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RESEARCH

The prevalence of chronic postmastectomy pain syndrome in female breast cancer survivors

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Background: Breast cancer is one of the most common cancer diagnoses in women. Surgical treatment is indicated in most patients. Postmastectomy pain syndrome (PMPS) is a 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. The current anecdotal perception is that the prevalence of PMPS in the African population is low.
Objectives: The objectives of this study were to determine the prevalence of PMPS in adult female breast cancer patients following general anaesthesia without regional anaesthesia at the Chris Hani Baragwanath Academic Hospital (CHBAH), as well as the impact of various clinical and demographic variables on the prevalence of PMPS.
Methods: The research design was that of a cross-sectional descriptive study. The validated DN4 pain questionnaire was used in this study.
Results: The study included 92 patients. The prevalence of PMPS was found to be 38.04% (n = 35). 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 difference between age group and PMPS (p = 0.47). The study also showed that no statistically significant association existed between pain experienced and adjuvant therapy administered.
Conclusion: Even though surgical procedures are becoming less invasive, the prevalence of PMPS after treatment for breast cancer remains a clinically significant problem, comparable to international literature. This necessitates the development of more effective prevention and treatment strategies to improve patients' quality of life.

Keywords: breast cancer, chronic pain, postmastectomy pain syndrome

Introduction

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, either to remove the primary tumour or for axillary staging and dissection.[3] More patients are surviving breast cancer as a result of progress in the development of diagnostic and treatment strategies. Therefore, the population at risk for late post-surgical complications such as chronic pain can be expected to increase in the future.[4]

Postmastectomy pain syndrome (PMPS) is a distinctive, persistent and debilitating neuropathic pain syndrome that can develop after breast surgery.[4] The International Association for the Study of Pain (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.[9] 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 usually felt in the region innervated by the affected nerves.[5] The exact mechanism is uncertain, but is thought to be the result of damage to nerve pathways, particularly the intercostobrachial nerve (lateral cutaneous branch of T2), during operative procedures on the breast and/or axilla.[6]

Chronic pain can have wide-ranging effects on health, functioning and quality of life. Studies[4,7,13] conducted previously show a significant number of postmastectomy breast cancer survivors (ranging from 20% to 40% in these studies[4,7,13]) experience chronic pain that interferes with physical functioning, work, mood, sleep, relationships and enjoyment of life. Furthermore, chronic pain syndromes are often underestimated and poorly managed by healthcare providers.[7]

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 tertiary referral hospital in Johannesburg. The majority of breast surgery at CHBAH is performed using general anaesthesia with intravenous analgesia. The current anecdotal perception is that the prevalence of PMPS at the CHBAH breast surgery follow-up clinic is low, contrary to international studies.

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, as well as the impact of various clinical and demographic variables (e.g. age, adjuvant therapy) on the prevalence of PMPS.

Research methodology

The research design was a cross-sectional descriptive study assessing chronic pain in breast cancer survivors. A convenience sample of women who had undergone mastectomy for breast cancer at the CHBAH were recruited and interviewed, using consecutive sampling, when returning to the breast surgery

clinic for routine follow-up examinations. Approval to conduct this study was obtained from the Postgraduate Committee and the Human Ethics Committee of the University of the Witwatersrand (M110705). Informed written consent was obtained from all the participants enrolled in this study. 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.[11]

According to international studies, the estimated average prevalence of PMPS is 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™ (version 6) (CDC, Atlanta, GA, USA). A total sample size of 100 patients was used in this study.

The inclusion criteria were: female adult patients 18 years and older who had radical or modified radical mastectomy, as well as breast-conserving surgery with axillary lymph node dissection (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 and able to communicate effectively with or without a translator.

Exclusion criteria included: 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 and patients whose medical records were incomplete.

The prevalence of chronic pain after mastectomy was assessed using the definition of PMPS, which 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.[5] The participants were asked the following initial question: 'Have you experienced pain in the region of the operation lasting more than three months?' The study questionnaire was then administered to those individuals who answered in the affirmative during the interview, in order to differentiate nociceptive from neuropathic (PMPS) pain.

The study questionnaire used for the purposes of this study was the DN4 Questionnaire (Didier Bouhassira, Paris, France). 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 enhanced precision rather than 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 10 items that are grouped in four sections. A score of 1 is given to each positive item and a score of 0 is given to each negative item. The cut-off value for the diagnosis of neuropathic pain is a total score of 4 out of 10.[15] 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.

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 that no regional block or local anaesthetic infiltration of the surgical site was performed.

Raw data were captured and analysed using the software program STATA/IC™ (version 12) (StataCorp LP, College Station, TX, USA), with the assistance of a biostatistician. The findings were described and analysed using descriptive and inferential statistics. Student's 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 analysis.

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; and stringent application of recruitment strategies and the inclusion and exclusion criteria to avoid the same patients being enrolled more than once.

Study results

During the seven-month data-collection period (September 2011 to March 2012), 100 African 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 postoperative pain (DN4 pain-score less than 4), therefore the data analysis included 92 patients. Figure 1 illustrates the data-collection procedure.

There was a wide variability in the duration of time since surgery (range 3–96 months) within the total sample interviewed. Of the 92 patients, 66 (71.74%) were between 3 and 20 months post-surgery, 22 patients (23.91%) were between 21 and 40 months post-surgery, and 4 patients (4.35%) were between 41 and 96 months post-surgery.

Of the 92 patients included in the data analysis, 35 fulfilled the 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. In addition, these patients received general anaesthesia with intravenous analgesia and no regional block. The prevalence of PMPS in this study was 38.04%.

The median DN4 pain score among the 35 patients interviewed within the PMPS group was 6 (ranging from 4 to 8). The majority of patients (60%) with PMPS scored between 6 and 7 on the DN4 Questionnaire (Table 1).

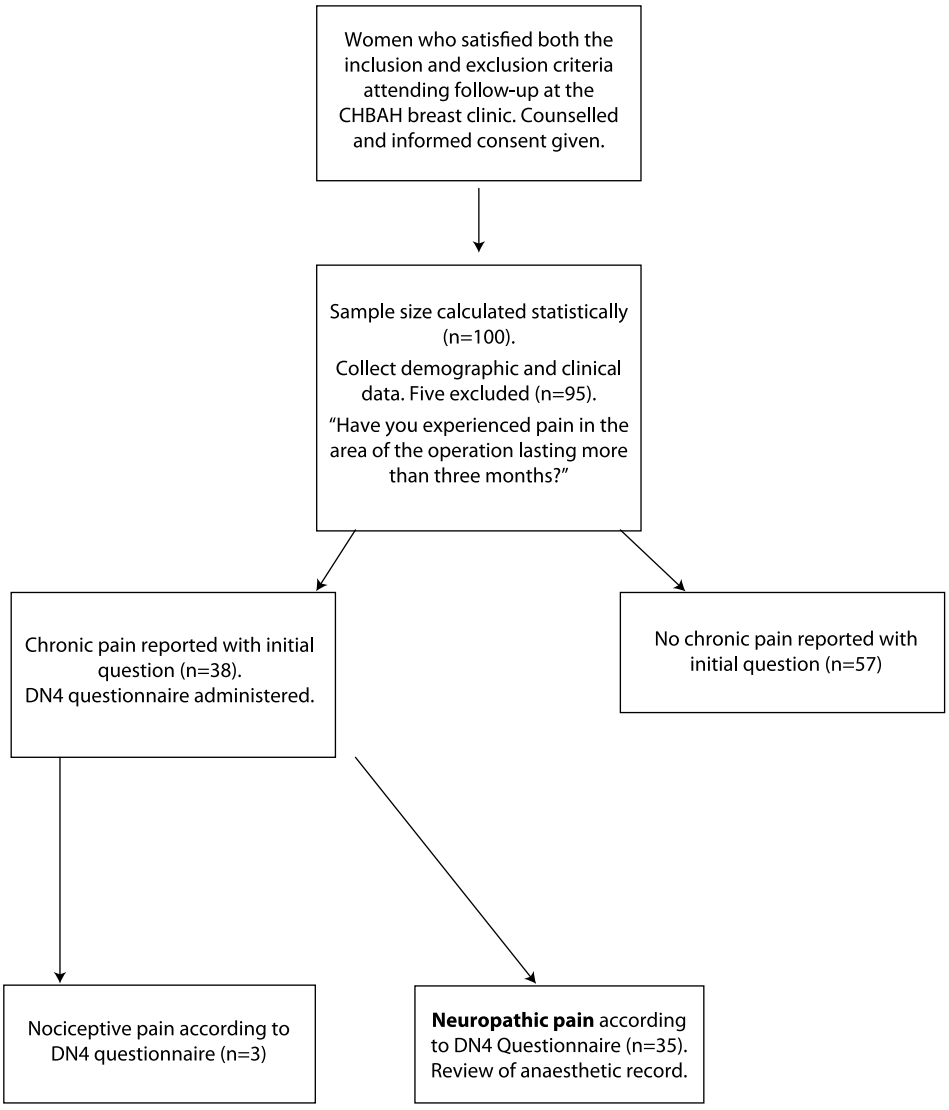

Figure 1: Flow diagram of data-collection procedure.

Table 1: DN4 pain scores within the PMPS group

DN4 pain score (/10)	Frequency	%	Cumulative
4	6	6.52	6.52
5	5	5.43	11.95
6	11	11.96	23.91
7	10	10.87	34.78
8	3	3.26	38.04
Total	35		38.04

The average duration that patients with PMPS (n = 35) had experienced neuropathic pain symptoms at the time of this study was 12.22 months (range 3–39 months). The majority of these patients (21 out of 35; 60%) had experienced neuropathic pain symptoms for between 3 and 10 months at the time of this study.

The mean age of patients interviewed (n = 92) was 58.54 years, ranging from 30 to 90 years (SD 14.22). Table 2 shows the age-group distribution of patients with PMPS. The majority of patients with PMPS (n = 20, 57.14%) were in the 41– to 60-year age group.

Further analysis of the data was carried out to test for the association between pain experienced and the age of patients. Patients with pain were slightly younger at 57.17 years (n = 35; SD 14.42) than those without pain at 59.38 years (n = 57; SD 14.16). The mean difference between the ages of the two groups was 2.21 years with a 95% CI of –3.87 to 8.30. Statistically there was no significant relationship between age and PMPS (t = 0.72; degrees of freedom = 90; p = 0.47).

Table 3 indicates that 52 of the 92 patients interviewed (56.52%) received adjuvant cancer therapy as part of their treatment

Table 2: Age distribution of patients with PMPS

Age group	Frequency	%	Cumulative
< 41 (young)	3	8.57	8.57
41–60 (middle-aged)	20	57.14	65.71
> 60 (older)	12	34.29	100.00
Total	35	100.00	

Table 3: Adjuvant therapy administered to patients with and without PMPS

	No adjuvant therapy, no. (%)	Chemotherapy, no. (%)	Radiation therapy, no. (%)	Combination chemo-radiation therapy, no. (%)	Total
No PMPS	27 (47.37%)	10 (17.54%)	2 (3.51%)	18 (31.58%)	57
PMPS	13 (37.14%)	9 (25.71%)	1 (2.90%)	12 (34.29%)	35
Total	40	19	3	30	92

regime. Of the 52 patients, 3 (3.26%) received radiotherapy, 19 patients (20.65%) received chemotherapy, and 30 patients (32.61%) received combination chemo-radiation therapy. Further analysis of the data was carried out to test for associations between pain experienced and adjuvant cancer therapy administered. No statistically significant associations existed between pain experienced and chemotherapy administered (p = 0.31; 0.05% level of significance), radiation therapy administered (p = 0.84; 0.05% level of significance) and combination chemo-radiation therapy administered (p = 0.79; 0.05% level of significance).

The probability of having pain following adjuvant cancer therapy was 42.31% (22 patients of 52). The probability of having no pain following adjuvant cancer therapy was 57.69% (30 patients of 52). The odds of having pain if adjuvant cancer therapy was received were calculated as 0.73. Similarly, the odds of having pain if no adjuvant cancer therapy was received were calculated as 0.48. 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 cancer 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 CHBAH breast surgery follow-up clinic were prescribed simple and combination analgesic medications for their chronic pain. These included: paracetamol, paracetamol/codeine combination, and non-steroidal anti-inflammatory drugs (e.g. ibuprofen, naproxen, indomethacin).

Discussion

The prevalence of PMPS among African patients in this study was found to be 38.04%. This is similar to results obtained in other studies.[5, 6, 8, 12–14] 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.[4]

It is essential to consider why the prevalence of PMPS is still regarded as being relatively infrequent, even though several studies, including this study, have shown that PMPS is a common occurrence. This may be due to the occurrence of PMPS in the context of a potentially life-threatening condition where it is perceived as relatively less important. Also, medical professionals may not specifically ask about PMPS or disregard the symptoms as innocent.[5]

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%) experienced symptoms for between 3 and 10 months post-treatment at the time of this study. Additionally, there was a wide variability in the duration of time since surgery within the total sample interviewed. This ranged from 3 to 96 months. The majority of patients (71.74%) were between 3 and 20 months post-surgery. Similarly, in the international literature, the mean time from surgery to questionnaire varied from 18 months to 9 years with the prevalence of PMPS ranging from 24% to 52% in these studies.[6,8,12,13] There is some evidence that the prevalence of chronic pain and its intensity diminish over time. This may be due to women developing adaptation mechanisms to learn to cope with their chronic pain.[4]

The mean age of patients interviewed in this study (58.54 years) was comparable with the mean age of study populations in other studies.[5,13] Of interest is the finding that the majority of patients with PMPS (n = 20, 57.14%) were middle-aged (41- to 60-year age group) compared with 34.29% (n = 12) in older patients (61- to 90-year age group), and 8.57% (n = 3) in young patients (20- to 40-year age group). However, this study failed to show any statistically significant relationship between age and PMPS (p = 0.47). Several other studies have identified younger age as a significant risk factor for PMPS.[5,6,8,12] 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.[5] However, Carpenter et al.[13] did not find any association between age and pain after breast surgery.

Adjuvant cancer therapy has been found to be associated with PMPS in various studies. Gartner et al.[8] 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 with pain.

Cairns et al.[5] stated that patients reporting PMPS were more likely to have received preoperative chemotherapy and postoperative radiotherapy and tamoxifen; however, there were no clear associations observed between pain and adjuvant therapy. Carpenter et al.[13] found a high prevalence of PMPS (33%) among women who underwent lumpectomy with combination chemo-radiation therapy.

In this study, no statistically significant association existed between pain and chemotherapy (p = 0.31), pain and radiotherapy (p = 0.84), and pain and combination chemo-radiation therapy (p = 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.[4]

The prescribed pharmacological treatment for chronic neuropathic pain experienced by breast cancer survivors in this study included simple and combination analgesic medication. Chronic neuropathic pain may not respond adequately to simple/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. Additionally, the lack of a quick and valid screening tool at the CHBAH 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.[10] Referral to an appropriate pain clinic for suitable evaluation of these patients is therefore an important consideration.

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 other post-breast cancer surgery populations.

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 the drawing of conclusions regarding causality, but merely describes factors associated with PMPS occurrence.

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 features of neuropathic pain that are not assessed by the DN4 Questionnaire include pain evoked by mild pressure, heat or cold, changes in weather, ongoing pain, response to blunt pressure and vibration, and skin changes.[16]

Other factors that 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.

In conclusion, PMPS is a frequent and important problem that is often underestimated in the African population. It has the potential to affect various aspects of patients' lives and poses a considerable economic and healthcare 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. This includes 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.[10,17] Additionally, regional analgesia may decrease the risk of recurrence or metastases after surgery for breast cancer.[17] 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.

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