a variable being investigated. Criterion-related validity involves assessing the sensitivity and specificity of an instrument/questionnaire. Predicted validity requires that the measure confirms a known hypothesised association. Inconsistent validity refers to a measure which is valid for one population, but might be different in other population (12).

The reliability and validity of this study was ensured by the following: use of a standardised patient interview process conducted by one researcher; use of the DN4 pain questionnaire which has been validated and standardised in several languages with a high sensitivity (83%) and specificity (90%) in discriminating neuropathic pain (PMPS); and stringent application of recruitment strategies and the inclusion and exclusion criteria that avoided the same patients being enrolled more than once.

3.9 SUMMARY

A detailed explanation of the research methodology has been presented under the headings of study design, study population and study sample (including sample size, sampling method, inclusion and exclusion criteria), description of data collection procedures including the DN4 Questionnaire, and the planned statistical analysis of the data.

The following chapter details the data analysis and discussion of the results of the study.
CHAPTER FOUR

STATISTICAL ANALYSIS AND DISCUSSION OF RESULTS

4.1 INTRODUCTION

This chapter contains the statistical analysis and results of the data captured during the data collection period. Results are presented as per the research objectives presented in Chapter One. The objectives of the study are therefore repeated.

The primary objective of this study was:

- to describe the prevalence of PMPS at the CHBAH breast surgery follow-up clinic in adult female patients by administering the DN4 Questionnaire to these patients.

Secondary objectives were:

- to describe the duration of time that the patients have experienced neuropathic pain symptoms
- to describe the age of all participants
- to describe the number of patients who had adjuvant therapy (chemotherapy, radiation therapy or combination chemo-radiation therapy)
- to describe the number of patients who had adjuvant therapy presenting with and without PMPS
- to describe the prescribed analgesic medications that patients were receiving.

4.2 RESULTS

The findings are described and analysed using descriptive and inferential statistics. Cross tabulations with the prevalence of PMPS are carried out. The Students t-test for continuous variables and the Chi Square test for categorical variables are used where appropriate. P-values of < 0.05 are considered statistically significant, and 95% confidence intervals are calculated where indicated.
4.2.1 Demographic characteristics of the study sample

During the seven month data collection period (September 2011 to March 2012), one hundred (n=100) patients were interviewed at the CHBAH breast surgery follow-up clinic. Four patients were excluded due to incomplete data capture and one patient was mistakenly interviewed twice. A further three patients reported non-neuropathic chronic post-operative pain (DN4 pain-score less than 4). The data analysis included ninety-two patients (n=92).

There was a wide variability in the duration of time since surgery (3-96 months) within the total sample interviewed (n=92). Of the 92 patients, 66 (71.74%) were between 3-20 months post-surgery, 22 patients (23.91%) were between 21-40 months post-surgery, and four patients (4.35%) were between 41-96 months post-surgery (Table 4.1 below). None of the patients interviewed were more than 96 months post-surgery. The time intervals were chosen to facilitate data analysis.

Table 4.1 Duration of time post-surgery for total study sample

<table>
<thead>
<tr>
<th>No. of months post-surgery</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 - 20</td>
<td>66</td>
<td>71.74</td>
<td>71.74</td>
</tr>
<tr>
<td>21 - 40</td>
<td>22</td>
<td>23.91</td>
<td>95.65</td>
</tr>
<tr>
<td>41 - 96</td>
<td>4</td>
<td>4.35</td>
<td>100.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>92</strong></td>
<td><strong>100.00</strong></td>
<td></td>
</tr>
</tbody>
</table>

4.2.2 Primary objective: to describe the prevalence of PMPS at the CHBAH breast surgery follow-up clinic in adult female patients by administering the DN4 Questionnaire to these patients

Of the 92 patients included in the data analysis, 35 fulfilled the specific criteria for chronic PMPS. These criteria excluded non-neuropathic pain, pain outside the distribution of the nerves affected, pain directly related to the surgery or wound healing process, and a DN4 pain score of <4. Table 4.2 below shows that the
prevalence of PMPS in this study was 38.04%, and that 57 of the 92 patients (61.96%) did not fulfil the specific criteria for PMPS.

Table 4.2 The prevalence of PMPS

<table>
<thead>
<tr>
<th>Pain experienced</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>57</td>
<td>61.96</td>
<td>61.96</td>
</tr>
<tr>
<td>Yes</td>
<td>35</td>
<td>38.04</td>
<td>100.00</td>
</tr>
<tr>
<td>Total</td>
<td>92</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

The median DN4 pain score among the 35 patients interviewed within the PMPS group was six (ranging from 4-8). The cut-off value for the diagnosis of neuropathic pain (PMPS) is a total score of 4 out of 10. As can be seen in table 4.3 below, six patients (6.52%) scored 4 out of 10, five patients (5.43%) scored 5 out of 10, 11 patients (11.96%) scored 6 out of 10, 10 patients (10.87%) scored 7 out of 10, and three patients (3.26%) scored 8 out of 10. None of the patients with PMPS in this study sample scored 9 or 10 out of 10. The majority of patients (60%) with PMPS scored between six and seven on the DN4 Questionnaire.

Table 4.3 DN4 pain scores within the PMPS group

<table>
<thead>
<tr>
<th>DN4 pain score (/10)</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>6</td>
<td>6.52</td>
<td>6.52</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>5.43</td>
<td>11.95</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>11.96</td>
<td>23.91</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>10.87</td>
<td>34.78</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>3.26</td>
<td>38.04</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td></td>
<td>38.04</td>
</tr>
</tbody>
</table>
4.2.3 Secondary objective: to describe the duration of time that the patients have experienced neuropathic pain symptoms

The average duration that patients in this study with PMPS (n=35) experienced neuropathic pain symptoms was 12.22 months (ranging from 3-39 months). Table 4.4 below shows that the majority of patients with PMPS (21 out of 35; 60%) experienced neuropathic pain symptoms for between 3 and 10 months. Also shown is that eight patients (22.86%) experienced neuropathic pain symptoms for between 11-20 months, and six patients (17.14%) experienced neuropathic pain symptoms for between 21-39 months. None of the patients interviewed with PMPS in this study sample experienced neuropathic pain symptoms for longer than 39 months. The time intervals were chosen to facilitate data analysis.

Table 4.4 Duration of neuropathic pain symptoms experienced within the PMPS group

<table>
<thead>
<tr>
<th>Duration of pain experienced (months)</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 -10</td>
<td>21</td>
<td>60.00</td>
<td>60.00</td>
</tr>
<tr>
<td>11 - 20</td>
<td>8</td>
<td>22.86</td>
<td>82.86</td>
</tr>
<tr>
<td>21 - 39</td>
<td>6</td>
<td>17.14</td>
<td>100.00</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

4.2.4 Secondary objective: to describe the age of all participants

The mean age of patients interviewed (n=92) was 58.54 years, ranging from 30-90 years (SD 14.22). Figure 4.1 below shows that the ages of patients in the study sample were normally distributed (variance 202.43, skewness 0.15, Kurtosis 2.34).
The sample was divided into three age groups, namely <41 years (young), 41-60 years (middle-age) and >60 years (older), in order to assess whether any particular age group had a higher prevalence of PMPS. Table 4.5 indicates the age-group distribution of the total study sample (n=92). Of the 92 patients, nine (9.78%) were in the <41 year age group, 45 (48.91%) were in the 41-60 year age group, and 38 (41.30%) were in the >60 year age group.

**Table 4.5 Age distribution of total study sample**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;41 (young)</td>
<td>9</td>
<td>9.78</td>
<td>9.78</td>
</tr>
<tr>
<td>41-60 (middle-age)</td>
<td>45</td>
<td>48.91</td>
<td>58.70</td>
</tr>
<tr>
<td>&gt;60 (older)</td>
<td>38</td>
<td>41.30</td>
<td>100.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>92</strong></td>
<td><strong>100.00</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>
Table 4.6 below shows the age-group distribution of patients with PMPS. As can be seen, three patients (8.57%) were in the <41 year age group, 20 patients (57.14%) were in the 41-60 year age group, and 12 patients (34.29%) were in the >60 year age group.

**Table 4.6 Age distribution of patients with PMPS**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;41</td>
<td>3</td>
<td>8.57</td>
<td>8.57</td>
</tr>
<tr>
<td>41-60</td>
<td>20</td>
<td>57.14</td>
<td>65.71</td>
</tr>
<tr>
<td>&gt;60</td>
<td>12</td>
<td>34.29</td>
<td>100.00</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Further analysis of the data was carried out to test for the association between pain experienced and the mean age of patients. Parametric analysis of continuous variables was carried out using the Two-sample Students t-test with equal variance. Table 4.7 shows that patients with pain were slightly younger at 57.17 years (SD 14.42) than those without pain at 59.38 years (SD 14.16). Statistically there was no significant difference between the ages of the two groups (t=0.72; degrees of freedom=90; p=0.47). The mean difference between the ages of the two groups was 2.21 years with a 95% confidence interval of -3.87 to 8.30, which was not significant.

**Table 4.7 Association between pain experienced and mean age of patients**

<table>
<thead>
<tr>
<th>Group</th>
<th>Obs.</th>
<th>Mean</th>
<th>Std. Err.</th>
<th>SD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pain</td>
<td>57</td>
<td>59.38</td>
<td>1.87</td>
<td>14.16</td>
<td>55.62-63.14</td>
</tr>
<tr>
<td>Pain</td>
<td>35</td>
<td>57.17</td>
<td>2.43</td>
<td>14.42</td>
<td>52.21-62.12</td>
</tr>
<tr>
<td>Combined</td>
<td>92</td>
<td>58.54</td>
<td>1.48</td>
<td>14.22</td>
<td>55.59-61.48</td>
</tr>
<tr>
<td>Diff.</td>
<td></td>
<td>2.21</td>
<td>3.06</td>
<td></td>
<td>-3.87-8.30</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.47</td>
</tr>
<tr>
<td>t value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>Deg. of freedom</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90</td>
</tr>
</tbody>
</table>
4.2.5 Secondary objective: to describe the number of patients who had adjuvant therapy (chemotherapy, radiation therapy or combination chemo-radiation therapy)

Table 4.8 below shows the number of patients who had adjuvant therapy within the total study sample (n=92). Of the 92 patients interviewed, 40 patients (43.48%) did not receive any adjuvant therapy as part of their treatment regime, 3 patients (3.26%) received radiotherapy, 19 patients (20.65%) received chemotherapy, and 30 patients (32.61%) received combination chemo-radiation therapy. Therefore, 52 patients (56.52%) received adjuvant therapy as part of their treatment regime.

Table 4.8 Adjuvant therapy administered within total study sample

<table>
<thead>
<tr>
<th>Radiotherapy</th>
<th>Chemotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>no. (%)</td>
<td>no. (%)</td>
</tr>
<tr>
<td>No</td>
<td>40 (43.48%)</td>
<td>19 (20.65%)</td>
</tr>
<tr>
<td>Yes</td>
<td>3 (3.26%)</td>
<td>30 (32.61%)</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>49</td>
</tr>
</tbody>
</table>

4.2.6 Secondary objective: to describe the number of patients who had adjuvant therapy presenting with and without PMPS

Table 4.9 and Fig 4.2 below show that of the patients with no PMPS (n=57), 27 (47.37%) did not receive any adjuvant therapy as part of their treatment regime, 10 (17.54%) received chemotherapy, 2 (3.51%) received radiotherapy, and 18 (31.58%) patients received combination chemo-radiation therapy.

Of the patients with PMPS (n=35), 13 (37.14%) received no adjuvant therapy, nine (25.71%) received chemotherapy, one (2.90%) received radiotherapy, and 12 patients (34.29%) received combination chemo-radiation therapy as part of their treatment (see Table 4.9 and Fig 4.2 below).
Further analysis of the data was carried out using the Chi-Square test for categorical variables to test for associations between pain experienced and adjuvant therapy administered. Table 4.10 below includes all patients who received chemotherapy, either alone or in combination with radiation therapy, and shows that no statistically significant association exists between pain experienced and chemotherapy/combination chemo-radiation therapy administered at a 0.05% level of.
significance (p=0.31). Of the 21 patients with PMPS who received chemotherapy, nine received chemotherapy alone and 12 received combination chemo-radiation therapy (see Table 4.9 above).

Table 4.10 Contingency table testing association between pain experienced and chemotherapy/combination chemo-radiation therapy

<table>
<thead>
<tr>
<th>Pain experienced</th>
<th>Chemotherapy/Combination chemo-radiation therapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No Pain</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>count (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>total %</td>
<td>31.52</td>
<td>30.44</td>
</tr>
<tr>
<td>row %</td>
<td>50.88</td>
<td>49.12</td>
</tr>
<tr>
<td>column %</td>
<td>67.44</td>
<td>57.14</td>
</tr>
<tr>
<td>Pain</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>count (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>total %</td>
<td>15.22</td>
<td>22.83</td>
</tr>
<tr>
<td>row %</td>
<td>40.00</td>
<td>60.00</td>
</tr>
<tr>
<td>column %</td>
<td>32.56</td>
<td>42.86</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>46.74</td>
<td>53.26</td>
</tr>
<tr>
<td>P Value</td>
<td></td>
<td>0.31</td>
</tr>
</tbody>
</table>

Table 4.11 includes all patients who received radiation therapy, either alone or in combination with chemotherapy, and shows that no statistically significant association exists between pain experienced and radiation therapy/combination chemo-radiation therapy administered at a 0.05% level of significance (p=0.84). Of the 13 patients with PMPS who received radiation therapy, one received radiation therapy alone and 12 received combination chemo-radiation therapy (see Table 4.9 above).
Table 4.11 Contingency table testing association between pain experienced and radiation therapy/combination chemo-radiation therapy

<table>
<thead>
<tr>
<th>Pain experienced</th>
<th>Radiotherapy/Combination chemo-radiation therapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No Pain</td>
<td>count (n)</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>total %</td>
<td>40.22</td>
</tr>
<tr>
<td></td>
<td>row %</td>
<td>64.91</td>
</tr>
<tr>
<td></td>
<td>column %</td>
<td>62.71</td>
</tr>
<tr>
<td>Pain</td>
<td>count (n)</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>total %</td>
<td>23.91</td>
</tr>
<tr>
<td></td>
<td>row %</td>
<td>62.86</td>
</tr>
<tr>
<td></td>
<td>column %</td>
<td>37.29</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>64.13</td>
</tr>
<tr>
<td>P Value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.12 below includes patients who received combination chemo-radiation therapy, and excludes patients who received chemotherapy or radiation therapy alone. This table shows that the association between receiving combination chemo-radiation therapy and pain experienced was not statistically significant at a 0.05% level of significance (p=0.79). Of the 35 patients with PMPS, 12 received combination chemo-radiation therapy as part of their treatment regimen (see Table 4.9 above).

Table 4.12 Contingency table testing association between pain experienced and combination chemo-radiation therapy

<table>
<thead>
<tr>
<th>Pain experienced</th>
<th>Combination chemo-radiation therapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No Pain</td>
<td>count (n)</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>total %</td>
<td>42.39</td>
</tr>
<tr>
<td></td>
<td>row %</td>
<td>68.42</td>
</tr>
<tr>
<td></td>
<td>column %</td>
<td>62.9</td>
</tr>
<tr>
<td>Pain</td>
<td>count (n)</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>total %</td>
<td>25.00</td>
</tr>
<tr>
<td></td>
<td>row %</td>
<td>65.71</td>
</tr>
<tr>
<td></td>
<td>column %</td>
<td>37.10</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>67.39</td>
</tr>
<tr>
<td>P Value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The odds ratio for the data presented was calculated. As is shown in Table 4.13 below, the probability of having pain following adjuvant therapy was 42.31% (22 patients of 52). The probability of having no pain following adjuvant therapy was 57.69% (30 patients of 52). The odds of having pain if adjuvant therapy was received were calculated as 0.73 (42.31/57.69). Similarly, the odds of having pain if no adjuvant therapy was received were calculated as 0.48 (32.50/67.50). The odds ratio of the “no adjuvant therapy group” versus the “adjuvant therapy group” was calculated as 1.52 (0.73/0.48). This meant that experiencing pain was 1.52 times more likely to occur in patients who received adjuvant therapy as part of their treatment, compared with no adjuvant therapy. Although the odds ratio for experiencing pain was 1.52, the 95% confidence interval was wide (95% CI 0.64-3.60, p>0.05, z score 1.96).

Table 4.13 Contingency table showing association between pain experienced and adjuvant therapy

<table>
<thead>
<tr>
<th>Adjuvant therapy</th>
<th>Pain experienced</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain</td>
<td>No Pain</td>
</tr>
<tr>
<td>Yes</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>23.91</td>
<td>32.61</td>
</tr>
<tr>
<td></td>
<td>42.31</td>
<td>57.69</td>
</tr>
<tr>
<td></td>
<td>62.86</td>
<td>52.63</td>
</tr>
<tr>
<td>No</td>
<td>13</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>14.13</td>
<td>29.35</td>
</tr>
<tr>
<td></td>
<td>32.50</td>
<td>67.50</td>
</tr>
<tr>
<td></td>
<td>37.14</td>
<td>47.37</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>57</td>
</tr>
</tbody>
</table>

4.2.7 Secondary objective: to describe the prescribed analgesic medications that patients were receiving

The majority of patients interviewed at the CHBAH breast surgery follow-up clinic were prescribed simple and combination analgesic medications for their chronic pain. These included: Panado, Spectrapain, Non-steroidal anti-inflammatory drugs (e.g. ibuprofen, naproxen, indomethacin), and Painblock. As discussed in chapter two, chronic neuropathic pain may not respond adequately to simple/combination analgesic medication.
There was a lack of a suitable neuropathic pain screening tool available at the clinic, resulting in possible underestimation of the extent of the problem. Additionally, there was no adequate referral system in place to refer patients suffering with PMPS to a specialised pain clinic for adequate multidisciplinary management of their chronic neuropathic pain.

4.3 DISCUSSION

Knowledge of the epidemiology of chronic neuropathic pain, in particular PMPS, following breast cancer surgery is limited, specifically at the CHBAH in South Africa. The aim of this study was to elucidate some of this information.

The prevalence of PMPS in this study was found to be 38.04%. This prevalence for PMPS in women after breast cancer surgery is similar to results obtained in other studies. Between 1988 and 1992, Wallace et al. (27) reported an incidence of pain occurring at least one year postoperatively of 31% in the mastectomy group. Carpenter et al. (26) determined the prevalence of PMPS to be 27%. Cairns et al. (25) conducted a retrospective cohort study in 1999 that revealed a 43% prevalence of PMPS. Macdonald et al. (24) undertook a long-term follow-up to assess the outcome of PMPS in the same cohort of women studied by Cairns et al (25). The cumulative prevalence of PMPS at a mean of nine years postoperatively was 52% for the follow-up sample. Vilholm et al. (9) assessed the prevalence of PMPS to be 24%. In 2009, Gartner et al. (10) conducted a nationwide cross-sectional questionnaire study showing that 47% of patients reported pain following breast surgery. In Brazil, Fabro et al. (46) examined 174 postmastectomy patients and showed an incidence of PMPS of 52%.

Estimates of the prevalence of PMPS vary widely in the literature. This may be due to differing measurements of pain and its consequences, differing definitions of persistent pain, varying combinations of surgery and adjuvant therapy, and variations in time since surgery (5). This underscores the need for a better case definition for neuropathic pain in breast cancer survivors to enable a more decisive evaluation of these patients (1).
It is essential to consider why the prevalence of PMPS is still regarded as being relatively infrequent, even though several studies (9, 10, 24, 25, 26, 27, 46), including this research report, have shown that PMPS is a common occurrence. This may be due to the fact that PMPS is occurring in the context of a potentially life-threatening condition where it is perceived as relatively less important (25). Also, medical professionals may not specifically ask about PMPS or disregard the symptoms as innocent (25).

In this study, patients with PMPS experienced neuropathic pain symptoms for between 3 and 39 months (average 12.22 months). The majority of these patients (60.00%) experienced symptoms for between 3 and 10 months post-treatment. Additionally, there was a wide variability in the duration of time since surgery within the total sample interviewed. This ranged from 3-96 months. The majority of patients (71.74%) were between 3 and 20 months post-surgery. In a study conducted by Gartner et al. (10), the mean time from surgery to questionnaire was 26 months (47% prevalence of PMPS). Vilholm et al. (9) conducted their postal survey one and a half years after surgery for breast cancer (24% prevalence of PMPS). The study undertaken by Macdonald et al. (24) was done at a mean time since surgery of nine years (52% prevalence of PMPS). Carpenter et al. (26) conducted their study at a mean time post-treatment of 35 months (27% prevalence of PMPS). There is some evidence that the prevalence of chronic pain and its intensity diminish over time (5). This may be due to the fact that women have developed adaptation mechanisms to learn to cope with their chronic pain.

The mean age of patients interviewed in this study (58.54 years) was comparable with the mean age of study populations in other studies (25, 26). Of interest is the finding that the majority of patients with PMPS (n=20, 57.14%) were middle-age (41-60 year age group) compared with 34.29% (n=12) in older patients (61-90 year age group), and 8.57% (n=3) in young patients (20-40 year age group). However, this study failed to show any statistically significant difference between age and PMPS (p=0.47). Several other studies have identified younger age as a significant risk factor for PMPS (9, 10, 24, 25, 28). It has been suggested that younger, pre-menopausal patients have more aggressive disease requiring more invasive surgery and adjuvant therapy. Younger
women can also be more anxious and have a lower threshold to unusual sensations (25). Carpenter et al. (26) did not find any relationship between age and pain after breast surgery.

Adjuvant therapy has been found to be associated with PMPS in various studies. Gartner et al. (10) found that radiation therapy was an independent and significant risk factor for reporting pain, but without relation to the extension of the radiation field on pain severity. Their study also showed that the use of chemotherapy had no independent association for pain. Cairns et al. (25) stated that patients reporting PMPS were more likely to have received pre-operative chemotherapy and post-operative radiotherapy and tamoxifen, however, there were no clear associations observed between pain and adjuvant therapy. Carpenter et al. (26) found a high prevalence of PMPS (33%) among women who underwent lumpectomy with combination chemo-radiation therapy. Fabro et al. (46) concluded that radiotherapy may cause persistent pain in breast cancer survivors, while the relationship between chemotherapy or hormone therapy and the risk of pain was not assessed. Poleshuck et al. (28) assessed risk factors for chronic pain following breast cancer surgery and identified radiation therapy after surgery as an independent predictor of more intense chronic pain 3 months after surgery.

In this study, 2.9% (n=1) of patients with PMPS (n=35) received radiotherapy alone, 25.71% (n=9) received chemotherapy alone and 34.29% (n=12) received combination chemo-radiation therapy as part of their treatment regime. In patients with no PMPS (n=57), 3.51% (n=2) received radiotherapy alone, 17.54% (n=10) received chemotherapy alone and 31.58% (n=18) received combination chemo-radiation therapy. No statistically significant association existed between pain and chemotherapy/combination chemo-radiation therapy (p=0.31), pain and radiotherapy/combination chemo-radiation therapy (0.84), and pain and combination chemo-radiation therapy (0.79).

Chemotherapy and radiation therapy are related to age and disease stage and can themselves be the cause of various neuropathic pain syndromes and it is thus uncertain whether they make an independent contribution to the development of
PMPS (5). Furthermore, comparison of results is difficult because studies, including this research report, have not indicated exact information regarding the type, dose and location of adjuvant therapy administered.

The prescribed pharmacological treatment for chronic neuropathic pain experienced by breast cancer survivors in this study included simple and combination analgesic medication. The prevalence of PMPS in this study suggests that these women were undertreated and obtained poor pain relief from their symptoms. This may be due to a lack of education and awareness among physicians, resulting in suboptimal assessment and management of neuropathic pain (47). Additionally, the lack of a quick and validated screening tool suggests that post-surgical neuropathic pain may be under-recognised among breast cancer survivors. A multidisciplinary approach to the treatment of chronic neuropathic pain, including physical, psychological and pharmacological therapies, is likely to influence the development and management of PMPS (14). Referral to an appropriate pain clinic is therefore an important consideration for suitable evaluation of these patients.

4.4 CONCLUSION

The prevalence of PMPS found in this study remains a clinically significant problem. Of interest was the finding that the majority of patients with PMPS were in the 41-60 year age group. However, this study failed to show any statistically significant difference between age and PMPS. This study also showed that no statistically significant association existed between pain experienced and adjuvant therapy administered. The odds ratio of the “no adjuvant therapy group” versus the “adjuvant therapy group” was calculated as 1.52 (95% CI 0.64-3.60, p>0.05, z score 1.96). The majority of patients interviewed at the breast clinic were prescribed simple and combination analgesic medications for their chronic pain.

4.5 SUMMARY

This chapter dealt with the statistical analysis and discussion of results of the data collected for this research report, according to the primary and secondary objectives of this study. The data presented included demographic characteristics of the study
population; the prevalence of PMPS in adult female breast cancer survivors; the
duration of time that the patients have experienced neuropathic pain symptoms; the
age of all participants; the number of patients who had adjuvant therapy
(chemotherapy, radiation therapy, or combination chemo-radiation therapy); the
number of patients who had adjuvant therapy presenting with and without PMPS; and
the prescribed analgesic medications that patients were receiving. The findings have
been described and analysed using descriptive and inferential statistics.

In the final chapter a summary, the limitations, recommendations and conclusions of
the study are presented.
CHAPTER FIVE

SUMMARY, LIMITATIONS, RECOMMENDATIONS AND CONCLUSIONS

5.1 INTRODUCTION

In this chapter the aim, objectives, study design and results of the study will be briefly reviewed. The limitations of the study will be addressed, recommendations for clinical practice and further research made, and a conclusion presented.

5.2 SUMMARY OF THE STUDY

5.2.1 The aim of the study

The aim of the study was to determine the prevalence of postmastectomy chronic pain in adult female breast cancer patients following general anaesthesia without regional anaesthesia at the CHBAH surgical follow-up breast clinic.

5.2.2 Objectives of the study

The primary objective of the study was:

• to describe the prevalence of PMPS at the CHBAH breast surgery follow-up clinic in adult female patients by administering the DN4 Questionnaire to these patients.

Secondary objectives were:

• to describe the duration of time that the patients have experienced neuropathic pain symptoms
• to describe the age of all participants
• to describe the number of patients who had adjuvant therapy (chemotherapy, radiation therapy or combination chemo-radiation therapy)
• to describe the number of patients who had adjuvant therapy presenting with and without PMPS
• to describe the prescribed analgesic medications that patients were receiving.

5.2.3 Summary of the methodology used in the study

The research design was that of a cross-sectional descriptive survey study assessing chronic pain in breast cancer survivors who previously received surgical treatment under general anaesthesia alone with/without adjuvant therapy at the CHBAH. A validated pain questionnaire (DN4 Questionnaire), including demographic and clinical data, was used to collect the necessary information from the patients.

Key factors that contributed to the use of the DN4 Questionnaire in this study included the following: the integration of self-reported symptoms and physical examination, leading to improved precision than self-report alone; high discriminatory value for the identification of neuropathic pain; brevity and ease of scoring.

The estimated average prevalence of PMPS from the literature was 35%. This was used, along with a 10% precision level (power 90%) and 95% confidence interval in consultation with a biostatistician, to statistically calculate the sample size. This revealed a minimum study sample of 80 patients.

A convenience sample of women were recruited and interviewed, using consecutive sampling, when returning to the breast surgery clinic for routine follow-up examinations.

The prevalence of chronic pain after mastectomy was assessed using the specific definition of PMPS provided under the research assumptions in chapter one. All patients who satisfied both the inclusion and exclusion criteria were counselled and required to give their written informed consent before entering the study.

The participants were then asked the following initial question: “Have you experienced pain in the region of the operation lasting more than three months?” The DN4 Questionnaire was administered to those individuals who answered in the affirmative, in order to differentiate nociceptive from neuropathic pain. Various demographic and clinical variables were obtained by examining the patients’ medical records and reviewing the patient database at the breast clinic. The anaesthetic record was
reviewed to ensure that the procedure was performed with general anaesthesia and intravenous analgesia alone, and no regional block.

5.2.4 Main findings of the study

The prevalence of PMPS in this study was 38.04%. The median DN4 pain score among the patients interviewed within the PMPS group was six (ranging from 4-8). The average duration that patients with PMPS experienced neuropathic pain symptoms was 12.22 months (ranging from 3-39 months).

The mean age of patients interviewed was 58.54 years, ranging from 30-90 years (SD 14.22). The ages of patients in the study sample were normally distributed. Of interest was the finding that the majority of patients with PMPS (57.14%) were in the 41-60 year age group (middle-age). However, this study failed to show any statistically significant difference between age and PMPS (p=0.47).

Adjuvant therapy has been found to be associated with PMPS in various studies (10, 25, 26, 28, 46). Of the patients with PMPS in this study, 37.14% received no adjuvant therapy, 25.71% received chemotherapy, 2.90% received radiotherapy, and 34.29% received combination chemo-radiation therapy as part of their treatment. At a 0.05% level of significance, this study showed that no statistically significant association existed between pain experienced and chemotherapy/combination chemo-radiation therapy (p=0.31), radiation therapy/combination chemo-radiation therapy (p=0.84), and combination chemo-radiation therapy (p=0.79). The odds ratio of the “no adjuvant therapy group” versus the “adjuvant therapy group” was calculated as 1.52. This meant that experiencing pain was 1.52 times more likely to occur in patients who received adjuvant therapy as part of their treatment, compared with no adjuvant therapy, however, the 95% confidence interval was wide (95% CI 0.64-3.60, p>0.05, z score 1.96).

The majority of patients interviewed at the breast clinic were prescribed simple and combination analgesic medications for their chronic pain. Many patients with neuropathic pain do not respond adequately to these treatments. Furthermore, there was a lack of a suitable neuropathic pain screening tool available at the clinic, and
there was no adequate referral system in place to refer patients suffering with PMPS to a specialised pain clinic for adequate management of their chronic neuropathic pain.

Many patients interviewed were interested in both the study’s results and impact on practice. Staff members at the CHBAH breast clinic were supportive of the research and hoped it would change practice at CHBAH.

5.3 LIMITATIONS OF THE STUDY

Results from this study should be examined in light of certain limitations. A contextual limitation applied to this study and, thus, the results may not be representative of the post-breast cancer surgery population. Limited generalisability to the target population was further compounded by the relatively small, non-random convenience sample of patients from one geographic location, who had undergone treatment for breast cancer at one centre. However, this study does have the potential to improve pain management at the CHBAH.

A cross-sectional study design provides only one estimate of pain prevalence and does not follow patients over time. Therefore, it cannot provide information on pain development after breast cancer treatment over time. Also, the cross-sectional design does not allow drawing conclusions regarding causality, but merely describes factors associated with PMPS occurrence.

The prevalence of PMPS in this study only reflected those patients who chose to participate in the study. Therefore, the results may have overestimated the problem of PMPS if women who chose to participate were those most likely to be experiencing pain. It could also have lead to an underestimation of the problem if patients experiencing pain lacked the energy necessary for participating. Probable biases in sampling were reduced by meticulous recruitment strategies that minimised the likelihood of excluding some people from the sample or over representing others.

The DN4 Questionnaire that was used in this study has not yet been validated in any African language. This posed a problem with non-English speaking patients understanding certain questions that were asked. This predicament was overcome.
with the aid of a translator who helped explain questions that the patients did not understand.

Other factors which may have had an impact on the prevalence of PMPS, such as preoperative quality of life, pain intensity and analgesic consumption in the acute postoperative period, and HIV status, were not taken into consideration in this study. Additionally, the type, dose and duration of adjuvant therapy (chemotherapy, radiation therapy or combination chemo-radiation therapy) administered to patients was beyond the scope of this study.

Another potential bias that could have been reflected in the results was the possibility that patients experiencing PMPS for a prolonged period of time could have adapted their response to the chronic pain that they were experiencing. This could have resulted in over-reporting or under-reporting of pain symptoms.

5.4 RECOMMENDATIONS FROM THE STUDY

5.4.1 Recommendations for clinical practice

PMPS is a frequent and important problem that affects various aspects of patients’ lives and poses a considerable economic and health-care burden. The development of more effective identification, prevention and treatment strategies is therefore recommended at the CHBAH. A multi-modal approach is most likely to influence the development of PMPS. These include the use of an appropriate diagnostic/screening tool for accurate identification of neuropathic pain (e.g. DN4 Questionnaire), nerve-sparing surgery, medical analgesic therapies (e.g. pregabalin, gabapentin, tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, opioids), and non-pharmacological therapies (e.g. psychotherapy, physiotherapy, transcutaneous electrical nerve stimulation).

Perioperative anaesthetic techniques for the relief of severe acute pain may also play a role in reducing the prevalence of PMPS. Preventative regional anaesthesia (e.g. epidural analgesia, paravertebral block) commenced before the surgical incision and continued into the postoperative period reduces the incidence of chronic postsurgical
pain (14). It is therefore recommended that these anaesthetic techniques be implemented on a regular basis at the CHBAH.

Referral to an appropriate pain clinic is an important consideration for suitable evaluation and management of these patients. This will involve discussion with, and education of, nursing staff, medical colleagues and patients, in both inpatient and outpatient settings.

5.4.2 Recommendations for further research

Should the above recommendations be introduced at CHBAH, it is suggested that their implementation and impact be followed up. A recommended focus for further research would be to evaluate the effect of general anaesthesia with regional anaesthesia, versus general anaesthesia alone, on the prevalence of PMPS.

Assessing the impact of various factors (e.g. preoperative quality of life, pain intensity and analgesic consumption in the acute postoperative period, HIV status, and the type, dose and duration of adjuvant therapy administered) on the prevalence of PMPS represents a further focus for future research.

5.5 CONCLUSION

The prevalence of PMPS after treatment for breast cancer remains a clinically significant problem that necessitates the development of more effective identification, prevention and treatment strategies at the CHBAH.
References


38. Arnstein P. Assessment of Nociceptive versus Neuropathic Pain in Older Adults. Speciality Practice Series. 2010(SP1).


## Appendix A

### Permission from Postgraduate Committee

- **UNIVERSITY OF THE WITWATERFALLS, JOHANNESBURG**
  - FACULTY OF HEALTH SCIENCES
  - ASSISTANT DEAN: A. ADAMS
  - CANDIDATE: ML VARIAWA

**Date of Assessment Group Meeting:** 13/1/2011  
**School/Department/Division:** Andrology

### Comments on Research Question

<table>
<thead>
<tr>
<th>No.</th>
<th>Question</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>How common is HIV in South Africa?</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Why is the clinical presentation of HIV unknown?</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>What is the prevalence of HIV?</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>How many cases of HIV are there?</td>
<td></td>
</tr>
</tbody>
</table>

- **Faculty:** Medicine

### Recommendations

1. **New Section:** Add a new section on the clinical presentation of HIV.
2. **Question:** Clarify the prevalence of HIV.
3. **Analysis:** Consider the prevalence of HIV in different populations.

### Discussion

- The prevalence of HIV in South Africa is a critical issue.
- The data should be presented more comprehensively.

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Appendix B

Permission from Ethics Committee

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/09 Dr Muhammad L Variawa

CLEARANCE CERTIFICATE
PROJECT

M114705
The Incidence of Chronic Postmastectomy Pain Syndrome (PMPS) in Female Breast Cancer Patients

INVESTIGATORS
Dr Muhammad L Variawa

DEPARTMENT
Department of Anaesthesiology

DATE CONSIDERED
29/08/2011

DECISION OF THE COMMITTEE*
Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE
29/08/2011

CHAIRPERSON
(Professor PE Cleaton-Jones)

cc: Supervisor: Mrs Juan Scolbans

DEPARTMENT OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10064, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the above mentioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. I agree to a completion of a yearly progress report.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

DR M.L. VARIAWA
26/08/2011
Appendix C

Permission from Medical Advisory Committee

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH HOSPITAL
PERMISSION TO CONDUCT RESEARCH

Date: 07 September 2011

TITLE OF PROJECT: The incidence of chronic postmastectomy pain syndrome (PMPS) in female breast cancer patients

UNIVERSITY: Witwatersrand

Principal Investigator: Dr ML Variawa

Department: Anaesthesiology

Supervisor (if relevant): Ms J Scribante

Permission Head Department (where research conducted): Not yet

Date of start of proposed study: Sept 2011

Date of completion of data collection: October 2011

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO/management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- Permission being obtained from the Head of the breast Clinic at CHBAH.
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital.
- The MAC will be informed of any serious adverse events as soon as they occur.
- Permission is granted for the duration of the Ethics Committee approval.

Recommended
(On behalf of the MAC)

Date: 07 September 2011

Approved/Not Approved
Hospital Management

Date: 08 Sept 2011
Letter to the CEO of CHBAH

Chief Executive Officer
Chris Hani Baragwanath Academic Hospital
R68 Old Potchefstroom Road
PO Bertsham
Johannesburg
2013

Attention: Ms J. More

Re: Permission to conduct research at the Chris Hani Baragwanath Academic Hospital (CHBAH).

Dear Ms More

My name is Dr Muhammed Luqmaan Variawa. I am a first year registrar in the Department of Anaesthesia, currently working at CHBAH. I am also registered for a Master of Medicine (Anaesthesia) degree at the Faculty of Health Sciences, University of the Witwatersrand. As part of the course requirement, I am expected to conduct clinical research under supervision. The title of my proposed research is: “The prevalence of chronic postmastectomy pain syndrome (PMPS) in female breast cancer survivors.”

PMPS is a distinctive postsurgical neuropathic pain syndrome and a common complication of breast surgery. It is associated with a significant effect on patients’ quality of life and poses a considerable economic and health-care burden. Knowledge of PMPS among breast cancer survivors is limited, particularly in South Africa at the CHBAH. Understanding the magnitude of the problem would facilitate accurate identification, treatment and prevention strategies.

With your permission I will interview the participants at the CHBAH surgical breast follow-up clinic, and complete a specific pain questionnaire to distinguish neuropathic (PMPS) from nociceptive pain. Various demographic and clinical data will also be obtained by reviewing the medical records. These include age, use of perioperative adjuvant therapy, and type of anaesthesia administered at the time of surgery. I will obtain permission from the Head of the Department of Anaesthesia and the Head of the breast clinic before undertaking this research.
I hereby apply for permission to carry out research at the CHBAH. The proposed study and its procedures have been approved by the Ethics Committee and the Postgraduate Committee of the University of the Witwatersrand. The clearance certificate number is M110705.

There will be no financial implications for the CHBAH, the Gauteng Provincial Department of Health, or the University of the Witwatersrand. All costs related to administration and stationary will be covered by me. A copy of the final report will be made available to you should you request this.

Should you require any additional information please contact me at 083 668 4570.

Yours faithfully,

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Dr ML Variawa
Registrar in the Department of Anaesthesia, University of the Witwatersrand
Chris Hani Baragwanath Academic Hospital
MBBCH (WITS), DA (SA)
Appendix E

Participant information letter

Hello,

My name is Dr Muhammed Variawa. I am Medical Doctor currently specialising in the field of Anaesthesia at the Chris Hani Baragwanath Academic Hospital. As part of the course requirement, I am expected to conduct clinical research. You are invited to take part in a research study conducted by me. I hope to learn more about long-term pain in women who had an operation to remove their breast/s (mastectomy) due to breast cancer. I would like to invite you as a possible participant in this study because you fit certain criteria for enrolment into this study. These criteria include, but not limited to, age older than 18 years, time of surgery more than three months ago, and type of surgery. I have gained this information from assessing your file at the breast clinic. The information that we learn from this study may help us to improve our treatment plan for future breast cancer patients who need operations.

If you decide to take part, I will ask you a few questions about your pain and perform a brief examination of the painful area, according to a specific questionnaire. The time taken to complete the questionnaire will be as quick as possible (approximately 20 minutes) to limit any inconvenience to you. We cannot guarantee, however, that you will receive any benefits from this study.

Any information that I get in connection with this study and that can be identified with you will remain anonymous and confidential (secret) and will only be made available with your permission or as required by law. Your decision whether or not to take part in this study is completely voluntary, and will not affect your future treatment plan at the breast clinic. If you decide to take part, you are free to stop taking part at any time without any consequences. The study has obtained approval from the Human Ethics Committee of the University of the Witwatersrand.

If you have any questions, please feel free to ask. You will be given a copy of this form to keep. If you have any questions later on, you can contact me on 011 933 9564 or the Chairman of the Ethics Committee, Professor Cleaton-Jones on 011 717 2301.

Thank you for your time.

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Dr ML Variawa
Appendix F

Informed consent form

YOU ARE MAKING A DECISION WHETHER OR NOT TO PARTICIPATE. YOUR SIGNATURE INDICATES THAT YOU HAVE DECIDED TO PARTICIPATE, HAVING READ THE INFORMATION PROVIDED ABOVE AND HAVING YOUR QUESTIONS ANSWERED TO YOUR SATISFACTION.

Print name of participant: ________________________________
Signature of participant: ________________________________

Print name of researcher/person taking consent: _________________________
Signature of researcher/person taking consent: _________________________

Date (dd/mm/yy): _________________________
Appendix G

DN4 Questionnaire

Please complete this questionnaire by ticking one answer for each item in the 4 questions below:

**INTERVIEW OF THE PATIENT**
Question 1: Does the pain have one or more of the following characteristics?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Question 2: Is the pain associated with one of more of the following symptoms in the same area?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**EXAMINATION OF THE PATIENT**
Question 3: Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Question 4: In the painful area, can the pain be caused or increased by:

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The total score is calculated as the sum of the 10 items and the cut-off value for the diagnosis of neuropathic pain is a total score of 4/10.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
</tr>
</thead>
</table>

Appendix H

Study Questionnaire

Patient Name:
Hospital Number:
Date & Time:
Age/DOB:
Date of Surgery:
Adjuvant Therapy: Radiotherapy Chemotherapy

“Have you experienced pain in the area of the operation lasting more than three months?”

Yes  No

If answer is “yes”, then proceed to DN4 questionnaire.

DN4 Questionnaire

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>No=0</th>
<th>Yes=1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the pain have the following characteristic? Burning?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the pain have the following characteristic? Painful cold?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the pain have the following characteristic? Electric Shocks?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the area of pain also have the following? Tingling?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the area of pain also have the following? Pins &amp; needles?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the area of pain also have the following? Numbness?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the area of pain also have the following? Itching?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exam: Decrease in touch sensation (tissue)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exam: Decrease in pinprick sensation (25-gauge needle)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exam: Does movement of a tissue in the painful area cause or increase pain?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0-3 = likely nociceptive pain; ≥4 = likely neuropathic pain

Total /10

Modified from: Paul Arnstein. Assessment of Nociceptive versus Neuropathic Pain in Older Adults. Speciality Practice Series. 2010(SP1). (1).

Review of Anaesthetic Record: General Anaesthesia alone (no Regional Blocks) –

Prescribed Medication/s: 

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