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Psychological and endocrine factors and pain after mastectomy

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Abstract

Background: This prospective study was designed to examine the associations of demographic, clinical, psychological and neuroendocrine factors with acute and chronic post-operative pain following partial mastectomy.

Methods: Sixty-four female patients scheduled for partial mastectomy were enrolled. Pre-operative anxiety/depression was assessed, using the Hospital Anxiety and Depression Scale (HADS). Pre-operative 24-h urinary cortisol levels were measured 2 days before surgery. Post-operative pain was examined using a visual analog scale (VAS) for acute pain on 0–2 post-operative day (POD), and a short-form McGill Pain Questionnaire for chronic pain at 6 months after surgery. In the last 29 subjects, post-operative 24-h urinary cortisol levels were also measured on 0 POD and were subjected to correlation analysis.

Results: Multivariate logistic regression analysis revealed that lower pre-operative cortisol secretion and greater pre-operative anxiety were significantly associated with an increased risk of moderate to severe acute post-operative pain [Odds Ratio (95% Confidence Interval); 0.96 (0.92–0.98), and 1.24 (1.04–1.54)], and that patients with greater pre-operative anxiety and moderate to severe acute pain were more likely to develop chronic post-operative pain [OR (95% CI); 1.63 (1.23–2.40), and 5.07 (1.30–24.6)]. Correlational analysis demonstrated that the post-operative cortisol level was inversely correlated with pre-operative anxiety and the intensity of acute post-operative pain ($r = -0.40$, $p < 0.05$, and $r = -0.50$, $p < 0.01$), but not with the intensity of chronic pain.

Conclusions: This study confirms that pre-operative anxiety is associated with both acute and chronic post-operative pain after partial mastectomy. It also suggests that lower perioperative cortisol secretion might be associated with greater acute post-operative pain.

Significance: Although the associations between psychological stress/stress hormone levels and chronic post-operative pain remain to be determined, pre-operative psychological stress and perioperative cortisol levels are correlated with acute post-operative pain.

1. Introduction

Pre-operative psychological distress, such as anxiety and depression, has been shown to exhibit strong correlations with acute and chronic post-operative pain (Caumo et al., 2002; Katz et al., 2005); however, the underlying mechanisms responsible for such links are poorly understood.

Previous reports have suggested that an association exists between psychological distress and hypothalamic-pituitary-adrenal (HPA) axis dysfunction

(Hughes et al., 2004; Vreeburg et al., 2009; Spijker and van Rossum, 2012). Away from the perioperative setting, a hyperactive HPA axis, which is characterized by increased cortisol secretion, was observed in patients with depressive disorders (Carroll et al., 1976; Pfohl et al., 1985; de Villiers et al., 1987), while a hypoactive HPA axis, which is characterized by reduced cortisol secretion, was seen in patients with other psychiatric conditions, such as post-traumatic stress disorder and anxiety symptoms (Yehuda et al., 1993; Grossman et al., 2003). In surgical patients, an inverse correlation between pre-operative anxiety and perioperative cortisol secretion has been detected, while the effects of such neuroendocrine changes on post-operative pain remain unclear (Salmon et al., 1986, 1989; Pearson et al., 2005).

In general, the HPA axis increases the release of glucocorticoids in response to surgical stress (a 'fight or flight' reaction) (Naito et al., 1992; Udelsman and Holbrook, 1994). Glucocorticoids are known to exert strong anti-inflammatory effects (Stahn and Buttgereit, 2008) and to inhibit the release of prostaglandins via the arachidonic acid pathway, and hence, play a role in the regulation of pain perception (Flower and Blackwell, 1979). The inhibition of HPA axis function has also been shown to attenuate stress-induced analgesia (Butler and Finn, 2009). Hence, low cortisol secretion during the perioperative period could augment acute post-operative pain.

In addition, dysregulation of the HPA axis has been observed in some chronic pain conditions, suggesting that HPA axis dysfunction might also be associated with persistent pain (Crofford et al., 1994; Lentjes et al., 1997; Cutolo et al., 2002; Eijsbouts et al., 2005). A recent study showed that reduced cortisol secretion promotes the post-operative secretion of pro-inflammatory cytokines, resulting in prolonged post-operative pain (Geiss et al., 2005).

These findings have led to us to hypothesize that pre-operative psychological distress might be associated with low cortisol secretion caused by HPA axis dysfunction, which could have implications for the acute and chronic post-operative pain.

Accordingly, the objective of the present prospective study was to investigate (1) the associations of demographic, clinical, psychological and neuroendocrine variables with acute and chronic post-operative pain following partial mastectomy; and (2) the associations between pre-operative psychological distress and perioperative cortisol levels.

2. Methods

This study was approved by the institutional ethics committee of Keio University School of Medicine (authorization number: 2011-279), and written informed consent was obtained from all subjects.

2.1 Study subjects

We enrolled female patients who were aged more than 20 years, had been diagnosed with stage 0–2 breast cancer, and were scheduled to undergo partial mastectomy combined with a sentinel lymph node biopsy at Keio University Hospital. Patients who were scheduled to undergo total mastectomy, bilateral total/partial mastectomy, axillary lymph node dissection, repeated surgery, or pre-operative chemo/radiotherapy; that were diagnosed with recurrent breast cancer; or who had received hormonal or steroid therapy within the past 6 months were excluded. Patients with chronic pain, Cushing's syndrome, or cognitive disorders were also excluded. From October 2012 to March 2015, 74 patients (age range: 35–80) met the study criteria. Six patients declined the invitation to participate in this study. In addition, one patient was excluded before surgery because the pre-operative urine collection procedure was not completed, and three were excluded because they underwent additional axillary lymph node dissection after a rapid intraoperative pathological examination. Therefore, acute post-operative pain was analysed in a total of 64 patients. Among them, six patients were excluded because they did not complete the 6-month post-operative follow-up period, and 1 was withdrawn because she underwent another surgical procedure during the follow-up period. Thus, 57 subjects completed the 6-month questionnaires, and chronic post-operative pain was analysed in these patients. In the last 32 subjects, who were enrolled between April 2014 and March 2015, post-operative 24-h urinary cortisol measurements were obtained to analyse the correlations among pre-operative anxiety, acute post-operative pain, and post-operative urinary cortisol levels. Among them, three patients were excluded because they underwent additional axillary lymph node dissection. Thus, the correlations between these variables were analysed in 29 subjects.

2.2 Diagnosis and treatment

The patients' breast cancer was diagnosed and staged (according to the TNM classification) based on mammography, ultrasonography, and magnetic resonance

imaging. The types of surgery and post-operative chemotherapy and/or radiotherapy performed were chosen according to the attending physicians' discretion in agreement with the patients. All surgical procedures were carried out by three experienced surgeons under general anaesthesia. Anaesthesia was induced with 2 mg/kg propofol, 1 μg/kg fentanyl, and 0.6 mg/kg rocuronium and maintained with sevoflurane (1.5–2.5%) and a continuous infusion of remifentanil (0.1–0.3 μg/kg/h). All of the patients received an intravenous dose of 1 μg/kg fentanyl approximately 30 min before the end of the procedure. For post-operative pain, flurbiprofen (60 mg, maximum frequency: every 6 h) and/or acetaminophen (1000 mg, maximum frequency: every 6 h) was administered intravenously to patients that requested analgesics.

2.3 Pre-operative psychological assessment

All of the patients were admitted to the hospital in the morning 2 days before surgery. On the day of admission, anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) (de Bock et al., 2004; Schlich-Bakker et al., 2006), which consists of 14 items on a self-reporting scale running from 0 to 3. Seven items are related to anxiety (HADS-A), and the others are related to depression (HADS-D). The possible scores for both the HADS-A and HADS-D range from 0 to 21, and higher scores indicate more severe anxiety or depression.

2.4 Neuroendocrine measurements

2.4.1 Pre-operative 24-h urinary cortisol measurements

Between 1 and 6 p.m. on the day of admission, the subjects started to collect their urine in a collecting bottle, and they continued to do so for 24 h. Immediately after the last sample was collected, the nurse in charge of the subject recorded the total volume of urine, and a 5-mL aliquot was collected in a sample tube, which was subsequently stored at 4 °C until the assay. The patients' urinary-free cortisol levels were measured, using a radioimmunoassay technique at the laboratory of SRL Corporation (Tokyo, Japan).

2.4.2 Post-operative 24-h urinary cortisol level measurements

Before entering the operating room, the patients were instructed to void urine. After the induction of anaesthesia, a urinary catheter was inserted and left in place for 24 h. Each patient's urine was collected in a collecting bag, and the total urinary volume was measured. A 5-mL aliquot was obtained for the subsequent assay, as described above.

2.5 Post-operative pain assessment

2.5.1 Acute pain

The patients were asked to rate their pain by marking the point on a 100-mm visual analog scale (VAS; 0 mm: no pain, 100 mm: the worst pain imaginable) that best described their average pain in the past 6 h. They were asked to do this at 6, 24, 36, 48, and 60 h after surgery. A cut-off value of 40 mm was used to define moderate to severe acute post-operative pain. (Gerbershagen et al., 2011) Moderate to severe acute pain was considered to be present when the maximum VAS score recorded at the 5 time points was ≥40 mm.

2.5.2 Chronic pain

The short-form McGill Pain Questionnaire (SF-MPQ) was used to assess chronic post-operative pain. The SF-MPQ consists of a pain rating index (PRI), a VAS, and an assessment of present pain intensity (PPI). The PRI includes 11 sensory descriptors and 4 affective descriptors. Each descriptor is rated on a scale of 0–3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe), and the total score is calculated as the sum of the scores for the 15 descriptors. PPI is ranked from 0 to 5 (0 = no pain, 1 = mild, 2 = discomforting, 3 = distressing, 4 = horrible, and 5 = excruciating) (Melzack, 1987). The questionnaires (SF-MPQ and HADS) were sent to the patients by mail at 3 and 6 post-operative months together with a cover letter asking the patients to rate the pain they were experiencing within and around the surgical field. After the questionnaires had been completed, they were returned in pre-paid envelopes. A cut-off VAS score of 30 mm was used to determine clinically significant chronic post-operative pain (Belfer et al., 2013). Chronic post-operative pain was considered to be present when the VAS score of the SF-MPQ was ≥30 mm at both 3 and 6 post-operative months.

2.6 Statistical analyses

The normality of the variables was assessed using the Shapiro–Wilk test. Using the data for all subjects, age, body mass index, the pre-operative 24-h urinary cortisol level, and the HADS score were compared

between the patients with and without moderate to severe acute post-operative pain or chronic post-operative pain using the unpaired Student's *t*-test (or the Wilcoxon rank sum test for variables that were not normally distributed). The significance of the differences in marital status, acute pain, post-operative chemotherapy, and post-operative radiotherapy between the groups was assessed, using Fisher's exact test. The significance of the differences in the TNM classification between the groups was evaluated using the Cochran–Armitage test. Multivariate logistic regression analyses were performed to identify risk factors for acute and chronic post-operative pain. Variables that revealed significant associations in the univariate analyses or that exhibited *p*-values of <0.2 in the stepwise forward selection procedure were included in the final multivariate logistic regression model. Since age and post-operative adjuvant therapy have been shown to influence the prevalence of chronic post-operative pain (Caumo et al., 2002; Gartner et al., 2009), these variables were included in the final model, regardless of their statistical significance. We estimated the sample size required for the multivariate logistic regression analyses based on the assumption that at least 10 observations are required for each of the included independent variables. As previous reports indicated that the incidence of moderate to severe acute post-operative pain after breast cancer surgery is about 50% (Katz et al., 2005) and the incidence of chronic post-operative pain after breast-conserving surgery ranges from 40% to 50% (Gartner et al., 2009; Edwards et al., 2013), we calculated that we would require 60–120 subjects to perform multivariate logistic regression analyses involving 3–6 variables appropriately. However, due to grant-related budget and time constraints, patient enrollment was stopped at the end of March 2015.

The correlations between the pre-operative HADS-A score, urinary cortisol levels, the maximum VAS score of acute pain recorded at the 5 time points in the 60 h after surgery, and the VAS score of SF-MPQ at 6 months after surgery were analysed using Spearman's correlation coefficient. All statistical analyses were performed, using JMP (version 10.0.2). *p*-values of <0.05 were considered statistically significant.

3. Results

Acute post-operative pain was analysed in 64 patients who underwent partial mastectomy without axillary lymph node dissection. The demographic and clinical data of the patients are summarized in Table 1. Post-operative chemotherapy was started at 1.6 ± 0.7 months (range: from 1 to 3 months) after surgery, and the regimens used included FEC (fluorouracil, epirubicin, and cyclophosphamide), PTX/HER (paclitaxel and trastuzumab), and TC (docetaxel and cyclophosphamide). Post-operative radiotherapy was started at 1.9 ± 1.6 months (range: from 1 to 5 months) after surgery, and a total dose of 50 Gy was administered.

Table 1 Patients' demographic and clinical characteristics (n = 64).

Age, yr (range)	60 ± 11 (35–80)
Age group, *n* (%)	
<35 years	0 (0)
35–39 years	3 (4.7)
40–49 years	11 (17.1)
50–59 years	14 (21.9)
60–69 years	24 (37.5)
≥70 years	12 (18.8)
Body mass index, kg/m^2	22.1 ± 2.9
Marital status, *n* (%)	
Married	49 (76.6)
Unmarried	15 (23.4)
TNM stage, *n* (%)	
0	13 (20.3)
1	45 (70.3)
2	6 (9.4)
Post-operative chemotherapy, *n* (%)	
Yes	14 (21.9)
No	50 (78.1)
Post-operative radiotherapy, *n* (%)	
Yes	51 (79.7)
No	13 (20.3)

Data are presented as mean ± standard deviation values or as the number of patients (percentage).

3.1 Effects of covariates on acute post-operative pain

Univariate analysis showed that the patients with moderate to severe acute post-operative pain exhibited higher pre-operative HADS-A scores and lower pre- and post-operative 24-h urinary cortisol levels than those with no to mild acute pain (Table 2). No differences in age, body mass index, marital status, TNM stage, or the pre-operative HADS-D score were observed between the groups.

Based on the information from the univariate analyses and the stepwise forward selection procedure, age, TNM stage, the pre-operative 24-h urinary cortisol level, and the HADS-A score were included in the final multivariate logistic regression model (Table 3). Among them, a lower pre-operative 24-h urinary cortisol level and a higher HADS-A score

Table 2 Univariate analysis of acute post-operative pain.

	No-mild acute pain (n = 33)	Moderate-severe acute pain (n = 31)	p-Value
Demographics factors			
Age (years)[a]	60.5 ± 10.5	58.1 ± 12.0	0.27
BMI (kg/m^2)[a]	21.9 ± 2.8	22.2 ± 2.6	0.71
Married (yes/no)[b]	23/10	26/5	0.23
TNM stage (stage 0/1/2, n)[c]	8/20/5	5/25/1	0.77
Pre-operative endocrine and psychosocial factors			
Pre-operative 24-h urinary cortisol (μg/day)[a]	47.1 ± 19.4	36.2 ± 15.4	0.02
HADS-A[d]	4.5 ± 3.1	6.5 ± 4.0	0.03
HADS-D[d]	3.3 ± 2.8	4.9 ± 3.8	0.12
Post-operative pain			
The maximum VAS score in the 60 h after surgery	18.9 ± 11.9	67.2 ± 16.2	<0.0001
	No-mild acute pain (n = 13)	Moderate-severe acute pain (n = 16)	p-Value
Post-operative 24-h urinary cortisol (μg/day)[d]	388 ± 288	155 ± 174	0.02

BMI, body mass index; HADS-A, hospital anxiety and depression scale-anxiety; HADS-D, hospital anxiety and depression scale-depression.

Data are presented as mean ± standard deviation values or as the number of patients.

[a]Student's t-test.

[b]Fisher's exact test.

[c]Cochran–Armitage test.

[d]Wilcoxon's rank test.

Table 3 Multivariate logistic regression analysis of predictors of moderate to severe acute post-operative pain (n = 64).

	Coefficient	Standard error	p-Value	OR (95% CI)
Age	−0.03	0.03	0.27	0.96 (0.91, 1.02)
TNM stage				
Stage 0				1 (Reference)
Stage 1	0.93	0.51	0.07	2.41 (0.60, 10.6)
Stage 2	−0.98	0.82	0.24	0.35 (0.02, 4.28)
Pre-operative 24-h urinary cortisol	−0.04	0.02	0.02	0.96 (0.92, 0.98)
Pre-operative HADS-A	0.22	0.09	0.03	1.24 (1.04, 1.54)

HADS-A, hospital anxiety and depression scale-anxiety; CI, confidence interval; OR, odds ratio.

The odd ratios for continuous variables correspond to a one-unit increase in the variable.

were found to be independently associated with an increased risk of moderate to severe acute post-operative pain.

3.2 Correlations among pre-operative anxiety, urinary cortisol levels, and acute/chronic post-operative pain

The pre-operative HADS-A score exhibited an inverse correlation with the post-operative 24-h urinary cortisol level, while it was not significantly correlated with the pre-operative urinary cortisol level. The post-operative 24-h urinary cortisol level as well as the pre-operative urinary cortisol level exhibited significant inverse correlations with the intensity of acute pain (Fig. 1), while these cortisol levels were not significantly associated with the intensity of chronic post-operative pain at 6 months (correlation coefficients with pre-, and with post-operative cortisol level; $r = 0.11$, $p = 0.39$, and $r = -0.15$, $p = 0.51$). There was no significant correlation between the pre- and post-operative urinary cortisol ($r = 0.32$, $p = 0.09$).

3.3 Effects of covariates on chronic post-operative pain

Of the 57 patients who were followed-up, 23 (40.3%) reported suffering from chronic post-operative pain at 6 post-operative months. Univariate analysis showed that the patients with chronic post-operative pain displayed higher HADS-A and HADS-D scores at the pre-operative assessment than those without chronic post-operative pain. In addition, these patients were more likely to report moderate to severe acute post-operative pain (Table 4). Age, TNM stage, body mass index, marital status, the pre- and post-operative 24-h urinary cortisol levels, and the use of post-operative chemotherapy or radiotherapy did not differ between the patients with and without chronic post-operative pain.

Based on the information from the univariate analyses and the stepwise forward selection procedure, age, the pre-operative HADS-A score, the presence of moderate to severe acute post-operative pain, post-operative chemotherapy, and radiotherapy were included in the final multivariate logistic regression model (Table 5). The pre-operative HADS-D score was not included in the final model because it did not contribute to it. As a result, higher pre-operative HADS-A scores and the presence of moderate to severe acute post-operative pain were found to be independently associated with an increased risk of chronic post-operative pain.

4. Discussion

This study showed that greater pre-operative anxiety and lower perioperative urinary cortisol levels are

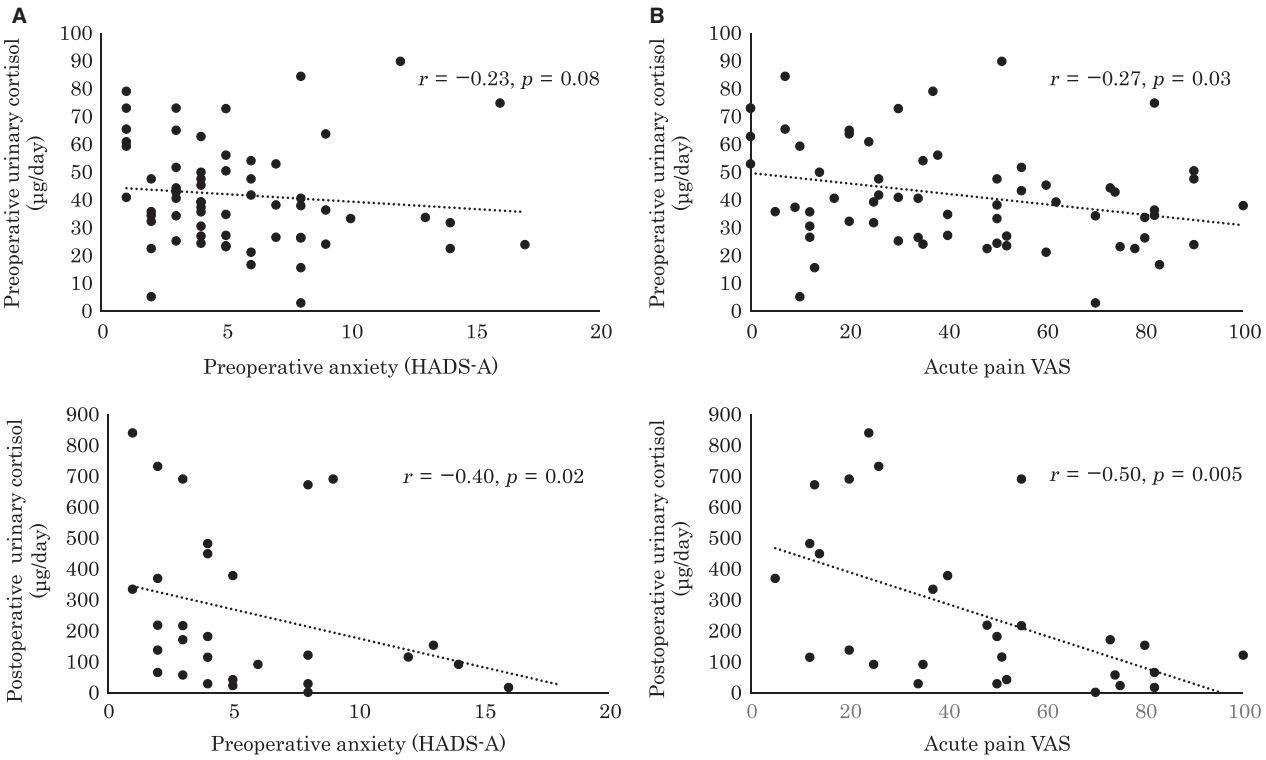

Figure 1 Correlations between preoperative anxiety or acute post-operative pain and perioperative urinary cortisol levels. (A) Correlations between pre-operative anxiety and pre/post-operative urinary cortisol levels. (B) Correlations between the maximum acute pain VAS and pre/post-operative urinary cortisol levels. Pre-operative anxiety had an inverse correlation with post-operative urinary cortisol levels but not with pre-operative urinary cortisol levels. Acute pain VAS had inverse correlations with both pre- and post-operative urinary cortisol levels. HADS-A, hospital anxiety and depression scale-anxiety; VAS, visual analog scale.

associated with greater acute pain, and that pre-operative anxiety exhibits a significant inverse correlation with post-operative urinary cortisol levels, but not with pre-operative urinary cortisol levels. It also demonstrated that greater pre-operative anxiety and worse acute post-operative pain are associated with an increased incidence of chronic post-operative pain after partial mastectomy.

4.1 Relationships between pre-operative anxiety and acute post-operative pain

Previous studies have shown that more invasive surgery, axillary lymph node resection, and adjuvant therapy are all significantly associated with greater post-operative pain (Gartner et al., 2009; Kaunisto et al., 2013). These factors might increase the risk of nerve damage, which is considered to be the main cause of increased post-operative pain (Jung et al., 2003). Therefore, in this study, to obviate these confounding factors and to simplify the interpretation of the data, only the effects of surgical stress associated with partial mastectomy were examined; that is, cases involving pre-operative adjuvant therapy and/or axillary lymph node resection were excluded. Under these conditions, our multivariate analysis showed that pre-operative anxiety, as evaluated, using the HADS, is one of the factors that can be used to predict the severity of acute post-operative pain.

As partial mastectomy without axillary lymph node dissection carries a lower risk of intercostobrachial nerve damage, which can cause post-operative neuropathic pain, acute post-operative pain might be mainly caused by tissue inflammation or minor peripheral nerve damage at the surgical site. Previous reports have shown that anxiety is associated with greater pain sensitivity to experimental heat and cold stimuli in the absence of nerve damage (Thompson et al., 2008; Kaunisto et al., 2013), suggesting that pre-operative anxiety could sensitize patients to noxious stimuli and augment acute post-operative pain. However, in order to detect causal relationships future research should examine whether psychological interventions that reduce pre-operative anxiety can attenuate acute post-operative pain.

Table 4 Univariate analysis of predictors of chronic post-operative pain at 6 post-operative months.

	No chronic pain (n = 34)	Chronic pain (n = 23)	p-Value
Demographic factors			
Age (years)[a]	59.4 ± 10.6	58.4 ± 11.6	0.78
BMI (kg/m^2)[a]	22.1 ± 2.6	22.2 ± 3.0	0.98
Married (yes/no, n)[b]	27/7	17/6	0.75
TNM stage (0/1/2, n)[c]	8/23/3	4/17/2	0.67
Pre-operative endocrine and psychological factors			
Pre-operative 24-h urinary cortisol (μg/day)[a]	43.5 ± 19.8	42.3 ± 18.5	0.98
HADS-A[d]	4.0 ± 2.2	7.9 ± 4.2	0.0002
HADS-D[d]	3.3 ± 2.8	5.4 ± 4.0	0.04
Post-operative factors			
Acute pain (none-mild/ moderate-severe, n)[b]	22/12	6/17	0.006
Chemotherapy (yes/no, n)[b]	9/25	5/18	0.76
Radiotherapy (yes/no, n)[b]	26/8	19/4	0.74

	No chronic pain (n = 15)	Chronic pain (n = 10)	p-Value
Post-operative 24-h urinary cortisol (μg/day)[d]	298 ± 264	181 ± 203	0.19

BMI, body mass index; HADS-A, hospital anxiety and depression scale-anxiety; HADS-D, hospital anxiety and depression scale-depression.
[a]Student's t-test.
[b]Fisher's exact test.
[c]Cochran–Armitage test.
[d]Wilcoxon's rank test.

Table 5 Multivariate logistic regression analysis of predictors of chronic post-operative pain (n = 57).

	Coefficient	Standard error	p-Value	OR (95% CI)
Age	−0.01	0.03	0.69	0.98 (0.92–1.10)
Pre-operative HADS-A	0.48	0.17	0.004	1.63 (1.23, 2.40)
Moderate-severe acute pain	0.81	0.36	0.03	5.07 (1.30, 24.6)
Post-operative chemotherapy	0.02	0.49	0.98	1.03 (0.14, 7.40)
Post-operative radiotherapy	0.49	0.52	0.35	2.67 (0.37, 25.5)

HADS-A, hospital anxiety and depression scale-anxiety; CI, confidence interval; OR, odds ratio.
Odds ratios are adjusted for the other variables included in the model. The odd ratios for age and HADS-A correspond to a one-unit increase in the variable.

4.2 Relationships between perioperative cortisol secretion and acute post-operative pain

Few previous reports have examined the relationship between perioperative neuroendocrine changes and the severity of post-operative pain. Our multivariate analysis showed that lower pre-operative urinary cortisol levels are also independent predictors of acute pain severity. Furthermore, we detected an inverse relationship between the VAS score for acute pain and the post-operative urinary cortisol level.

Acute noxious stimuli, such as surgical stress, stimulate the HPA axis to enhance the synthesis and release of glucocorticoids (Udelsman and Holbrook, 1994). Among the various glucocorticoid responses to such stimuli, the suppression of the production of proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumour necrosis factor-α (Rhen and Cidlowski, 2005), and the inhibition of prostaglandin synthesis have been described in the literature (Flower and Blackwell, 1979; O'Banion et al., 1992). In addition, the HPA axis plays an important role in the expression of stress-induced analgesia (Finn et al., 2006). Furthermore, recent studies have suggested that glucocorticoids induce endocannabinoid synthesis as a rapid response to stress (Hill and McEwen, 2009), which might be involved in the modulation of acute pain. Thus, one possible explanation for our findings is that lower cortisol secretion during the perioperative period has an adverse influence on acute post-operative pain by blunting the anti-inflammatory and antinociceptive responses to surgical stress. Future studies should examine the effects of lower perioperative cortisol secretion on biomarkers of inflammatory and/or nociceptive responses.

4.3 Relationships between pre-operative anxiety and perioperative cortisol secretion

The HADS-anxiety typically assesses the generalized symptoms of anxiety and fear experienced by the subject in the past week (Julian, 2011). Therefore, HADS-based pre-operative evaluations of anxiety performed 2 days before surgery might reflect a patient's current fears about their upcoming surgery. Assuming that these measures reflect transient fear about the upcoming surgery, higher HADS scores would be expected to be associated with increased cortisol secretion due to acute activation of the HPA axis (Bosch et al., 2009). However, in this study greater pre-operative anxiety was found to be associated with lower post-operative cortisol secretion. The subjects of this study underwent surgery at least a few weeks after they were initially diagnosed with cancer. Acute psychological stress, such as that caused by being diagnosed with cancer, could

initially activate the HPA axis (Seok et al., 2010). Although the effects of prolonged exposure to psychological stress on HPA axis function have yet to be fully elucidated, it seems plausible that prolonged psychological distress, such as anxiety/depression caused by being diagnosed with cancer, might eventually reduce the release of glucocorticoids due to the effects of negative feedback on the regulation of the HPA axis. However, as we did not perform HADS assessments immediately after the diagnosis of cancer or at other time points during the pre-operative period, it remains unknown whether patients awaiting breast surgery experience prolonged anxiety/fear about their cancer diagnosis. Furthermore, assuming that psychological distress decreases cortisol secretion, the question as to why the data did not show a significant relationship between pre-operative anxiety and pre-operative cortisol secretion remains. This might be explained in part by the fact that the impaired cortisol secretion associated with anxiety might be unmasked after extraordinary stress (i.e. surgical stress) rather than in relatively calm conditions (i.e. 2 days before surgery). Further studies in which psychological assessments and cortisol measurements are performed at different time points are required to clarify the longitudinal changes in pre-operative anxiety and its relationship with perioperative cortisol secretion.

4.4 Chronic post-operative pain

Chronic post-operative pain; that is, pain that lasts for more than 3 months after surgery, is reported to occur after 20–50% of surgical procedures for breast cancer (Jung et al., 2003; Gartner et al., 2009). Although the prevalence of such pain might differ according to the type of surgery, the time after surgery, and the definition of chronic pain (i.e. whether it was defined as any pain or just severe pain), it should be noted that, even after breast-conserving surgery without axillary lymph node dissection, persistent pain occurs in close to 50% of cases (Gartner et al., 2009; Edwards et al., 2013). As this study showed, pre-operative psychological distress seems to be a consistent risk factor for chronic post-operative pain (Thorvaldsen and Sorensen, 1990; Peters et al., 2007). Previous studies have indicated that HPA axis dysfunction is involved in susceptibility to chronic pain (Crofford et al., 1994; Lentjes et al., 1997; Cutolo et al., 2002; Eijsbouts et al., 2005), suggesting that HPA axis dysfunction is one possible mechanism through which pre-operative psychological distress influences the development of chronic post-operative pain. However, contrary to our expectations, pre-operative cortisol secretion was not associated with the prevalence of chronic pain in the multivariate analysis. Moreover, no direct relationship was detected between post-operative cortisol secretion and chronic post-operative pain. This might be explained as follows: First, the limbic region of the brain, which is involved in processing emotion and stress, has functional connections with various other brain regions, including the somatosensory region, periaqueductal grey, and rostral ventromedial medulla, which modulate pain circuits (Tracey, 2008; Bolwerk et al., 2013). Pre-operative psychological stress could alter these functional connections and influence the development of chronic post-operative pain, regardless of HPA activity. Secondly, cortisol levels were not measured after the perioperative period in this study. The HADS scores obtained at 3 and 6 months after surgery both exhibited positive associations with the pre-operative HADS score ($r = 0.68$ and 0.38, respectively), indicating that pre-operative anxiety and/or depression tend to continue until at least 6 months after surgery. Such prolonged psychological distress could lead to more profound HPA axis dysfunction, resulting in the development of chronic post-operative pain. Further studies are required to obtain sequential measurements of neuroendocrine changes and to clarify the association between HPA axis function with chronic post-operative pain.

Our multivariate analysis showed that acute post-operative pain is another predictor of chronic pain, which is consistent with the findings of a recent large prospective study (Andersen et al., 2015). Greater acute pain per se might evoke long-lasting central sensitization, which could lead to the development of chronic post-operative pain (Bennett, 2000; Voscopoulos and Lema, 2010).

4.5 Limitations

This study had several limitations. First, the small sample size of this study limited its statistical power to assess the predictive value of each of the examined factors. Therefore, we do not have sufficient evidence to conclude that perioperative cortisol levels are associated with chronic pain. Moreover, it might also explain the lack of an association between pre-operative anxiety and pre-operative cortisol levels. Further studies with larger sample sizes are required. However, as little research has been conducted on the associations between psychological stress/HPA axis function and post-operative pain, our results provide information about the

possible implications of perioperative cortisol secretion on the link between pre-operative psychological distress and post-operative pain. Second, we decided to measure post-operative urinary cortisol levels from April 2014 onwards because we considered that obtaining cortisol measurements at different time points would be more useful for evaluating psychological distress-related neuroendocrine changes. However, post-operative measurements were not obtained in all subjects. Finally, our study population was entirely limited to Japanese women; therefore, it might be necessary to examine whether our findings are applicable to different ethnic groups.

5. Conclusions

This study confirms that pre-operative anxiety is associated with both acute and chronic post-operative pain after partial mastectomy. It also suggests that low perioperative cortisol secretion might be related to acute post-operative pain, whereas so far there is no sufficient evidence that it influences chronic post-operative pain. Furthermore, this study indicates that pre-operative anxiety is associated with reduced cortisol secretion after surgery, but not before surgery. Additional studies should be conducted to clarify the relationships among pre-operative psychological distress, HPA axis function, and acute/chronic post-operative pain.

Author contributions

D.N. contributed to data acquisition, analysis, and interpretation; S.K. contributed to data analysis and interpretation, the drafting and revising of the article; Y.O.: contributed to study conception and design and the data analysis and interpretation; N.I. contributed to data acquisition, analysis, and interpretation; K.W., H.N., T.Y, and T.S.; contributed to data collection and final approval of the version to be published; S.H. contributed to study conception and design, H.M. contributed to data interpretation and approval of the article. All authors discussed the results and commented on the manuscript.

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