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ORIGINAL ARTICLE

Nausea and vomiting after breast cancer surgery, and relationship with tumor receptor status

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Abstract
Background Breast surgery is associated with frequent post-operative nausea and vomiting (PONV). Studies have suggested that hormonal status affects PONV. Estrogen has been implicated in many emetic syndromes. Estrogen receptor (ER) and progesterone receptor (PR) status in breast tissue are hormonally affected. Kakugawa et al., in 2007, found a clear trend toward higher serum level of estrone, estradiol, and dehydroepiandrosterone sulfate in post menopausal women with PR-positive cancer.
Purpose To investigate the possibility of an association between ER and/or PR status of breast tumor and incidence of PONV after breast cancer surgery.
Methods This observational study included 315 female patients undergoing major breast surgery. Relevant patient data, and intra-operative and postoperative details were noted. Incidence of PONV was noted using the PONV score. Patients were divided into two age groups: less than or equal to 50 years and more than 50 years of age. The ER and/or PR status of the patient was unknown to the investigator until the final analysis.
Results Use of the chi-squared test revealed no association between ER and/or PR and total PONV. Patients below 50 years had higher incidence of total PONV ($p = 0.023$). In patients above 50 years, the incidence of PONV was higher in the ER-positive group ($p = 0.018$).
Conclusion The incidence of PONV is higher for patients below 50 years of age. The positive association between ER positivity and PONV in patients above 50 years of age could be attributed to the altered hormonal milieu in these patients and should be investigated further.

Keywords PONV · Hormonal effect · Tumor receptors

Introduction

Breast surgery is associated with frequent post operative nausea and vomiting (PONV), with incidence as high as 60% [1]. The physiology of emesis involves complex receptor interaction at higher cortical centers and the chemoreceptor trigger zone (CTZ). Studies of menstruating females and of females during pregnancy have suggested that hormonal status may affect the incidence of nausea and vomiting [2, 3]. Estrogen has been implicated in many emetic syndromes [2]. Lower levels of prolactin and higher levels of estradiol have been found to contribute to, or correlate with, the occurrence of nausea, with or without vomiting, during pregnancy [3].

Endogenous sex hormones are involved in the development of breast cancer [4]. Estrogen receptor (ER) and progesterone receptor (PR) status in breast tissue is hormonally affected and has been used to predict a patient's clinical course and response to adjuvant endocrine therapy

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[4]. Kakugawa et al. [4], in 2007, found a clear trend toward higher serum levels of estrone, estradiol, and dehydroepiandrosterone sulfate in post-menopausal women with PR-positive cancer.

On the basis of these clinical and hormonal observations we hypothesized on the possibility of a relationship between ER and/or PR positivity and PONV after breast cancer surgery. Because our hypothesis is not based on direct evidence but on the hormonal basis that estrogen has been implicated in most emetic syndromes, and PR positivity is also related to high serum levels of estrone, estradiol and dehydroepiandrosterone, we decided to investigate this association further, by means of an observational study. The clinical relevance of the association, if found, would be to use the receptor status for stratification of the risk of incidence of PONV. As multiple factors are associated with PONV, we also studied other confounding patient-related and anesthetic factors in this group.

Materials and methods

After approval from the Institutional Review Board, this study included 318 female patients undergoing major breast surgery. Because this study was an observational study (audit) involving collection of patient data and noting of incidence of nausea and vomiting in the post-operative period, patient consent was waived.

Data collection

A case record sheet "Appendix" was used for data collection. This included patient details for example age, weight, ASA physical status, chemotherapy received and its details, smoker or non-smoker status, history of previous PONV and motion sickness. Anesthetic details, for example duration of anesthetic, opioid and anesthetic drugs used, any episodes of intra-operative hypotension, details of analgesics used, and usage of antiemetic, were noted. Duration and type of surgery was also recorded. In accordance with our hospital policy, all patients in the immediate post-operative period were kept in the recovery area for few hours before being moved to their ward and most of them were discharged the next day. The case record sheet was completed by the anesthesiologist conducting the case in the operating theater, and subsequently by the recovery registrar. The post-operative course in the wards was recorded later by an anesthesiology registrar.

Patients were followed up at 2, 6, and 24 h post surgery. PONV was analyzed as early (0–2 h), late (2–24 h), and total (0–24 h). The PONV score was used for assessment. Score 0, if no PON or POV occurred; score 1 if PON occurred but no POV; score 2, if both PON and POV occurred [5].

The ER and PR status of the patient was unknown to the investigator until the final analysis, to avoid bias and the data were retrieved from the central database maintained by the hospital. The receptor status of the tissue, in our hospital, was scored by use of the Shoushas modification of the immuno histology score [6]. By use of this score, receptor positivity was graded from 1 to 9 on the basis of the intensity and percentage of staining. A score of 0 indicated negative receptor status whereas scores of 1–9 were indicative of positive receptor status [6].

Statistical analysis

Because this was an observational study, and considering the incidence of PONV in breast cases in the available literature to be approximately 60%, it was decided to follow up at least three hundred post-operative breast patients in a defined time frame.

The incidence of PONV recorded as PONV score was analyzed by considering a PONV score of 0 as a negative event and PONV scores of 1 and 2 as positive events. For simplification of calculation the patients were divided into two age groups: less than or equal to 50 and 128 more than 50 years of age.

Since multiple factors affects PONV, we analyzed the effect of different patient factors on PONV by use of the chi-squared test. These factors included age, associated illness, chemotherapy, history of motion sickness and past history of PONV. The duration of surgery and duration of anesthesia were compared between both the groups—with and without PONV—by use of Student's t test. Other intra-operative factors including induction drugs, use of nitrous oxide, use of opioids, and post-operative analgesic requirement, were analyzed for their effects on PONV by use of the chi-squared test. The ordered categorical variable chi-squared test (Kendall's tau-b) was used to analyze post operative pain score and PONV. A p value of ≤ 0.05 was taken as significant. ER and PR status and PONV was compared by use of the chi-squared test. To seek any association between individual factors we ran a logistic regression (multivariate analysis) using all the variables that were significant in individual chi-squared tests, and the variables that were clinically relevant and the ER and PR status. All p values presented are two-sided. Predictive Analytics Software (PASW) statistics 18, (SPSS, Chicago, IL, USA) was used for all analysis.

Results

The total (0–24 h) incidence of PONV was found to be 44.4%. Early (0–2 h) PONV was approximately 24.4% and late (2–24 h) PONV was approximately 32.4%. All three incidences were used for further calculations. Prophylactic antiemetic was used in 89.2% of patients. Data from 318 patients were initially included. For three patients the PONV data were incomplete and, hence, excluded from all calculations resulting in a study group size of 315 patients. Table 1 enumerates the surgical procedures performed in the study group. When we looked at associated factors, including Apfel criteria (Table 2), age had a significant association with PONV. ER and PR status were not found to have any association with PONV.

The mean weight between the group with and without (total) PONV did not show any significance in the Student *t* test. No patient had a positive history of smoking. None of the intra-operative factors was significantly associated with PONV (Table 3). There was no association between post-operative pain score and analgesic requirement with PONV.

Twenty-nine patients had undergone hysterectomy in the past and 112 patients received chemotherapy. For simplicity of calculation, patients were grouped as equal to or below 50 years and above 50 years of age.

Factors that were found significant in univariate analysis (chi-squared test), high risk factors according to the Apfel score, and ER and PR status were then checked for any association by use of multivariate analysis. Age was found to be a significantly associated factor for early and total PONV (Table 4). The association between previous chemotherapy and late vomiting was significant ($p = 0.036$).

Table 1 Number of patients recruited and surgical details

Sr no.	Type of surgery	No. of patients
1	Breast conservation therapy (BCT)	129
2	Modified radical mastectomy (MRM)	84
3	Simple mastectomy with axillary clearance (SMAC)	43
4	Latissimus dorsi reconstruction needed after mastectomy	13
5	Others (axillary clearance only, revision mastectomy, MRM + oophorectomy)	46
	Total no. of patients	315

Table 2 Chi-squared test (univariate analysis) between various factors and PONV

Factor	Groups	Total no. of patients	No. of patients positive for early PONV	No. of patients positive for late PONV	No. of patients positive for total PONV
Age	≤50 years	175	52/175	67/175	88/175
			$p = 0.017$*	$p = 0.236$	$p = 0.023$*
	>50 years	140	25/140	44/140	52/140
Associated illness	ASA gr I	175	51/175	62/175	82/175
			$p = 0.035$*	$p = 1.00$	$p = 0.362$
	≥ASA gr II	140	26/140	49/140	58/140
Chemotherapy (details missing in 3 patients)	Received	112	30/112	48/112	58/112
			$p = 0.584$	$p = 0.049$*	$p = 0.075$
	Not received	200	47/200	63/200	82/200
History of motion sickness	Positive history	41	15/41	20/41	23/41
			$p = 0.77$	$p = 0.052$	$p = 0.130$
	No history	274	62/274	91/274	117/274
Past history of PONV	Positive history	26	6/26	13/26	16/26
			$p = 1.0$	$p = 0.132$	$p = 0.98$
	No history	289	71/289	98/289	124/289
ER status	ER positive	146	39/146	55/146	70/146
			$p = 0.697$	$p = 0.367$	$p = 0.289$
	ER negative	146	35/146	48/146	60/176
PR status	PR positive	132	35/132	49/132	61/132
			$p = 0.687$	$p = 0.623$	$p = 0.637$
	PR negative	160	39/160	54/160	69/160

* $p \leq 0.05$ statistically significant

Table 3 Association between intra-operative factors and PONV

Factor	Mean value	Result of test for early PONV (p value)	Result of test for late PONV (p value)	Result of test for total PONV (p value)
Duration of surgery[a]	86 ± 50 min	0.539	0.199	0.229
Duration of anesthesia[a]	104 ± 53 min	0.534	0.265	0.705
Induction agent used[b]	Propofol 285 cases, thiopentone 30 cases	0.503	0.329	0.083
Intra-operative hypotension[b]	Present in 29 cases	0.821	0.257	0.438
Use of nitrous oxide[b]	Used in 312 cases	1.000	0.295	0.505
Use of opioids over 3 μg/kg[b]	Used in 63 cases	0.970	0.156	0.095
Prophylactic use of antiemetic[b]	Given in 281 cases	0.833	0.257	0.147

[a] Student t test used for analysis

[b] Chi-squared test used for analysis

Table 4 Multivariate analysis for PONV

Variables	Results for early PONV			Results for late PONV			Results for total PONV		
	Odds ratio	95%CI	p value	Odds ratio	95%CI	p value	Odds ratio	95%CI	p value
Age 50	2.078	1.1–3.9	0.023*	1.497	0.82–2.6	0.161	1.826	1.0–3.1	0.030*
Associated disease	0.697	0.37–1.3	0.261	1.310	0.74–2.3	0.350	1.136	0.65–1.9	0.651
History of motion sickness	2.280	1.0–4.7	0.030*	1.786	0.84–3.6	0.106	1.627	0.80–3.2	0.177
History of PONV	0.724	0.24–2.1	0.557	1.29	0.51–3.2	0.585	1.567	0.62–3.9	0.336
Chemotherapy	0.977	0.53–1.7	0.936	1.73	1.0–2.8	0.036*	1.533	0.92–2.5	0.095
ER status	1.394	0.57–3.3	0.464	1.326	0.58–2.9	0.497	1.773	0.80–3.9	0.159
PR status	0.950	0.38–2.3	0.912	0.944	0.41–2.1	0.891	0.774	0.34–1.7	0.536
Constant	0.205		0.000	0.253		0.000	0.358		0.001

* $p \leq 0.05$ statistically significant

We repeated the chi-squared test between receptor status and PONV in each age group separately. In the age fifty or below group, no association was seen between ER and PR and PONV. In the group above 50 years the incidence of PONV was higher in the ER-positive group (for total PONV, $p = 0.018$) (Table 5). Though the incidence of PONV was also higher in the PR-positive group for patients above 50 years of age, this was not statistically significant (Table 6).

When we looked at the age distribution of patients who had received chemotherapy, 73 out of 200 patients received chemotherapy in the below 50 years of age group compared with 39 out of 112 patients in the above 50 years of age group. This was statistically significant ($p = 0.013$).

Discussion

In our data, the incidence of total PONV in the first 24 h was 44%. Most studies have looked at PONV up to 24 h and have further divided it as early and late, because anesthetic-related causes may affect early PONV and late PONV differently [1, 7]. In our study, early PONV was 24.4%, late PONV 32.4%. The chi-squared test result for intra-operative factors and PONV was not statistically significant (Table 3); this could be attributed to the similar anesthetic management for all our breast patients, which resulted in little difference between the group with and group without PONV. One-hundred and seventy-five patients were ASA grade I and 140 patients were ASA grade II and above. The incidence of early PONV was more in the ASA grade I group than in the ASA grade II and above groups ($p = 0.035$). This is similar to previous data on PONV [8].

A total of 112 patients received chemotherapy, and 29 patients had undergone hysterectomy in the past. Menopausal status was difficult to ascertain in the patients who received chemotherapy because it was difficult to differentiate post-chemotherapy amenorrhea from menopause. The global mean age at menopause varies widely, and the mean age at menopause in Indian women is less than in developed countries [9]. For comparison and statistical calculations the patients were divided into two

Table 5 Analysis of ER status and PONV in both age groups by use of the chi-squared test

	Total no. of patients	Patients with early PONV	Patients with late PONV	Patients with total PONV
Age 50 years or below				
ER +ve	68	22	25	34
ER −ve	91	28 ($p = 0.864$)	36	46 ($p = 1.00$)
Age above 50 years				
ER +ve	77	17 ($p = 0.253$)	30 ($p = 0.040$*)	36 ($p = 0.018$*)
ER −ve	55	7	12	14

* $p \leq 0.05$ statistically significant

Table 6 Analysis of PR status and PONV in both age groups by use of the chi-squared test

	Total no. of patients	Patients with early PONV	Patients with late PONV	Patients with total PONV
Age 50 years or below				
PR +ve	64	20	24	31
PR −ve	95	30 ($p = 1.000$)	37 ($p = 0.870$)	49 ($p = 0.748$)
Age above 50 years				
PR +ve	68	15 ($p = 0.263$)	25 ($p = 0.198$)	30 ($p = 0.152$)
PR −ve	65	9	17	20

groups according to age—equal or less than 50 ($n = 175$) and more than 50 years of age ($n = 140$), considering the universal menopausal age as 50 years. Age had a significant effect on PONV, with patients below 50 years having higher incidence of early PONV ($p = 0.017$) and total PONV ($p = 0.023$). These data are consistent with previous studies on PONV [2]. It is known that because of hormonal influence, the incidence of vomiting increases as girls approach menarche. The incidence in postmenopausal females is similar to that in men [2].

Estradiol has been positively associated with nausea with or without vomiting risk [3]. Endogenous estrogen and progesterone bind specifically to ER and PR in breast tissue and affect tumor growth [4]. Kakugawa et al. [4] found a clear trend toward higher serum levels of estrone, estradiol, and dehydroepiandrosterone sulfate in women with PR-positive cancer.

In our study, no association between ER or PR status and PONV was found by use of the chi-squared test. Because the hormonal milieu in a premenopausal woman is different from in a post-menopausal woman we looked at these two groups separately.

In the 50 and below age group, no association was found between ER or PR positivity and PONV. To probe this further, we looked at studies on monthly cyclical hormonal variation and the effect of chemotherapy on ER and PR receptor status.

Pujol et al. [10] studied the variability of the ER and PR receptors in 2020 patients, including 575 premenopausal women. In premenopausal women, there was higher proportion of ER-positive tumors in the follicular phase than in the ovulatory phase and the luteal phase. They concluded by saying that interpretation of hormonal dependency on the basis of steroid receptor values should take into account hormonal status at the time of surgery.

The effects of commonly used chemotherapeutic drugs on the estrogen receptor were studied by Yang and Samaan [11], by exposing MCF-7 human breast cancer cells to methotrexate, 5-fluorouracil, and vincristine in serum and hormone-free medium. The data indicate that the cytotoxic drugs may cause dose-dependent reversible depletion of ER in human breast cancer and the effect is because of inhibition of receptor synthesis rather than inhibition of the binding of estradiol to its receptors [11]. Also, patients who received chemotherapy had significantly lower primordial follicle count than controls [12]. In vitro, ovarian cortical pieces from individuals previously exposed to chemotherapy produced less estradiol [12]. In our study, it is interesting to note that the number of patients who had received chemotherapy was significantly higher in the group below 50 years of age ($p = 0.013$).

One limitation of our study is that ER and PR status was noted retrospectively from the central database. In accordance with the disease-treatment plan, receptor status was determined at the time of core biopsy taken for diagnosis or before the start of chemotherapy; approximately 30% of our study patients were in this category. For approximately 14% of patients the ER and PR status was known either on the basis of an out of hospital collected specimen or

previous consultation. For approximately 56% of cases for whom immediate surgery was planned, receptor status was determined from the specimen sent for histopathology. However, in our study, because details of receptor status were taken from the central database, the time of sample collection relative to the individual patient's menstrual cycle or last dose of chemotherapy could not be ascertained.

The effect of phasic hormonal changes in premenopausal women and the effect of chemotherapy on receptor status and on ovarian function could be one reason why correlation between ER and PR status and PONV was not seen in patients belonging to the 50 and below age group. We postulate that the fact that fewer patients in the post-menopausal group received chemotherapy and the absence of the cyclical hormonal variation after menopause could be reasons receptor status and serum hormonal levels were better correlated in the above 50 age group. This explains the finding of a statistically significant correlation between ER positivity and PONV in the above 50 age group. The incidence of PONV was higher in the PR positive group, although it was not statistically significant. This is further supported by the study by Bernstein et al., who compared hormone levels in blood and urine between post-menopausal women with and without breast cancer [13]. In the breast cancer group serum estradiol was 15% higher, urinary estradiol 40% higher, and urinary oestriol 44% higher than in controls. This increase in post-menopausal serum estrogen concentration has been implicated in breast cancer pathogenesis [13].

Conclusion

Although this study has many limitations, including the fact it was an observational study, the association between ER and PR status and PONV was investigated on the basis of factual clinical and hormonal evidence. Probably because of the cyclical hormonal effect on receptor status, and the effect of chemotherapy both on the ovaries and on the breast tissue receptor, no direct association was found between ER and PR status and PONV in patients below 50 years of age. The positive association between ER positivity and PONV in patients above 50 years of age could be attributed to the altered hormonal milieu, which itself is responsible for cancer pathogenesis in these patients. This positive association should be investigated further by means of well designed randomized trials.

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Appendix

Case Record Sheet

Name	Reg no	
Age	wt	BMI

Nature of surgery Menopausal / LMP:

Chemotherapy: Y/N . If yes , details:

Tumor marker status: ER +/- PR +/-:

Associated Diseases ASA grade

Patients risk for PONV (Apfel score)

-female gender √	-nonsmoker
-history of motion sickness	- history of PONV

other risk factors:

duration of surgery	duration of anesthesia
induction agent	nitrous oxide used
use of inhalation agent	use of Opioids (with dose)
other analgesic used	intra-operative hypotension

prophylactic use of anti emetic (with dose/time of administration)

Duration of Surgery	From	to
Duration of Anesthesia	From	to

Vomiting at end of surgery: Y/N, if Y- drugs given:

(In the recovery):

PONV score

Score =0, if no PON or POV occurred

Score=1, if PON occurred but no POV

Score=2, if both PON and POV occurred

time	PONV score	If vomiting, no of times	Treatment of PONV	Pain score	Analgesic used
0-2 hrs					
2-6 hrs					

Time of transfer to ward:

Any other remarks:

(At Discharge) Date and time of discharge:

time	PONV score	If vomiting, no of times	Treatment of PONV	Pain score	Analgesic used
0-2 hrs					
2-6 hrs					
6-24 hrs					

Any other remarks:

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