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Research Article

The Effect of Surgical Treatment Option on inflammatory Response in Breast Cancers

Meme Kanserlerinde Cerrahi Tedavi Seçeneğinin İnflamatuar Yanıt Üzerine Etkisi

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Abstract

Aim: The aim of the study was to assess effect of different breast surgery techniques on the inflammatory response.

Material and Methods: The study executed between February 2013 and April 2013 in the General Surgery Clinic.The 42 patients aged between 18-70 years, who were diagnosed with breast cancer by tru-cut or incisional biopsy, were evaluated as stage I and II breast cancer according to AJCC criteria and underwent surgical treatment.In this prospectively study, descriptive statistics are given as mean±standard deviation, percentage and frequency.In comparison of groups, Kruskal-wallis test was used in comparison of three groups and Mann-Whitney-U test was used in comparison of two groups. Wilcoxon test was used for in-group comparison. The chi-square test was used to compare the count values between groups.The $p<0.05$ value at the 95% confidence interval was considered statistically significant.In correlation;Pearson correlation and Spearman correlation test were used.

Results: The total number of cases was 42. The mean age of the patients included in the study was 52.54±12.7 years old. Especially in terms of comparison of the preoperative and postoperative inflamatuvar markers;Postoperative IL-6 values were significantly higher than the preoperative IL-6 values in all three groups($p=0.001$), postoperative white blood cell count too was found to be significantly higher in all three groups ($p=0.003$, $p=0.001$, $p=0.001$).Additionally, CRP levels were found to increase significantly in all three groups after surgery compared to preoperatively . While there was no difference between the groups in terms of preoperative CRP levels, CRP levels were found to be higher in the group that underwent lumpectomy and axillary dissection in the postoperative period compared to the other groups ($p=0.004$).

Conclusion: In the surgical methods to be chosen in breast cancer, methods that can keep the inflammatory reactions to a minimum by considering the severity of the trauma and fully meet the oncological principles for the patient should be kept in mind first.

Keywords: breast cancer, surgical treatment , inflammatory response

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Öz

Amaç: Bu çalışmanın amacı, farklı meme cerrahisi tekniklerinin inflamatuar yanıt üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntemler: Çalışma Şubat 2013-Nisan 2013 tarihleri arasında Genel Cerrahi Kliniği'nde gerçekleştirildi. Tru-cut veya insizyonel biyopsi ile meme kanseri tanısı konulan 18-70 yaş arası 42 hasta AJCC kriterlerine göre evre I ve II meme kanseri olarak değerlendirilerek cerrahi tedavi uygulandı. Bu prospektif çalışmada, tanımlayıcı istatistikler ortalama±standart sapma, yüzde ve frekans olarak verilmiştir. Grupların karşılaştırılmasında üç grubun karşılaştırılmasında Kruskal-wallis testi, iki grubun karşılaştırılmasında Mann-Whitney-U testi kullanıldı. Grup içi karşılaştırmada Wilcoxon testi kullanıldı. Gruplar arasındaki sayım değerlerinin karşılaştırılmasında ki-kare testi kullanıldı. %95 güven aralığındaki $p<0,05$ değeri istatistiksel olarak anlamlı kabul edildi. Korelasyonda; Pearson korelasyonu ve Spearman korelasyon testi kullanıldı.

Bulgular: Toplam olgu sayısı 42 idi. Çalışmaya alınan hastaların yaş ortalaması 52,54±12,7 idi. Özellikle preoperatif ve postoperatif inflamatuvar belirteçlerinin karşılaştırılması açısından; Postoperatif IL-6 değerleri her üç grupta da preoperatif IL-6 değerlerinden anlamlı olarak yüksek bulundu($p=0,001$), postoperatif lökosit sayısı da her üç grupta da anlamlı olarak yüksek bulundu ($p=0,003$, $p=0,001$, $p =0.001$).Ayrıca ameliyattan sonra her üç grupta da ameliyat öncesine göre CRP düzeylerinin anlamlı olarak arttığı bulundu. Preoperatif CRP düzeyleri açısından gruplar arasında fark bulunmazken, postoperatif dönemde lumpektomi ve aksiller diseksiyon uygulanan grupta CRP düzeyleri diğer gruplara göre daha yüksek bulundu($p=0,004$).

Sonuç: Meme kanserinde seçilecek cerrahi yöntemlerde öncelikle travmanın şiddeti göz önünde bulundurularak inflamatuar reaksiyonları minimumda tutabilen ve hasta için onkolojik prensipleri tam olarak karşılayan yöntemler akılda tutulmalıdır.

Anahtar Kelimeler: meme kanseri, cerrahi tedavi, inflamatuar yanıt

Introduction

In recent years, it has been observed that there is a general trend towards less invasive approaches in the surgical treatment of cancer. For example, laparoscopic and endoscopic treatment methods are increasingly used in abdominal cancer surgery (1). Similarly, recently, the surgical treatment of breast cancer has evolved from mastectomy to breast-conserving surgery, from axilla dissection to sentinel lymph node biopsy (2). Surgical treatment of breast cancer is managed without compromising oncological principles and clinical results, but also considering cosmetic concerns, and more limited, less morbid surgical procedures are preferred. These treatments, referred to as "minimally invasive breast surgery" or "oncoplastic breast surgery", have become very popular among breast surgeons (surgical treatment of breast cancer) in recent years (3). While minimally invasive breast surgery originally referred to breast-conserving surgery and sentinel lymph node biopsy, it has recently been used to describe endoscopic breast and axillary surgery.The main point here is; It is to improve cosmetic results by using smaller incisions (4,5). In addition, for another purpose, more minimal surgery means less tissue trauma and less inflammatory response. As is known, surgical procedures are an important cause of trauma to the body. Tissue damage caused by surgery, anesthetic and analgesic drugs, hypothermia, blood loss, transfusion, pain and perioperative stress trigger hormonal and inflammatory response and cause immunosuppression (6). Postoperative immunosuppression is a well-known complication and has been extensively studied. Postoperative period especially for major surgery, there is a prominent augment in plasma concentrations of acute inflammatory cytokines (Interleukin; IL-6 and IL-8), prostaglandins (PGE2), stress hormones (such as catecholamines and corticosteroids) whereas on the other hand in cytotoxic and helper T lymphocyte functions decrease (7). These changes form the basis of the profound suppression of post-surgical cellular immunity, especially natural killer cell cytotoxicity (7,8). Immunosuppression develops hours after surgery, lasts for a few days, and increases in direct proportion to the magnitude of surgical trauma (9,10). There is a direct relationship between the extent of surgical trauma and the amount of cytokines that enter the systemic circulation (11). It is therefore natural that different surgical techniques, which cause different amounts of tissue damage, cause different degrees of trauma response. This situation has been clearly demonstrated in the literature in studies comparing laparoscopic and open cholecystectomy; It was found that laparoscopic cholecystectomy caused less elevation of IL-6 and CRP levels compared to open cholecystectomy (12), and peripheral leukocyte functions were better preserved (13).

Smaller incisions and less tissue trauma minimize surgical stress and reduce morbidity (13,14). It has been shown that changes in surgical procedures increase or decrease the probability of tumor recurrence by causing more or less immunosuppression (6). For instance, minimally invasive surgeries such as laparoscopy are known to be less immunosuppressive than standard procedures such as laparotomy. It is not clear whether a similar effect also applies to surgical treatment techniques for breast cancer. In a recent study, although surgical treatment of breast cancer was considered as a minor surgery, it was shown that it significantly affected the immune system by decreasing natural killer cell activity and HLA-DR expression, and increasing the proinflammatory response (15). In another study, it was shown that decreased perioperative natural killer activity and increased inflammatory cytokines increase cancer-related morbidity and mortality in patients with breast cancer (16). But furthermore, the differences between different surgical techniques used in the treatment of breast cancer are unknown. Therefore, the aim of the study was to assess effect of different breast surgery techniques on the inflammatory response.

Material and Methods

The study included 42 patients aged 18-70 years, who were diagnosed with breast cancer by tru-cut or incisional biopsy in the General Surgery Clinic of Ankara Oncology Hospital. The patients were recruited between February 2013 and April 2013. The evaluation were done to the patients who as stage I and II breast cancer according to AJCC criteria underwent surgical treatment. The patients were divided into 3 groups according to the surgical treatment to be applied. The study coordinator did not interfere with the surgical treatment decision, the surgical treatment decision to be applied was determined by the physician conducting the patient's treatment.In terms of exclusion criterias; The patients who over 70 years of age, concomitant systemic disease, autoimmune disorders, infection, bilateral breast cancer, concurrent or a history of other malignant diseases, receiving immunostimulant or immunosuppressive therapy for any reason, or using nonsteroidal anti-inflammatory drugs patients were excluded. The first group includes patients who underwent breast-conserving surgery and sentinel lymph node biopsy, the second group included patients who underwent axillary dissection in addition to breast-conserving surgery, and the third group included patients who underwent modified radical mastectomy. Blood sample was drawn from the patients in each group on the day before the operation and at the 24th hour after the operation, after they were allowed to rest in the supine position for 15 minutes.The serum samples obtained were kept at -20 degrees until the measurement time. IL-6 levels in the samples were evaluated with the commercially available ELISA (enzyme-linked immunosorbent assay) human IL-6 kit (Biosource, California, USA). Test samples of serum IL-6, whose standard curve showed linearity between 0-300 pg/mL, were diluted before measurement.C-reactive protein levels were determined quantitatively by turbudimetric method in a fully automatic device (Rosch Diagnostic Noduler P, Germany). Serum leukocyte count was done with laser method and automatic device (Siemens Diagnostics, Bayer Adria 2120, Germany). The results of the measurements were calculated automatically by the device. The expected leukocyte value in healthy subjects was accepted as between 4000-10000/mm3.

Statistical analysis

Statistical analyzes were performed using the SPSS 15.0 computer package program (SSPS Inc., Chicago, USA) to evaluate the findings obtained in the study. Frequency and percentage distribution were used for descriptive analyses, and the averages were given as mean-standard deviation. The Mann-Whitney-U test was used for two-group comparisons of continuous variables, and the Kruskal Wallis test for three-group comparisons. Subgroup comparisons were made with the Wilcoxon test. Chi-square test was used to compare categorical data. A p value of <0.05 was considered statistically significant in the analyses.

Results

Some clinicopathological demographic distinctives of the patients included in the study are summarized in Table 1. Among the working groups; No statistically significant difference was found in terms of age (p=0.73), pathological tumor diameter (p=0.08), estrogen receptor (p=0.82), progesterone receptor (p=0.88) and HER-2 status (p=0.14). There was no difference between groups 2 and 3 in terms of the number of lymph nodes removed, axillary involvement and the number of metastatic lymph nodes. On the other hand; In group 1 (patients who underwent sentinel lymph node biopsy), the total number of lymph nodes removed (p=0.001), axillary involvement (p=0.001) and the number of metastatic lymph nodes (p=0.002) were significantly less than the other two groups. Similarly, lymphovascular invasion (p=0.02) and extracapsular invasion rate (p=0.04) were significantly lower in patients in this group than in other

groups (group 2-3). In terms of mean white blood cell counts, there was no significant difference among these three groups in both preoperative and postoperative periods (Figure 1). When the mean preoperative and postoperative mean white blood cell counts were compared; Postoperative white blood cell count was found to be significantly higher in all three groups (p=0.003, p=0.001, p=0.001).

Preoperative and postoperative mean IL-6 values of the groups are shown in Figure 1. When the preoperative and postoperative mean IL-6 values of the patients in the groups were compared, it was found that the postoperative IL-6 values were significantly higher than the preoperative IL-6 values in all three groups (p=0.001). However, when the groups were compared in terms of both preoperative and postoperative IL-6 values, no statistically significant difference was found among the groups (p=0.21, p=0.33).In terms of the preoperative leukocyte levels of the three groups were compared, there was not statistically significancy among the groups. Additionally, for the postoperative leukocyte levels for these three groups were compared, again there wasn't any statistically significancy among the groups (Figure 2). Like other inflammation parameters, CRP levels were found to increase significantly in all three groups after surgery compared to preoperatively (Figure 3). While there was no difference between the groups in terms of preoperative CRP levels, CRP levels were found to be higher in the group that underwent lumpectomy and axillary dissection in the postoperative period compared to the other groups (p=0.004). The mean age of the patients included in the study was 52.54±12.7 in Group 1, 54.15±13.1 in Group 2 and 53.25±11.8 in Group 3. There was no statistically significant difference between the groups in terms of age. There is a statistically significant difference between preoperative IL-6 and postoperative IL-6 values in group 1, group 2 and group 3. Postoperative IL-6 values were higher in all three groups.When the preoperative IL-6 values of the three groups were compared; There was a statistically significant difference between the groups. This difference is due to group 2 with a higher preoperative IL-6 value (Mann-Whitney-U test). When the postoperative IL-6 values of the three groups were compared, no statistically significant difference was found between the groups. There was a statistically significant difference between preoperative and postoperative leukocyte values in group 1, group 2 and group 3. Postoperative leukocyte values were higher in all three groups. When the preoperative leukocyte values of the three groups were compared; No statistically significant difference was found between the groups. When the postoperative leukocyte values of the three groups were compared, no statistically significant difference was found between the groups. There was a statistically significant difference between pre-op CRP and post-op CRP values in group 1, group 2 and group 3. Postoperative CRP values were higher in all three groups. When the preoperative CRP values of the three groups were compared; No statistically significant difference was found between the groups. When the postoperative CRP values of the three groups were compared, a statistically significant difference was found between the groups. This difference is due to group 3 with higher postoperative CRP value (Mann-Whitney-U test). The Ki-67 values of the patients included in the study are given in Table 5, there was not any statistically significant difference between the three groups. When the tumor diameters of the patients in the three groups were compared, no statistically significant difference was found between the groups.When the Total Number of Lymph Nodes of the Patients Included in the Study was compared, a statistically significant difference was found between the three groups. The difference is source from group 1 with a low number of lymph nodes.When the Metastatic Lymph Node Numbers of the Patients Included in the Study were compared, a statistically significant difference was found between the three groups. The difference is due to group 1 without metastatic lymph nodes.When the three groups were compared in terms of the presence of estrogen receptors, no statistically significant difference was found between the groups. When the three groups were compared in terms of the presence of progesterone receptors, no statistically significant difference was found between the groups. When the three groups were compared in terms of the presence of HER-2, no statistically significant difference was found between the groups. When the three groups were compared in terms of pathological tumor staging, no statistically significant difference was found between the groups. When the three groups were compared in terms of axillary lymph node involvement, a statistically significant difference was found between the groups. The difference is source from group 1 without lymph node involvement.When the three groups were compared in terms of lymphovascular invasion, a statistically significant difference was found between the groups. It is group 1 that makes the difference.When the three groups were compared in terms of Extracapsular Invasion, a statistically significant difference was found between the groups. This difference sourced from 1 th group.

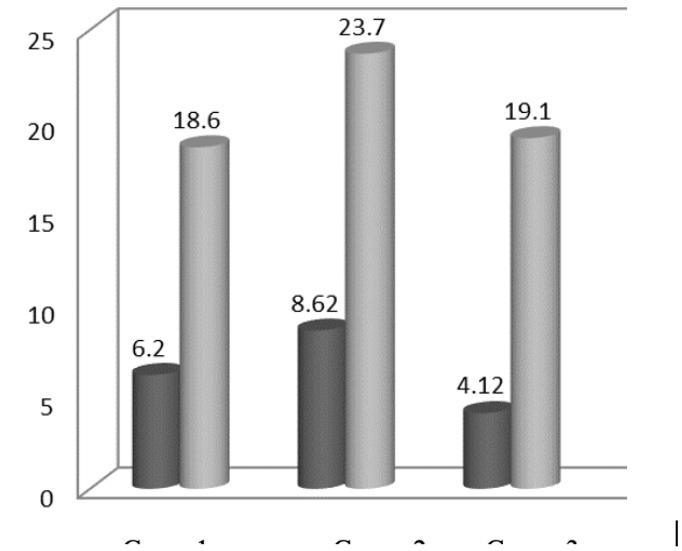

Figure 1: IL-6 Mean of the cases included in the study

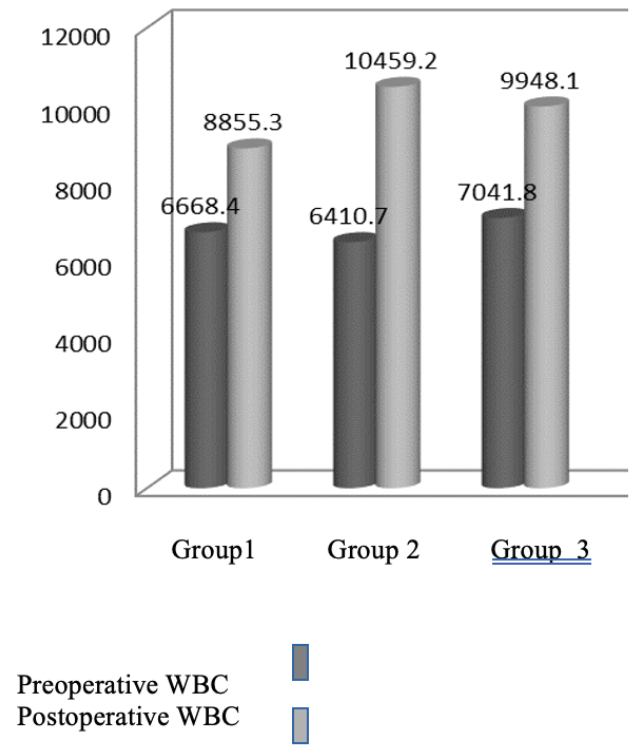

Figure 2: The mean of the white blood cells of the cases included in the study.

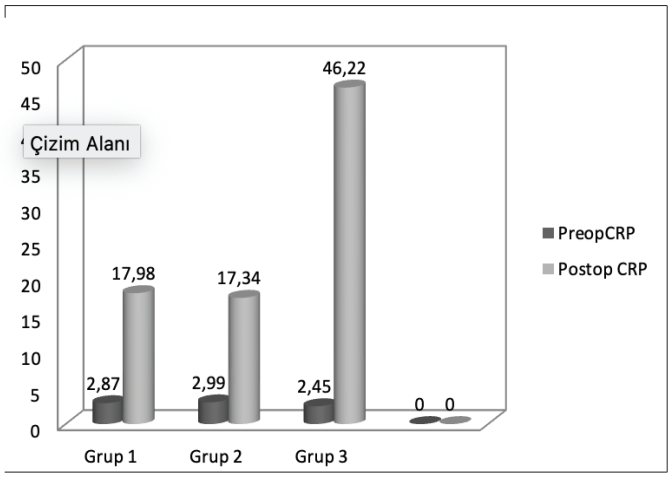

Figure 3: The mean of the CRP for cases included in the study

Table 1: The distribution age of the patients included to the study

Age	Mean± Std.Dv.	Median(Min-Max)	
Group 1	52.54±12.7	50(33-73)	*P=0.73
Group 2	54.15±13.1	52(33-74)	
Group 3	53.25±11.8	53(31-79)	

*:The test of Kruskal-Wallis
Minimum and maximum range
Std.Dv. :Standard deviation

Discussion

Surgical intervention naturally triggers the inflammatory response. This is actually the body's response to surgery-related trauma. Post-traumatic physiological orientation has always been based on the strategy of overcoming the trauma with the least damage. The euroendocrine and inflammatory response that occurs in the organism with trauma is a compensatory mechanism that develops for survival, and this response increases in direct proportion to the amount of various hormones and mediators that occur during this response, and this may show differences in response depending on the type and severity of the trauma. (17,18). Acute phase proteins that emerge in the inflammatory response are a group of proteins synthesized in the liver and whose levels change depending on infection, trauma and malignancy. These proteins include CRP, fibrinogen, C3 complement, haptoglobulin, serum amyloid A and α-1 antichymotrypsin. In post-surgical cases, CRP level is used as an indicator that can show the severity of the inflammatory response and thus the infection, and whether the response to treatment is adequate (19). The increase in CRP levels is mediated by IL-6, a proinflammatory cytokine (20). IL-6, the major regulator of the inflammatory response, is produced by

Table 2: The IL-6 mean and median values of patients included to the study

	Preoperative IL-6		Postoperative IL-6		
	Mean± Std.Dv.	**Median (Min-Max)**	**Mean± Std.Dv.**	**Median (Min-Max)**	
Group 1	6.20±9.53	2.95 (1.56-36.90)	18.6±10.8	18.6 (5.26-42.86)	**#p=0.001**
Group 2	8.62±5.11	7.62 (1.81-17.25)	23.7±19.6	18.4 (8.52-85.60)	**#p=0.001**
Group 3	4.12±3.11	2.54 (1.56-10.99)	19.1±18.1	19.1 (2.22-66.69)	**#p=0.001**
	*p=0.021		*p=0.33		

*:Kruskal-Wallis test #:Wilcoxon test

Table 3: The mean and median values of leukocytes of the patients included to the study

	Preoperative leukocyte		Postoperative leukocyte		
	Mean± Std.Dv.	Median (Min-Max)	Mean± Std.Dv.	Median (Min-Max)	
Group 1	6668.4±1892.6	7160 (4190-10280)	8855.3±3377.3	9340 (3670-15280)	**#p=0.003**
Group 2	6410.7±2041.7	6400 (3670-10170)	10459.2±3200.1	11040 (4920-16800)	**#p=0.001**
Group 3	7041.8±1811.8	7165 (4560-10440)	9948.1±2685.7	9750 (5280-15020)	**#p=0.001**
	*P=0.59		*P=0.41		

*:Kruskal-Wallis test #:Wilcoxon test

Table 4: CRP mean and median values of the patients included to the study

	Preoperative CRP		Postoperative CRP		
	Mean± Std.Dv.	**Median (Min-Max)**	**Mean± Std.Dv.**	**Median (Min-Max)**	
Group 1	2.87±2.77	1.79 (0.60-11.10)	17.98±8.65	18.29 (1.10-35.77)	**#p=0.002**
Group 2	2.99±2.49	3.10 (0.30-8.90)	17.34±14.89	13.30 (1.97-43.90)	**#p=0.001**
Group 3	2.45±2.37	1.29 (0.23-8.73)	46.22±23.84	47.14 (2.44-88.91)	**#p=0.001**
	* P=0.73		*P=0.001		

*:Kruskal-Wallis test #:Wilcoxon test

Table 5: Ki-67 mean and median values of the patients included to the study

Ki-67	**Mean± Std.Dv.**	**Median (Min-Max)**	
Group 1	21.46±15.0	30(4-40)	*P=0.37
Group 2	29.58±23.68	20(5-70)	
Group 3	32.31±24.28	38(5-80)	

*:Kruskal-Wallis test

Table 6: The mean and median tumor diameter of the patients included to the study

Tm çapı	**Mean± Std.Dv.**	**Median(Min-Max)**	
Group 1	2.22±0.58	2.10(1.50-3.0)	*P=0.08
Group 2	2.13±0.84	2.0(1.20-4.0)	
Group 3	3.23±1.67	3.10(1.0-6.70)	

*:Kruskal-Wallis test

Table 7: The mean and median values of total lymph node counts of patients included to the study

Total lymph nodes LN	**Mean± Std.Dv.**		**Median (Min-Max)**	
Group 1	2.46	1.33	2.0(1-5)	*P=0.001
Group 2	18.92	7.97	17(9-32)	
Group 3	20.10	6.45	19(12-39)	

*:Kruskal-Wallis test

Table 8: The mean and median of metastatic lymph node counts of patients included to the study

Metastatic Lymph Node Counts	**Mean± Std.Dv. SS**		**Median (Min-Max)**	
Group 1	-	-	-	*P=0.002
Group 2	5.0	10.1	1(0-31)	
Group 3	2.75	3.85	1(0-14)	

*:Kruskal-Wallis test

Table 9: The presence of estrogen receptors in patients included to the study

	(n)	**Percentage (%)**	
Group 1			
Negative	1	7.7	
Pozitive	12	92.3	
Group 2			*p=0.82
Negative	2	15.4	
Positive	11	84.6	
Group 3			
Negative	2	12.5	
Positive	14	87.5	

* :χ2 test

Table 10: The presence of progesterone receptors in patients included to the study

	(n)	**Percentage (%)**	
Group 1			
Negative	2	15.4	
Positive	11	84.6	
Group 2			*p=0.88
Negative	3	23.1	
Positive	10	76.9	
Group 3			
Negative	3	18.8	
Positive	13	81.3	

*: χ2 test

Table 11: Presence of HER-2 in patients included to the study

	(n)	Percentage (%)	
Group 1			
Negative	11	84.6	
Positive	2	15.4	
Group 2			*p=0.14
Negative	11	84.6	
Positive	2	15.4	
Gruop 3			
Negative	9	56.3	
Positive	7	43.8	

*: χ2 test

Table 12: The pathological stage distribution of the patients included to the study

	(n)	Percentage (%)	
Group 1			
pT0	1	7.7	
pT1	5	38.5	
pT2	7	53.8	
Group 2			*p=0.21
pT0	1	7.7	
pT1	6	46.2	
pT2	6	46.2	
Group 3			
pT0	6	37.5	
pT1	6	37.5	
pT2	4	25.0	

*:χ2 test

Table 13: The axillary lymph node involvement of the patients included to the study

	(n)	Percentage (%)	
Group 1			
Negative	13	100	
Positive	-	-	
Group 2			*p=0.001
Negative	5	38.5	
Positive	8	61.5	
Group 3			
Negative	6	37.5	
Positive	10	62.5	

*:χ2 test

Table 14: The lymphovascular invasion status of the patients included to the study

	(n)	Percentage (%)	
Group 1			
Negative	13	100	
Pozitive	-	-	
Group 2			*p=0.02
Negative	8	61.5	
Positive	5	38.5	
Group 3			
Negative	9	56.3	
Positive	7	43.8	

*:χ2 test

Table 15: The extracapsular invasion status of the patients included to the study with χ2 test

	(n)	Percentage (%)	
Group 1			
Negative	13	100	
Positive	-	-	
Group 2			*p=0.04
Negative	8	61.5	
Positive	5	38.5	
Group 3			
Negative	13	81.3	
Positive	3	18.7	

*:χ2 test

stimulated macrophages, monocytes, endothelial cells, and fibroblasts. It plays a central role especially in the acute phase of inflammation and tends to rise rapidly within the first few hours after surgical incision (21). It has been reported that mediators responsible for the inflammatory response, especially IL-6 and CRP, correlate with the severity and duration of trauma (21). In our study, IL-6, its induced CRP and leukocyte values were examined in order to evaluate the effects of three different surgical procedures performed for breast cancer on the inflammatory response. Lumpectomy + sentinel lymph node dissection (SLND) was performed on patients in Group 1 due to breast cancer , the patients in group 2 underwent modified radical mastectomy and for group 3; Lumpectomy + axillary lymph node dissection was performed. Post-op IL-6 levels in all three groups were higher than pre-op IL-6 values, and this difference was statistically significant ($p<0.05$). Although post-op IL-6 levels were found to be higher in patients in group 2, no statistically significant difference was found when the groups were compared with each other ($p>0.05$). However, IL-6 values in the post-op period were

found to be higher in patients in groups 2 and 3 than in patients in group 1. As mentioned before, as the severity and duration of the trauma increase, the release of proinflammatory cytokines increases in order to adapt the organism to this situation. Here, the most important points are; Along with all these general principles, it is important to apply a careful and gentle surgery, on the condition that the patient is diagnosed correctly, the stage of the disease is determined well, the most accurate choice is made according to the current surgical treatment guidelines, and the patient is informed throughout this process, and on the condition that the cancer surgery safety is the basis during the surgery. As a result; all these factors are very important in terms of alleviate this inflammatory process, which impairs its life quality. There are studies showing that the level of IL-6, the most important of these cytokines, is directly related to the duration of surgery (22). Among the surgical procedures performed, post-op IL-6 values were found to be higher in the modified radical mastectomy group with the most tissue damage and the longest operation time, and in the axillary dissection group, which is consistent with the literature. On the other hand, considering that circulating cytokines such as adipose tissue inflammation, tumor necrosis factor (TNF)-α and interleukin (IL)-6 have the potential to affect breast cancer cells systemically; Since breast tissue is a tissue rich in fat, recent studies have focused on the local effects of the inflammatory process on the adipose tissue, and the levels of these cytokines in the adipose tissue have been measured in different studies (23,24). In our study, when post-op leukocyte values were compared with pre-op leukocyte values in all three groups, post-op leukocyte values were found to be higher and this situation was statistically significant. However, when the groups were compared within themselves, no statistically significant difference was found in terms of pre-op and post-op values. Since it is the most important indicator of the microvascular inflammatory response in trauma, increased leukocyte adhesion in this region and adhesion of leukocytes to the endothelium are the main cornerstones of this inflammatory response(25). It has been shown that these events become more evident when tissues are manipulated with excessive amounts of hands and pulled with hard movements, forgetting the principle of respect for the tissue (25). As the general opinion; It is a condition that the leukocyte values are predicted to increase at first after surgery. In our study, as expected, leukocyte levels were found to be high in all three groups in thepost-op period. As is known, one of the functions of IL-6 is to stimulate the release of acute phase reactants fromhepatocytes. In our study, the increasing occur in post-op IL-6 also causes an increase to CRP. Furthemore in terms of statistically; There was found significancy different preoperative and postoperative CRP levels in all patients in each group.In addition, when post-op CRP values were compared between the groups, it was found to be higher in group 3 who underwent axillary dissection, and this was statistically significant ($p<0.05$). We can see this by adding a cut-off value. In addition, this study; It showed that the CRP values were higher in the group with the most dissection, which is consistent with the literature. HER-2 is one of the epidermal growth factor receptor family (26). When Her-2 receptors become active, they activate the signal transduction pathways in the cell, causing the cell to change and multiply. Her-2 positive breast cancer usually has high grade and proliferation rate, and hormone receptors are negative. In this group, the tumor is larger, lymph node positivity, and visceral and central nervous system metastases are more common(27). In our study, there was a strong positive correlation between Post-op IL-6 and Her-2 in group 2, and this was statistically significant ($r=0.64, p=0.02$). In other words, if Her-2 receptor was positive, IL-6 values were found to be higher. This situation causes the CRP value to be found high in Her-2 positivity with the mechanism mentioned above. This situation creates the need for dissection in our patients with positive Her-2 receptors, since axillary lymph node metastases are more common. In this regard, the inflammatory response becomes more dominant in the postoperative period. However, on the other hand; In support of this situation, no relationship was found between post-op IL-6, leukocyte and CRP values and other parameters in group 1; So it can be said very clearly that the less surgical dissection, the cause of the less the inflammatory response. Ki-67 antigen; It is a "non-histone" bimolecular complex weighing between 345 and 397 kDa. Ki-67 is a proliferation-associated nuclear antigen and is monitored throughout the cell cycle, except in the G0 phase; It is expressed in growth and synthesis phases (G1, S, G2, mitosis) (28). It is used as a marker of cell proliferation (28). Therefore, a high Ki-67 proliferation index is accepted as a negative prognostic factor. For this reason, the fact that the tumor is more likely to metastasize to lymph nodes and other organs by displaying a more aggressive behavior creates the need for axillary dissection in these patients. In support of this

information, in our study, there was a strong positive correlation between the post-op leukocyte value and Ki-67 and it was statistically significant (r=0.59 p=0.04). Similarly, there re a strong positive correlation between leukocytes and total lymph node and it is statistically significant (r=0.63 p=0.02). Extra capsular invasion, which is one of the features of the tumor, is another negative prognostic factor. This case depend on , the spread and metastasis of the tumor to the lymph node becomes more frequent as mentioned above. There is a strong positive correlation between post-op IL-6 and extra capsular invasion in the group, and this correlation is statistically significant (r=0.60 p=0.01). In case of extra capsular invasion in the tumor, the IL-6 value was found to be much higher. This indicates that the wider the surgery, the greater the inflammatory response.

Conclusion

In all surgical methods which performed for breast cancer, an inflammatory response occurs due to the severity of trauma. However, the degree of this response directly depend to the surgical procedure and duration. Of course, the characteristics of the tumor limit the surgical procedure to be performed, but in terms of reducing the mortality and morbidity that may occur in the post-operative period, it should be ensured that the oncological principles are fully implemented, but on the other hand, the applied surgery should be carefully chosen so that for the least invasive level.

Ethic

In this retrospective study, national and international ethical rules were complied with.

Conflict of Interest

No conflict of interest was declared by the authors. In addition, no financial support was received for this study.

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