DOI: https://doi.org/10.47391/JPMA.946

Persistent post-surgical pain following breast cancer surgery: an observational study in a tertiary care hospital

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Abstract

Objectives: To determine the frequency of persistent pain in patients after breast cancer surgery, and to assess the distribution and characteristics of pain in such patients.

Method: The prospective observational single cohort study was conducted at the Department of Anaesthesiology and in the Breast Clinic of the Department of Surgery, Aga Khan University Hospital, Karachi, from August 2016 to January 2017, and comprised adult female patients with biopsy-proven carcinoma of breast who were scheduled for elective definitive breast cancer surgery. The patients were followed up for up to three months post-surgery and those with persistent pain were followed up for six months post-operation. Data was analysed using SPSS 19.

Results: Of the 120 patients, 26(21.7%) developed persistent post-surgical pain for up to three months, while in 17(14.2%) patients, the pain continued for up to six months after the operation. Among those with persistent post-surgical pain, 11(42.3%) had burning pain, 10(38.5%) had throbbing pain, 3(11.5%) had numbness and 2(7.7%)had mixed character of pain. Also, 11(42.3%)patients

developed pain at more than one site including axilla, chest wall, upper arm and surgical scar area, and the site of pain in majority patients 15(57.7%) was axilla.

Conclusion: The incidence of persistent pain following breast cancer surgery was found to be 21.7%.

Key Words: Persistent post-surgical pain, PPSP, Breast cancer surgery, Mastectomy, Neuropathic pain.

Introduction

Carcinoma of breast is the most common cancer among women in Pakistan.[1] In Asia, Pakistan has the highest rate of breast cancer, affecting 1 in every 9 women with an incidence rate of 50/100,000.[1] The affected women are typically young and often present with advanced disease. In cities like Karachi, breast cancer constitutes up to one-third of all malignant tumours in female patients.[2] Majority of the cancer patients undergo breast surgery, chemotherapy and radiotherapy for cancer management. Acute postoperative pain and persistent pain are issues of significant concerns following breast cancer treatment. Incidence of persistent post-surgical pain (PPSP) in patients after breast cancer surgery is 25-60%.[3,4] Persistent pain can be severe in about 2-10% of these patients.[5]

Among breast cancer patients, PPSP is rated as the most troubling aspect leading to disability and psychological distress, and it is often resistant to management.[6,7] Incidence of PPSP in Pakistani patients is currently not known. PPSP is a type of chronic neuropathic pain disorder that can occur following breast cancer surgeries, particularly those operations that remove tissue from the upper outer quadrant of the breast and / or axilla due to association with nerve fibre injury.[8,9] There is no exact definition of PPSP, but Macrae described three important criteria for labelling a patient as having PPSP: pain that develops after surgery; pain of at least two-month duration; and no other causes of pain.[10,11] Most authors consider persistent pain for a duration of 3 - 6 months as PPSP.[5]

PPSP after breast surgeries is typically localised to the anterior and / or lateral chest wall, axilla, medial side of upper arm and is said to occur when all other causes of pain, such as infection or recurrence, have been eliminated. The characteristics include classic features of neuropathic pain, such as burning, tingling, shooting, stinging, stabbing pains and hyperesthesia.[7,12] Phantom breast pain (PBP) is another painful condition related to the operated site.[13] It is disturbing and is characterised by painful sensations in the region of the nipple alone or involving the entire area of the breast or the segment that has been resected.[14]

The current study was planned to determine the frequency of persistent pain in patients after breast cancer surgery, and to assess the distribution and characteristics of pain in such patients.

Patients and Methods

The prospective observational single cohort study was conducted at the Department of Anaesthesiology and in the Breast Clinic of the Department of Surgery, Aga Khan University Hospital, Karachi, from August 2016 to January 2017. After approval from the departmental and institutional ethics review committees, the sample was raised approaching all adult female patients with biopsy-proven carcinoma of breast who were scheduled for elective definitive breast cancer surgery, both mastectomy and conservation.

The patients were enrolled once the operative procedure was finalised and consent for enrolment was taken in the Breast Clinic prior to the surgery. Those who did not give consent and patients who required re-operation on the same side for recurrence of cancer or for any other reason were excluded.

Data regarding patients' age, weight, height, chemotherapy and / or radiotherapy received or not, number of drains placed, any wound complication, type of breast and axillary surgery was obtained from patient's medical record, interview of patients on follow-up visits and telephonic communication with the patients.

Variables were defined and a special form was designed for data collection. All patients were followed up for three months after surgery and those who had persistent pain were followed up for six months after the operation.

Study forms were filled by one of the reserachers. Severity of pain was determined using numerical rating scale (NRS) from 0 to 10, where 0 = no pain and 10 = worst pain imaginable.[15,16] Score of 1-3 was taken as mild pain, 4-6 as moderate and a 7 and beyond as severe. Patients with persistent pain were asked about the distribution and characteristics of pain on their follow-up visit or on telephonic interview.

Data was analysed using SPSS 19. Frequencies and percentages were computed for qualitative variables, while mean and standard deviation (SD) were used to express quantitative variables. Univariate analysis was performed to assess PPSP in relation to age groups, body mass index (BMI), breast surgery, axillary dissection, chemotherapy, radiotherapy, number of drains placed and wound complications.

Associations between pain and other factors were analysed using chi-square or Fisher's exact test. The level of significance was set $p<0.05$. Multivariate logistic regression models were then used and adjusted odds ratios (AOR) and 95% confidence intervals (CIs) were calculated and the Wald $\chi 2$ test was used to test the overall significance of each parameter.

Results

Of the 120 patients, 63(%) were aged <49 years. The overall mean age was 50.08±12.86 and mean BMI was 28.16±5.25 kg/m^2. Of them, 26(21.7%) patients developed PPSP up to three months and 17(14.2%) had it for up to six months post-operation (Figure).

Significant risk factors were identified at three months (Table 1) and six months (Table 2) postoperatively.

Of the total, 85(71%) patients underwent mastectomy and 35(29%) had breast conservation. Of the 85 mastectomised patients, 23(27%) developed persistent pain, while 3(8.5%) patients who underwent breast conservation surgery developed persistent pain.

Axillary clearance was done in 64(53.3%) patients, while limited axillary dissection, like sentinel lymph node biopsy and axillary sampling, was done in 55(45.8%). One (0.8% patient being stage-IV did not have any axillary procedure. Of the 64 patients in whom axillary clearance was done, 18(28%) developed persistent pain, while 7(12.7%) patients developed persistent pain from among those who underwent limited axillary procedure.

Of the 26(21.7%) patients who developed PPSDP, 11(42.3%) had burning pain, 10(38.5%) had throbbing pain, 3(11.5%) had numbness and 2(7.7%) had mixed character of pain. Also, 21(81%) of these patients had mild pain, 3(11.3%) had moderate pain and 2(7.7%)had severe pain at 3 months. Overall, 5(4.16%) patients had PBP and complained of pain in the region of the operated breast and nipple. Further, 11(42.3%) of these patients developed pain at more than one site including axilla, chest wall, upper arm and surgical scar area, and the majority of these patients 15(57.7%) had pain in axilla.

Overall, 80(66.7%) patients required radiotherapy postoperatively, and, of them, 17(21.25%) developed PPSP. Of the 26 patients who developed PPSP at 3 months, 17(65.4%) had radiotherapy postoperatively. Also, 7(6%) patients who did not complain of post-surgical pain, later developed mild burning and throbbing pain due to radiation therapy over chest wall and axillary areas.

Out of the 26 patients who developed PPSP, 21(80.8%) developed mild pain that was managed with simple analgesics, such as paracetamol and short course of non-stroidal anti-inflammatory drugs (NSAIDS). Besides, 3(11.5%) patients developed moderate pain and 2(7.7%) developed severe pain. These patients were managed with multi-modal analgesics, including opioids.

Discussion

To the best of our knowledge, the current study is the first to have been conducted on this topic in Pakistan, while PPSP following different surgical procedures has received increasing recognition over the last decade.[12,17,18] It is a substantial problem that compromises patients' quality of life.[19]

In the current study, 26(21.7%) patients reported persistent pain three months after surgery and 17(14%) of them had persistent pain six months after surgery. Prevalence of PPSP after breast cancer surgeries has been variably reported from other parts of the world ranging between 25% and 60%.[3,19] Juhl et al. found the prevalence to be 38.3% after a median follow-up of three years in Denmark.[20]

Age <50 years was found to be an independent risk factor for PPSP at three-month follow-up and had borderline significance at six months after surgery in the current study. Stdues have also identified young age to be an important risk factor for persistent pain after mastectomy.[12,19,2122,23] The reasons suggested for young age to be a risk factor include advanced disease at presentation, larger tumour size, more extensive dissection, higher histological grade, age-related alterations in pain perception and different psychological thresholds.[24,25,26] However, a study did not find these factors to be associated with persistent pain and stated that other factors may account for increased prevalence of persistent pain in young patients.[12]

Patients who underwent mastectomy were found to have a greater prevalence of persistent pain at three and six months postoperatively on univariate analysis compared to those having breast conservation procedures. However, this was not consistent on multivariate analysis. Therefore, this is either not an independent risk factor or the sample size of the current study was not large enough to capture it as an independent risk factor. Gartner et al. did not find mastectomy to be significantly associated with pain compared to breast conservation surgery, but patients having had mastectomy had higher pain scores compared to those having breast conservation procedures.[8] Mejdahl et al., however, reported a higher

prevalence of persistent pain in patients with breast conservation rather than mastectomy.[19] Anderson et al. found mastectomy to be a weak but significant predictor for PPSP but non-significant after adjusting for lymphedema.[21]

Axillary clearance was found to be significantly associated with PPSP compared to limited axillary intervention (sentinel biopsy / sampling) on univariate but not on multivariate analysis. Axillary clearance was found to be associated with an increased risk of PPSP by several studies.[12,20,27] Primary reason considered responsible for this is injury to inter-costobrachial nerve during dissection which occurs in 80-100% cases of axillary clearance, but sufficient data to prove this is still lacking.[27,28] Anderson et al. reported that preservation of inter-costobrachial nerve as a significant predictor for higher levels of pain following axillary clearance. This may be due to unidentified damage or pulling of the nerve caused during dissection.[21]

Prevalence of PPSP after breast cancer surgery in Pakistan has not previously been assessed, although breast cancer is the most common malignancy among women in this country. It was found to be lower in our population, and the effects of socio-cultural and ethnic factors on pain and its expression could be one reason for this difference.[29] Research has shown that cross-cultural differences are evident in many aspects of human behaviour and perception, including the perception of chronic pain.[30]

The current study has its limitations, as it was a single-centre study with a relatively small sample size and with a limited follow-up of 6 months. There was some delay in reporting results of the study as the researchers involved happened to be busy clinicians.

Multi-centre studies with larger sample sizes are required to assess the prevalence and would further enhance our understanding on the reasons behind this difference in prevalence of PPSP in Pakistan. Preventive measures along with better pain control strategies need to be identified in order to reduce the incidence of persistent pain after breast cancer surgeries.

Conclusion

Persistent pain following breast cancer surgeries was found to be 21.7%. Young age, mastectomy and axillary clearance were identified as significant risk factors. Those who developed persistent pain reported having burning and throbbing pain as well as numbness.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

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Table 1: Multivariate logistic regression analysis for possible risk factors to predict persistent post-surgical pain at three months

Variables	Total n=120	PPSP (n=26)	UOR [95%CI]	P-Value	AOR [95%CI]	P-Value
Age (Years)						
≤ 49	**63**	18(28.6%)	5.60[1.21 - 5.99]	0.028†	10.92[1.29 – 92.0]	0.028†
50 to 59	**27**	6(22.2%)	4.0[0.73 - 21.84]	0.109	8.12[0.87 – 75.41]	0.066
≥60	**30**	2(6.7%)	Ref		Ref	
BMI (kg/m^2)						
Normal	**33**	07(21.2%)	1.10[0.38 - 3.23]	0.856		
Overweight	**48**	11(22.9%)	0.96[0.31 - 2.99]	0.974	-	-
Obesity	**39**	8(20.5%)	Ref			
Breast						
Mastectomy	**85**	23(27.1)	3.97[1.11 - 4.18]	0.035†	2.20[0.33 – 14.85]	0.418
Conservation	**35**	3(8.6%)	Ref		Ref	
Axilla (n=119) *						
Clearance	**64**	18(28.1%)	2.68[1.02 - 7.02]	0.040†	0.937[0.18 - 4.72]	0.937
Sampling	**55**	7(12.7%)	Ref		Ref	
Chemotherapy						
With	**102**	25(24.5%)	5.52[0.69 - 43.59]	0.105	2.99[0.25 –34.77]	0.382
Without	**18**	1(5.6%)	Ref		Ref	
Radiotherapy						
Yes	**80**	17(21.3%)	0.93[0.37 - 2.32]	0.875	0.746[0.22 – 2.49]	0.635
No	**40**	9(22.5%)	Ref		Ref	
Number of drains placed						
None / One	**38**	3(7.9%)	Ref		Ref	

Two / Three	**82**	23(28%)	4.55[1.27 - 16.25]	0.02†	3.22[0.60 – 17.15]	0.171
Wound complication						
Yes	**16**	4(25%)	1.24[0.36 - 4.23]	0.728	-	-
No	**104**	22(21.2%)	Ref			
History of operation on same breast						
Yes	**15**	3(20%)	0.89[0.23 - 3.42]	0.867	-	-
No	**105**	23(21.9%)	Ref			

PPSP: Persistent post-surgical pain**, UOR:** Unadjusted Odd Ratio, AOR: Adjusted Odd Ratio, Ref: Reference. CI: Confidence interval.

Table 2: Multivariate logistic regression analysis for possible risk factors to predict persistent post-surgical pain at six months

Variables	Total n=120	PPSP (n=17)	UOR [95%CI]	P-Value	AOR [95%CI]	P-Value
Age (Years)						
≤ 49	**63**	13(20.6%)	3.64[0.76 – 17.30]	0.104	8.29[0.98-69.94]	0.052
50 to 59	**27**	02(7.4%)	1.12[0.15-8.55]	0.913	2.38[0.19-28.76]	0.493
≥60	**30**	02(6.7%)	Ref		Ref	
BMI (kg/m^2)						
Normal	**33**	4(12.1%)	1.21[0.28-5.25]	0.488		
Overweight	**48**	9(18.8%)	0.27[0.57-7.14]			
Obesity	**39**	4(10.3%)	Ref			
Breast						
Mastectomy	**85**	16(18.8%)	7.89[1.00-61.96]	0.023	3.53[0.22-55.74]	0.371
Conservation	**35**	1(2.9%)	Ref		Ref	
Axilla (n=119) *		n=16				
Clearance	**64**	13(20.3%)	4.42[1.19-16.43]	0.018	1.45[0.226-9.304]	0.693
Sampling	**55**	3(5.5%)	Ref		Ref	
Chemotherapy						
With	**102**	17(16.7%)	NA	0.072	-	
Without	**18**	0(0%)				
Radiotherapy						
Yes	**80**	12(15%)	1.23[0.40-3.78]	0.711	1.02[0.25-4.11]	0.983
No	**40**	5(12.5%)	Ref		Ref	
Number of drains placed						
None / One	**38**	1(2.6%)	Ref		Ref	
Two / Three	**82**	16(19.5%)	8.97[1.14-70.36]	0.014	3.39[0.26-42.87]	0.344
Wound complication						
Yes	**16**	3(18.8%)	1.48[0.37-5.87]	0.572	-	
No	**104**	14(13.5%)	Ref			
History of operation on same breast						
Yes	**15**	2(13.3%)	0.92[0.18-4.51]	0.921	-	
No	**105**	15(14.3%)	Ref			

PPSP: Persistent post-surgical pain**, UOR:** Unadjusted Odd Ratio, AOR: Adjusted Odd Ratio, Ref: Reference. CI: Confidence interval. BMI: Body mass index.

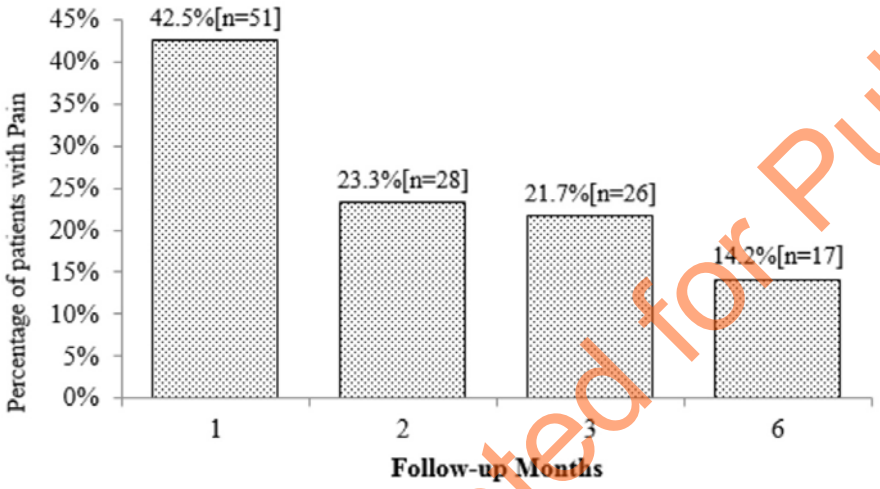

Figure: Patients having persistent pain with respect to follow-up (n=120)