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Original Article

Postmastectomy Pain Syndrome: A Retrospective Cohort Study About the Relationship of Histopathological Type and Comorbidities

Aslınur Sagün,[1] Şebnem Rumeli Atıcı,[1] Güldane Karabakan,[2] Ahmet Dağ,[3] Mustafa Azizoğlu[1]

[1]Department of Anestesiology and Reanimation, Mersin University Faculty of Medicine, Mersin, Turkey
[2]Department of Anesthesiology and Reanimation, Algology Clinics, Mersin City Training and Research Hospital, Mersin, Turkey
[3]Department of General Surgery, Mersin University Faculty of Medicine, Mersin, Turkey

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Correspondence: Aslınur Sagün, Mersin Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, Mersin, Turkey
E-mail: aslinur_aslan@hotmail.com

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ABSTRACT

Objective: Although many risk factors that cause postmastectomy pain syndrome (PMPS) have been searched, in literature, no study was found on the pathological type and the presence of additional diseases. Its aimed to evaluate the frequency of PMPS and probability of being a risk factor of pathological type and the presence of additional diseases in whom underwent mastectomy for breast cancer.

Methods: The data of 392 patients who underwent mastectomy for breast cancer between the years 2008 and 2016 were analyzed retrospectively. Demographic data, surgery type, radiotherapy, chemotherapy, presence of additional diseases, the pathologic diagnosis of the tumor, axillary dissection, number of total and metastatic lymph nodes, application status of the patients to Algology Clinic, VAS, Gabapentin, and/or Pregabalin usage were investigated. Gabapentin and/or Pregabalin usage was accepted as the presence of PMPS.

Results: In our study, PMPS incidence was 24.4%. Statistically significant difference was detected between older age (>50; 72.6%) and hypertension (33.3%) with PMPS. The type of surgery, axillary dissection, number of total and metastatic lymph nodes, radiotherapy, chemotherapy, and the pathological diagnosis of tumor were not determined as risk factors.

Conclusion: Our determination of hypertension as a risk factor for PMPS with advanced age suggests that there is a need for prospective studies that address advanced age and hypertension. In addition, due to the retrospective study feature, an equal number of subgroups could not be made for all pathological types. Therefore, we think that this relationship can be revealed more clearly with prospective studies in which every pathological diagnosis is grouped equally.

INTRODUCTION

Breast cancer accounts for 23% of all cancer cases worldwide.[1] The incidence of breast cancer in last 25 years increased from 24% up to 40–50% in Turkey.[2] Chronic pain after surgical treatment of breast cancer was defined as postmastectomy pain syndrome (PMPS) by the International Pain Study Group.[3]

The pathogenesis of PMPS is not clearly explained, but the most probable mechanisms; thought to be intercostobrachial nerve damage during the surgery, paraneoplastic syndrome, complex regional pain syndrome, chemotherapy-induced neuropathy or radiation plexopathy, and lymphedema. In a recent study, the prevalence of neuropathic pain after breast surgery is reported as between 20% and 50%.[4]

Although many risk factors for the development of PMPS have been investigated, the most frequently studied factors are age, presence of pre-operative pain, type of surgery, presence of axillary dissection, post-operative chemotherapy, and/or radiotherapy.[5] In the literature, there is no study related to the pathological type of the tumor and the presence of some additional diseases as a risk factor. The objective of this study to assess the relationship between histopathological type of the tumor and presence of additional disease with PMPS, in addition to the frequently discussed risk factors in patients undergoing mastectomy for breast cancer.

MATERIALS AND METHODS

This study obtains approval from Mersin University, Clinical Studies Ethical Committee under number E803819 (date: 26.07.2018). In this retrospective study, data of 405 patients who underwent surgery for breast cancer between 2008 and 2016 were collected from Hospital Information Management System. Furthermore, the patients' follow-up forms by Department of Algology were evaluated.

The inclusion criterions are: Aged >18 years, operated for breast cancer in Mersin University Hospital between 2008 and 2016. Patients who were operated at a different center and out of the specified dates, breast surgery was performed for a reason other than breast cancer, and patients aged <18 years were excluded from the study.

A form was prepared for the study. Demographic data, type of surgery, radiotherapy, chemotherapy, additional diseases, histopathological type of tumor, axillary dissection, number of total and metastatic lymph nodes, usage of gabapentin and/or pregabalin, and value of VAS were recorded by the form.

The usage of gabapentin and/or pregabalin was based on the diagnosis of PMPS in patients.

Statistical analysis

For statistical evaluation, data were entered into the "Statistical Package for the Social Sciences version 24 program (SPSS v.24)" and "e-PICOS" program was used in calculations based on "Medicres Good Biostatistics Practices." Descriptive statistics were used for categorical variables and frequency calculations were expressed in percent. "Chi-square" test was applied for cross comparison tables and $p<0.05$ value was considered statistically significant.

RESULTS

Data of 405 patients were collected for the study. Seven of these patients were excluded because of reregistration. At the end totally, 392 patients were included in the study.

A total of 95 (24.4%) patients using pregabalin and/or gabapentin were detected (Table 1), two patients were using two drugs at the same time.

The average age of the patients included in the study was 56.5±13.2 years (lowest; 21, highest; 94), while the average age of patients with PMPS was 58.6±12.7 ($p>0.05$). However, when 50 years was used as the cutoff value for age, patients evaluated as PMPS at the age of >50 years were more frequent (n=69; 72.6%) ($p=0.048$).

Table 1. Distribution of patients by type of drug

Use of drug status	Number of patients	Percent
Drug users (Total)	95	24.4
Pregabalin	76	19.4
Gabapentin	21	5.4

When the presence of PMPS was compared with the type of surgery, the relationship between them was not found statistically significant (Table 2) ($p>0.05$).

Radiotherapy was taken by 122 patients (31.1%) totally and 35 (36.8%) of 95 patients with PMPS. The number of patients taking chemotherapy was 331 (84.4%). Chemotherapy (89.5%) was taken by 85 of 95 patients with PMPS. The relationship between both radiotherapy and chemotherapy with PMPS was not statistically significant ($p=0.10$, $p=0.79$, respectively).

From existing diseases only, the relationship between hypertension and PMPS was found to be statistically significant ($p=0.01$) (Table 3).

There was no statistically significant relationship between the histopathological type of the tumor and PMPS ($p=0.574$) (Table 4).

Table 2. The type of surgery in relation to PMPS

Type of surgery	Number of patients		PMPS	
	n	%*	n	%*
Modified radical mastectomy	146	37.2	32	33.7
Breast conserving surgery + Lymph node dissection	125	31.9	31	32.6
Simple mastectomy	121	30.9	32	33.7
Total	392	100	95	100

*Percentages are determined by column values. PMPS: Postmastectomy pain syndrome.

Table 3. Distribution of additional diseases in patients with PMPS

Additional disease	Patients		PMPS	
	n	%	n	%
Diabetes mellitus	45	11.5	15	33.3
Cerebrovascular disease	13	3.3	5	35.5
Hypertension	117	29.8	39	33.3

PMPS: Postmastectomy pain syndrome.

Table 4. Distribution of pathological types in patients with PMPS

Histopathological types	PMPS	
	n	%
Ductal	69	72.6
Apocrine	3	3.1
Lobular	7	7.3
Papillary	14	14.7
Metaplastic	2	2.1
Total	95	100

PMPS: Postmastectomy pain syndrome.

Table 5. The relationship between the presence of ALND and PMPS

ALND	Total (n)	PMPS (n)
Yes	209	53
No	183	42
Total	392	95

ALND: Axillary lymph node dissection; PMPS: Postmastectomy pain syndrome.

Table 6. Distribution of the total number of lymph nodes in patients with PMPS

PMPS (n)	Total lymph node		Total
	≤15	>15	
Yes	31	22	53
No	78	78	156
Total	109	100	209

PMPS: Postmastectomy pain syndrome.

The relationship between Axillary Lymph Node Dissection (ALND) and PMPS is shown in Table 5; there was no statistically significant relationship ($p>0.05$).

The average number of lymph nodes removed in patients who underwent ALND and accepted as PMPS (n=53) was 14.8±7.6, and the average number of lymph nodes was 16.5±8.8 in non-PMPS patients (n=156). There was no statistically significant relationship between the number of lymph nodes removed and the frequency of PMPS ($p>0.05$) (Table 6).

In addition, 21 of 80 patients (26.3%) with metastatic lymph nodes reported as PMPS. There was no statistically significant difference between PMPS development and presence of metastatic lymph node ($p>0.05$).

Of the 392 patients included in the study, 65 (43.9%) applied to the Department of Algology, and 57 (87.6%) of the applicants had values >4 cm on a 10 cm visual analog scale (VAS).

DISCUSSION

In this retrospective study, PMPS incidence was 24.4%. Unlike other studies in the literature, the histopathological type of the tumor was assessed, but no difference was found. Significant results were found between the presence of hypertension and advanced age with the development of PMPS.

Different age groups have been studied in several studies. In one study, PMPS development was found to be significantly higher in patients aged under 50 years,[6] while in another study, the frequency of PMPS in those with <40 was reported to be 1.67 times higher.[7] The reason for younger age predicting PMPS is that breast cancer is more aggressive at this age and causes worse symptoms.[6–9] However, in our study, the incidence of PMPS was found to be 72.6% in patients over 50 years of age. We think that analyzing the groups formed with standardized age ranges in the new studies to be planned may yield more obvious results in defining the age risk.

The type of surgery for the development of PMPS is often compared in the literature. In a study, it was reported that the incidence of pain was less after "breast-conserving surgery."[10] However, in a meta-analysis published by Wang et al.,[11] the data of 8566 patients were examined and no statistically significant relationship was found between the type of surgery (breast conserving surgery, mastectomy, and modified radical mastectomy) and PMPS. In a review by Andersen et al.,[5] they reported that the number of studies resulted in there is no difference between surgery types and PMPS is more than others. In our study, there was no statistically significant relationship between PMPS in comparison to the types of surgery.

Axillary dissection was also investigated as a risk factor for PMPS development. It has been emphasized in different studies[5,10,12] that ALND is associated with increased frequency of neuropathic pain. In contrast, it was showed that ALND is not a risk factor for postmastectomy chronic pain in another study.[4] In our study, it was found that the performing ALND is not a risk factor for PMPS development.

The number of studies investigating the relationship between the total number of surgically excised lymph nodes and PMPS is very low. In a study about the risk factors of PMPS, 174 patients were included, and classified number of excised lymph nodes as >15 and <15, it was reported that the incidence of PMPS was 2 times higher in the group >15.[7] Although we classified the total number of excised lymph nodes <15 and >15 in our study, it was not found to be a risk factor for PMPS. No study related to the number of metastatic lymph nodes has been found in the literature. In our study, it was found that the number of metastatic lymph nodes is not a risk factor for PMPS.

There are conflicting publications about whether radiation therapy that can be a risk factor for PMPS.[7,13] Increased tissue fibrosis, neural entrapment, and disruption of glenohumeral movement are some of the possibilities related to the mechanism as a risk factor. In a review published in 2016,[13] the increment of the incidence of PMPS in patients receiving radiotherapy after breast cancer surgery was shown with a high level of evidence. In another study, no significant relationship was found between radiotherapy and PMPS.[7] In our study, statistically significant relationship was not detected in terms of the development of PMPS in patients with and without radiotherapy.

Chemotherapy is a common approach after breast cancer surgery and its effect on survival is important. Many studies about risk factors for PMPS have also evaluated the effect of chemotherapy, but the results are contradictory. In some studies, chemotherapy has been evaluated as a risk factor for the development of PMPS,[4,14] while fewer

studies have not been considered it as a risk factor.[10] In our study, 331 of 392 patients took chemotherapy, but there was no statistically significant relationship between chemotherapy and PMPS development.

In the literature, the presence of additional disease has been questioned but no risk analysis related to PMPS has been found. In our study, a statistically significant relationship was found between hypertension and PMPS. We think that the increase in the frequency of neuropathic pain in the presence of hypertension may be due to impaired nutrition in atherosclerotic tissues. Considering the high PMPS risk of patients over 50 year old in our findings, the relationship between age and history of hypertension also makes sense. We believe that this situation can be revealed more clearly with prospective studies examining these two variables.

Any study investigating the relationship between histopathological type and PMPS has been found. It is known that pathological types of breast tumor show different tissue invasion characteristics.[15,16] It is stated that metaplastic cancers are more aggressive compared to other types. In our study, considering that this situation may be related to pain, risk analysis was performed and no difference was found. However, since the number of patients with the most invasive spread metaplastic type was low, the difference could not be revealed.

Perhaps more accurate results can be obtained by questioning the relationship between pathological diagnosis and pain before surgery in new studies to be planned.

Limitations

Since it is a study conducted with retrospective file scanning, not all of the data to be evaluated about patients could be reached. For example, the presence of pain or drug use in the pre-operative period could not be obtained from digital media. And also, exact information on the presence of postoperative acute pain could not be obtained. Failure to obtain these critical data led to inability to explain some findings. The distribution of patients was not similar according to pathological diagnoses. This is questionable in terms of whether it is a risk factor or not.

CONCLUSION

The pathological subtypes of the tumor had not been determined as a risk factor in patients with PMPS; however, age and hypertension were found as risk factors.

As a result, advanced age and hypertension were determined as risk factors. However, pathological diagnosis was not determined as a risk factor. We think that more accurate evaluations can be made by carrying out studies involving a similar number of patients for each pathological diagnosis. In addition, we think that studies evaluating pathological diagnosis and pre-operative pain are another subject that can be investigated in terms of the emergence of PMPS.

Ethics Committee Approval

The study was approved by the Mersin University, Clinical Studies Ethical Committee (date: 26.07.2018, decision no: E803819).

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: Ş.R.A., A.S.; Design: Ş.R.A., A.S., G.K.; Supervision: Ş.R.A., M.A.; Materials: A.D., G.K., Ş.R.A.; Data: A.S., G.K.; Analysis: M.A., Ş.R.A., A.D.; Literature search: Ş.R.A., A.S., G.K.; Writing: A.S., M.A.; Critical revision: Ş.R.A., A.D., G.K., M.A.

Conflict of Interest

None declared.

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Postmastektomi Ağrı Sendromu: Histopatolojik Tip ve Komorbidite ile İlişkisi Hakkında Geriye Dönük Bir Kohort Çalışma

Amaç: Literatürde, postmastektomi ağrı sendromuna (PMPS) yol açan birçok faktör araştırılsa da, tümörün patolojik tipi ve ek hastalık varlığı ile ilişkisi hakkında bir çalışma bulunmamaktadır. Amacımız, meme kanseri nedeniyle mastektomi uygulanmış hastalarda, PMPS sıklığını ve patolojik tip ve ek hastalık varlığının risk faktörü olma olasılığını değerlendirmektir.

Gereç ve Yöntem: Meme kanseri nedeniyle 2008–2016 yılları arasında mastektomi uygulanmış 392 hastanın verileri geriye dönük olarak incelendi. Demografik verileri, cerrahi tipi, radyoterapi, kemoterapi, ek hastalık varlığı, tümörün patolojik tipi, aksiller diseksiyon, toplam ve metastatik lenf nodu sayısı, hastaların algoloji kliniğine başvuru durumu, Vizüel Analog Skala değeri, gabapentin ve/veya pregabalin kullanımı araştırıldı. Gabapentin ve/veya pregabalin kullanımı, PMPS varlığı açısından anlamlı kabul edildi.

Bulgular: Çalışmamızda, PMPS insidansı %24.4 idi. İleri yaş (>50; %72.6) ve hipertansiyon (%33.3) ile PMPS arasında istatistiksel olarak anlamlı ilişki saptandı. Cerrahi tipi, aksiller diseksiyon, total ve metastatik lenf nodu sayısı, radyoterapi, kemoterapi ve tümörün patolojik tanısı risk faktörü olarak değerlendirilmedi.

Sonuç: Hipertansiyonun ileri yaş ile birlikte risk faktörü olması, bu konularla ilgili ileriye yönelik çalışmalara ihtiyaç olduğunu düşündürmektedir. Ayrıca, geriye dönük çalışma olması nedeniyle, tüm patolojik tipler için eşit subgrup sayıları düzenlenememiştir. Sonuç olarak, her patolojik tanının eşit olarak gruplandırılığı ileriye yönelik çalışmalarla bu ilişkinin daha net ortaya çıkarılabileceğini düşünüyoruz.

Anahtar Sözcükler: Hipertansiyon; ileri yaş; meme kanseri; nöropatik ağrı.