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Postoperative Immunosuppression Following Breast-Conserving Surgery vs. Mastectomy: The Role of Surgical Injuries and Intraoperative Sympathetic Activation

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ABSTRACT

Breast cancer is the second most prevalent cancer among all types of cancers. **Objectives:** To evaluate the role of surgical tissue injury and intraoperative sympathetic activation in postoperative immunosuppression after breast-conservative surgery and mastectomy. **Methods:** This prospective/observational study investigated 36 breast cancer patients in the Department of Surgery Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences, Gambat from June 2022 to May 2023. Patients who were on schedule to undergo either mastectomy or breast-conserving surgery enrolled. Patients were categorized into two groups; Group I (breast-conserving surgery group n=18) and Group II (mastectomy group n=18). The intraoperative sympathetic activation, plasma Damage-associated molecular patterns, and postoperative immune function were compared in both groups. Descriptive statistics were done using SPSS version 28.0. **Results:** The overall mean age and body mass index of Group I and Group II were 62.8 ± 8.9 vs. 60.6 ± 10.6 years and 26.9 ± 3.8 vs. 25.8 ± 3.7 kg/m2, respectively. The overall duration of surgery (minutes) was 56 ± 18 and 85 ± 22, respectively. The prominent indication for surgery in Group I and Group II was Invasive carcinoma 17(94.4%) and 11(61.1%), respectively. The concentration of plasma alarmins and IL-6 was significantly higher in patients who underwent mastectomy as compared to breast-conserving surgery. **Conclusions:** It was concluded that differences in Damage-associated molecular patterns release and intraoperative sympathetic activation between mastectomy and breast-conserving surgery may influence, and potentially contribute to, postoperative immune homeostasis to improve survival seen after breast-conserving surgery.

INTRODUCTION

Breast cancer is the second most prevalent cause of malignancy-associated mortality among all types of cancers [1]. Delays in the treatment of breast cancer can lead to worse outcomes and survival. Remarkably, the survival rates of breast cancer significantly vary from developing countries like Brazil 58%, India 52.1% to developed world 83.2% [2, 3]. The majority of cases in Pakistan delay their treatment due to various factors such as lack of ignorance and adequate facilities. Other contributing factors include fear of surgery and chemotherapy delays in seeking treatment. As a result, breast conservation is often not possible for many patients with breast cancer [4]. Surgery for breast cancer depends on many factors, including timing, availability of resources, and patient preference. Numerous studies compared the survival rates of mastectomy with breast-conserving

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surgery (BCS) and reported that BCS showed a higher survival rate as compared to mastectomy [5]. A potential contributor to this diagnosis is radiotherapy, as most patients with BCS receive radiotherapy, whereas few patients receive radiotherapy after mastectomy [6]. An earlier study reported an increased prevalence of surgical trauma associated with higher susceptibility to post-operative complications [7]. However, patients who underwent conservative breast cancer showed lower complication rates. In contrast, another study revealed that a higher incidence of postoperative complications was reported in mastectomy as compared to BCS [8]. Damage-associated molecular patterns (DAMPs) act as a ligand for receptors inducing inflammation followed by an immunosuppressive state. In addition, activation of sympathetic pain nerves is known to stimulate the immune system. Greater surgical trauma can cause greater pain and greater visceral sympathetic activation. Several DAMPs have been associated with postoperative immunosuppression and infectious complications. Individual DAMPs generally reflect tissue damage or surgical injury. Elevated DAMP levels contribute to the higher rate of mortality and morbidity [9]. This study should be regarded as hypothesis-generating rather than definitive since it is not clear why minimally invasive surgery for early-stage breast cancer might improve survival rates compared to mastectomy. Since radiation is administered to most patients undergoing BCS, as opposed to fewer people after mastectomy, it is reasonable to assume that it plays a role in this finding. On top of that, mastectomy involves more severe surgical trauma, which raises the risk of complications after the procedure. After breast cancer surgery, the risk of complications is minimal. Despite this, a new study found that compared to BCS, the risks of medical and surgical complications following a mastectomy were greater [10]. Following major surgeries like cholecystectomy and oesophagectomy, the risk of postoperative complications and death is greater in older individuals [11]. Nevertheless, there is no correlation between age and the risk of complications following breast surgery, even when undergoing extensive reconstruction [7–10]. Significantly, the main complication rates are 2.1% lower with therapeutic mammaplasty or even more intensive oncoplastic breast-conserving surgeries compared to mastectomy without (5.0%) or with breast reconstruction (14.4%). Other cancer types, including colorectal, gastric, lung, and head and neck cancers, have demonstrated that POCs have a deleterious effect on survival rates. Findings in breast cancer have been inconclusive. New research from Sweden's National Quality Register for Breast Cancer confirms a strong correlation [12].

This study aims to assess the impact of intraoperative sympathetic activation and surgical tissue damage on postoperative immunosuppression following mastectomy and breast conservatoire procedures.

METHODS

This prospective/observational study investigated 36 breast cancer patients in the Department of Surgery Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences, Gambat from June 2022 to May 2023 with study approval Ref No. IRB/22/18. Non-consecutive sampling technique was used. The calculation of the sample size was based on the prevalence of 18%, the margin of error was 10%, and the confidence interval was 95%. This was done since the required sample size was 36 patients [1]. Patients who were on schedule to undergo either mastectomy or breast-conserving surgery (BCS) enrolled. Patients were categorized into two groups; Group I (BCS group n=18) and Group II (mastectomy group n=18). Each individual provided a consent form. Before surgery, blood samples were taken from each individual. Other specimens were taken after 1 and 3 hours of surgery. Plasma DAMP levels were measured using anti-coagulation blood prepared after the withdrawal of the blood. Baseline, tumor and treatment type, and postoperative data were recorded. Patient details including age, body mass index, tumor characteristics, ASA grades, anesthesia, and pain-related parameters were compared in both groups. The intraoperative sympathetic activation, plasma Damage-associated molecular patterns (DAMPs) [1]. and postoperative immune function were compared in both groups. Postoperative immune function was measured by ANOVA and ELISA tests. Qualitative variables were presented as mean with standard deviation (SD) and quantitative variables were presented as frequencies and percentages. Independent samples T-tests and chi-squared tests were used to determine differences between the groups (BCS versus mastectomy) for each of the time points. Descriptive statistics were done using SPSS version 28.0. $p<0.005$ was considered significant.

RESULTS

The overall mean age and body mass index of Group I and Group II were 62.8 ± 8.9 vs. 60.6 ± 10.6 years and 26.9 ± 3.8 vs. 25.8 ± 3.7 kg/m2, respectively. The overall duration of surgery (minutes) was 56 ± 18 and 85 ± 22, respectively. Baseline parameters such as age, body mass index, and ASA grade in both groups were similar and comparable. Demographic details are shown in table 1.

Table 1: Demographic Details of the Presented Cases

Variables	Group I (BCS)	Group II (Mastectomy)	p-value
Age (Years)	62.8 ± 8.9	60.6 ± 10.6	0.189
BMI (Kg/m^2)	26.9 ± 3.82	5.8 ± 3.7	0.318
Duration of Surgery (Minutes)	56 ± 18	85 ± 22	<0.001

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ASA n (%)			
I	5 (27.8%)	4 (22.2%)	0.669
II	12 (66.7%)	13 (72.2%)	
III	1 (5.6%)	1 (5.6%)	

The prominent indication for surgery in Group I and Group II was Invasive carcinoma found in 17 (94.4%) and 11 (61.1%), respectively. The concentration of plasma alarmins and IL-6 was significantly higher in patients who underwent mastectomy as compared to BCS. Clinical characteristics are shown in table 2.

Table 2: Comparison of Outcomes among Both Groups

Variables	Group I (BCS)	Group II (Mastectomy)	p-value
Invasive Carcinoma	17 (94.4%)	11 (61.1%)	0.018
Carcinoma in Situ	1 (5.6%)	3 (16.7%)	
Invasive Lobular Carcinoma	0	4 (22.2%)	
Sentinel Node Excision			
Yes	14 (77.8%)	15 (83.3%)	0.672
No	4 (22.2%)	3 (16.7%)	
Type of Tumor			
Unilateral	17 (94.4%)	17 (94.4%)	0.699
Bilateral	1 (5.6%)	1 (5.6%)	
Oestrogen Receptor			
Positive	16 (88.9%)	15 (83.3%)	0.699
Negative	2 (11.1%)	2 (11.1%)	
Unknown	0	1 (5.6%)	
Progesterone Receptor			
Positive	14 (77.8%)	13 (72.2%)	0.918
Negative	4 (22.2%)	4 (22.2%)	
Unknown	0	1 (5.6%)	
Postoperative Pain	2.5 ± 4.10	3.9 ± 2.27	0.004

Neither the pre- nor the post-operative DAMP plasma concentrations varied significantly across the groups. Nevertheless, individuals who had undergone a mastectomy had noticeably elevated amounts of S100A8/A9 and S100A12 on postoperative day 3, as shown in table 3.

Table 3: Concentrations of DAMPs in Plasma Before and After Surgery

DAMPs (pg/ml)	Group I (BCS)	Group II (Mastectomy)
Before Surgery	4023.7 ± 5.784	4317.44 ± 12.367
1h After Surgery	4000.7 ± 5.784	4327.13 ± 11.228
3 Days After Surgery	10000.1 ± 2.235	20000.78 ± 16.478

DISCUSSION

The present study mainly focused on the comparison of conservative breast surgery versus mastectomy and investigating the role of surgical tissue injury and intraoperative sympathetic activation. Significant variances were reported between mastectomy and breast-conservative surgery. Several previous studies have reported increases in these DAMPs after surgical procedures [13-15]. There is the possibility of no increase in DAMPs or growth occurring after the time of measurement. Breast cancer surgery is a critical milestone in a female's life. Its treatment improved dramatically over the past decades, with an increasing number of patients opting for breast conservation combined with various therapies [16-18]. Many of these patients follow treatment regimens affecting chemotherapy and radiotherapy together. Although strict adherence to such procedures may improve surgical outcomes, any delay in treatment due to comorbidities may adversely affect overall survival [19]. In Pakistan, most women are reluctant to seek medical advice on breast-related issues, mainly due to unemployment living standards. This highlights the need to address the unmet psychosocial aspects of breast cancer patients in Pakistan, from medical counselling to social support and referral to appropriate healthcare plants. Although surgeons strive to perform operations with excellent postoperative outcomes, achieving optimal cancer-related outcomes often requires a multifaceted approach, including patient education. The increased surgical trauma experienced during mastectomy may increase sympathetic and adrenergic prostaglandin responses. It is widely accepted that primarily autoimmune is the initial postoperative immune response. Propofol was found to impair the function of several monocytes and neutrophils, while remifentanil also exhibited potent immunosuppressive effects. Generally, severe depression occurs in cytokine production immediately after surgery in cancer patients, which often with comorbidities requires reassessment management of anesthesia. Previous studies have reported no difference or serious adverse events, but a reasonable difference may occur during the analgesic phase of triple anesthesia [20].

CONCLUSIONS

It was concluded that differences in DAMP release and intraoperative sympathetic activation between mastectomy and breast-conserving surgery may influence, and potentially contribute to, postoperative immune homeostasis to improve survival seen after BCS.

Authors Contribution

Conceptualization: HR
Methodology: HR, MAQ, NY
Formal analysis: AI, NF,
Writing review and editing: S

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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