

Effects of Mammary Surgery on Prolactin Secretion in Common and in Triple Negative Breast Cancer Patients

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Abstract: Despite the well documented potential stimulatory activity of prolactin (PRL) on mammary tumors, hyperprolactinemia following breast surgery has been proven to predict a more favourable prognosis in breast cancer. This apparent controversial result is probably due to the fact that in normal conditions each mammary stimulation has to induce PRL secretion, then the failure of PRL increase after breast surgery could reflect an alteration in the neuroendocrine control of mammary tissue growth and differentiation. On this basis, a study was planned to investigate the effects of breast surgery on PRL secretion in triple negative breast cancer (TNBC), which represents the most malignant subtype of mammary tumors. The study included 100 breast cancer patients treated by quadrantectomy, by evaluating PRL serum levels before and 7 days after surgery. The diagnosis of TNBC occurred in 16/100 investigated patients. Post surgical hyperprolactinemia was observed in 53/84 (63%) patients with common breast cancer and in only 2/16 (13%) TNBC patients. This difference was statistically significant. The present preliminary study, by showing a lower frequency of surgery-induced hyperprolactinemia in TNBC with respect to the other mammary tumor histotypes would suggest that the more aggressive behaviour of TNBC could depend at least in part on a more pronounced alteration in the neuroendocrine control of mammary tissue.

Keywords: Breast cancer, Breast surgery, Hyperprolactinemia, Prolactin, Triple negative breast cancer.

1. INTRODUCTION

Several experimental studies have shown that prolactin (PRL) may be a growth factor for breast cancer (1-3). Despite the well demonstrated stimulatory activity of PRL on breast cancer growth, either on its development, or progression, the evaluation of PRL secretion in patients with mammary tumors is not generally taken into consideration by the Oncologists. At present, the only available data concerning the relation between PRL blood concentrations and prognosis of human breast cancer are referred to many years ago, and they are in agreement to show that the evidence of high PRL levels is associated with a poor prognosis in all conditions (4-6), except one clinical condition, represented by the occurrence of mammary surgery-induced hyperprolactinemia, which in contrast has appeared to predict a lower percentage of relapse and with a longer survival (7). This finding is not surprising, since PRL secretion has to respond to each mammary stimulation, including breast surgery. Then, the lack of PRL increase after mammary surgery would be a biological sign of

the presence of altered neuroendocrine control of mammary tissue growth. Moreover, it is known that the most aggressive type of mammary tumor is represented by the triple negative breast cancer (TNBC) (8,9), which constitutes about 15-20% of the overall mammary tumors and is characterized by the lack of expression of the all three main receptors involved in the pathogenesis of breast cancer, including ER, PgR and HER-2. Moreover, recently it has been shown that the expression of PRL receptor (PRL-R) tends to be reduced in TNBC, and the lack of PRL-R expression has appeared to predict a more aggressive disease (10). Then, within the group of TNBC, it would be possible to identify a more malignant sub-type of cancer characterized by a negativity also for PRL-R, by constituting a quadruple negative breast cancer. At present, It is known that tumor malignancy depends not only on its genetic characteristics, but also on the regulation of its growth by the immune and the neuroendocrine system (11-13). Therefore, it could be interesting to investigate PRL response to breast surgery in TNBC. This preliminary study was performed in an attempt to analyze

PRL blood levels before and after mammary surgery in TNBC patients, by comparing the results with those observed in the common breast cancer.

2. PATIENTS AND METHODS

The study included 100 breast cancer women, who underwent breast surgery. The clinical protocol was explained to each patient, and written consent was obtained. Eligibility criteria were, as follows: histologically proven breast cancer, breast surgery consisting of quadrantectomy, no chronic therapy with drugs stimulating PRL secretion, and no administration of anti-dopaminergic drugs for at least 1 day prior to study. For PRL detection, venous blood samples were drawn in the morning after an overnight fast on the day of surgery and 7 days after surgery. Serum levels of PRL were measured in duplicate with an immunoradiometric method (IRMA) by using commercially available kits. Normal values of PRL for women observed in our laboratory (95% confidence limits) were less than 23 ng/ml. Data were reported as mean ±SE, and statistically analyzed by the chi-square test and the Student's t test, as appropriate.

3. RESULTS

TNBC occurred in 16/100 (16%) patients, while the remaining 84 patients had tumor histotypes other than the TNBC. As shown in Table 1, the characteristics of the two groups of patients were well comparable for the main clinical variables, including age, performance status and menopausal status. No significant difference was seen in presurgical PRL serum levels between TNBC and common breast cancer patients (Post surgical hyperprolactinemia with values higher than 23 ng/ml occurred in 53/84 (63%) patients with mammary tumors other than TNBC and in only 2/16 (13%) TNBC patients. Then, the percentage of surgery-induced hyperprolactinemia observed in TNBC was significantly lower with respect to that found in patients with less malignant histotypes ($P < 0.001$). PRL mean levels observed before and after surgery are illustrated in Figure 1. No significant difference in the presurgical values of PRL was seen between TNBC and common breast cancer patients (10.2 ± 0.6 vs 8.6 ± 0.4 ng/ml). On the contrary, PRL mean levels observed in the post surgical period in TNBC patients were significantly lower than those found in patients with other cancer histotypes ($P < 0.005$).

Table1: Clinical characteristics of patients with common or triple negative breast cancer (TNBC)

Characteristics	Common Breast Cancer	Tnbc
N	84	16
Median age (years)	52 (29-75)	54 (28-73)
Median performance status (ECOG)	0 (0-1)	0 (0-1)
Postmenopausal status	48 (57%)	7 (44%)

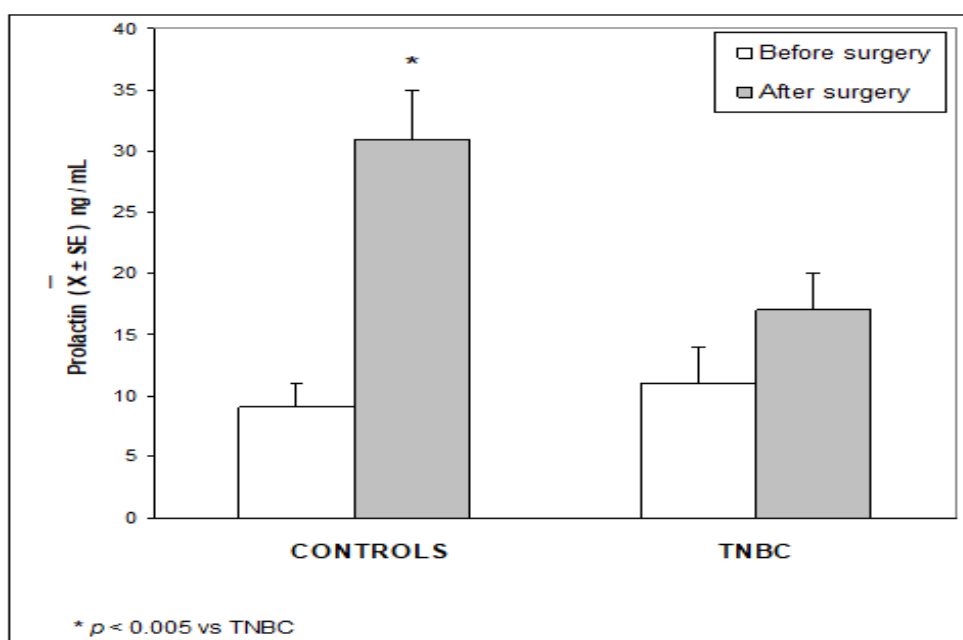


Figure1: PRL serum mean levels observed before and after breast surgery in triple negative breast cancer (TNBC) or common breast cancer as a control group

4. DISCUSSION

This preliminary study, carried out in a considerable number of patients, shows a reduced occurrence of surgery-induced hyperprolactinemia in TNBC patients with respect to the other histotypes. Since previous study, when the existence of the TNBC subtype was still unknown, had already shown that the lack of surgery-induced PRL increase was associated with a more negative prognosis in breast cancer (7), the low frequency of surgery-induced hyperprolactinemia in TNBC could already constitute a biological sign of its higher malignancy, by reflecting an altered neuroendocrine control of mammary tissue. PRL has been proven to either stimulate cell proliferation in TNBC, or promote its biological differentiation (10). Then, the post surgical levels of PRL could modulate the growth and the differentiation of eventual micro metastases in TNBC. Therefore, longitudinal studies will be required to establish whether the occurrence of post surgical hyperprolactinemia may predict a more favourable prognosis in TNBC patients.

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Citation: Paolo Lissoni, et al. *Effects of Mammary Surgery on Prolactin Secretion in Common and in Triple Negative Breast Cancer Patients*. *ARC Journal of Gynecology and Obstetrics* 2019; 4(3):8-10. DOI: [dx.doi.org/10.20431/2455-9792.0403001](https://doi.org/10.20431/2455-9792.0403001).

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