Anesth Pain Med. 2018 August; 8(4):e79331. doi: 10.5812/aapm.79331.

Published online 2018 August 7. **Research Article**

C-reactive Protein Level on Postoperative Day One is Associated with Chronic Postsurgical Pain After Mastectomy

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Received 2018 May 19; **Revised** 2018 June 21; **Accepted** 2018 August 03.

Abstract

Background: C-reactive protein (CRP) is an acute phase reactant released in response to inflammation or tissue injury. Inflammation is one of the pathogenic factors related to transition from acute postsurgical pain (APSP) to chronic postsurgical pain (CPSP). Although several risk factors are reportedly associated with CPSP, the effects of CRP levels on CPSP have not been examined.
Objectives: The present study investigated the relationship between perioperative risk factors, including CRP levels on postoperative day one and CPSP, in patients undergoing mastectomy.
Methods: Preoperative anxiety and depression levels were evaluated in female patients undergoing mastectomy under general anesthesia, with or without peripheral nerve block. Patients with chronic preoperative pain and/or preoperative breast pain were excluded. The intensity of postoperative pain was prospectively examined one and six days, and three and twelve months after surgery using a numerical rating scale (NRS).
Results: The current researchers conducted univariate and multivariate linear regression analyses to explore risk factors for CPSP in 36 patients. Patient demographics, preoperative psychological states, and anesthetic managements showed no relationship with CPSP. On the other hand, pain intensity of APSP and CRP levels on postoperative day one was significantly associated with the pain intensity of CPSP.
Conclusions: Postoperative CRP level is likely to be associated with the development of CPSP after mastectomy.

Keywords: Breast Cancer, Chronic Pain, Mastectomy, Postoperative Pain

1. Background

Chronic postsurgical pain (CPSP) is an important clinical problem in breast cancer treatment (1). Persistence of CPSP for at least three months after breast surgery is a personal and social problem among breast cancer survivors (2-7). Several perioperative risk factors, including patient demographics, preoperative psychological states, preoperative chronic pain, acute postsurgical severe pain (APSP), anesthetic management, and genetic predisposition, are known to be associated with CPSP (8).

Inflammation is also a potential risk factor for the transformation of APSP to CPSP (9). Surgical incision induces inflammation, which activates pro-nociceptive systems causing APSP, followed by activation of the anti-nociceptive systems suppressing APSP. Disequilibrium of these systems can cause CPSP (10). C-reactive protein (CRP) is an acute phase reactant produced in response to inflammation or tissue damage. Although higher levels of CRP were reportedly associated with higher APSP (11, 12), the relationship between CRP levels and the development of CPSP have not been studied. Here, the researchers investigated the association between perioperative risk factors, including early postoperative CRP levels and CPSP in patients undergoing mastectomy.

2. Methods

This prospective cohort study was approved by the Ethics Committee of Hyogo College of Medicine.

2.1. Population

All female Japanese patients with breast cancer scheduled for breast surgery at Hyogo College of Medicine Hospital from March 2014 to November 2014 were assessed for eligibility. Written informed consent was obtained from

all participants, who met the following criteria: Age of over 20 years, American Society of Anesthesiologists (ASA) physical status I–II, and scheduled to undergo elective mastectomy with or without axillary lymph node dissection and/or sentinel lymph node biopsy. Exclusion criteria included chronic preoperative pain (e.g., chronic lower back pain and chronic headache), preoperative pain in the area to be operated, previous breast surgery, contraindications to peripheral nerve block, allergic responses to local anesthetics, presence of a psychiatric or neurological disorder, liver or renal dysfunction, preoperative radiation therapy, and preoperative chemotherapy.

2.2. Perioperative Management

The patients did not receive premedication. Intravenous dexamethasone at 3.3 mg was routinely injected for prevention of postoperative nausea and vomiting before induction of anesthesia. General anesthesia was induced with 1 to 2 $mg.kg^{-1}$ of propofol and 2 $\mu g.kg^{-1}$ of fentanyl, with or without 0.6 to 0.9 $mg.kg^{-1}$ of rocuronium for prevention of laryngospasm, followed by insertion of a supraglottic airway (LMA ProSealTM, Teleflex Medical Europe Ltd., Ireland), and was maintained with 0.7 minimum alveolar concentration of sevoflurane, fentanyl, and a continuous infusion of 0.05 to 0.3 $\mu g.kg^{-1}.min^{-1}$ of remifentanil.

In patients, who were preoperatively selected for receiving peripheral nerve block by an anesthesiologist, the same anesthesiologist performed pectoral nerve block type I block with serratus plane block using 10 and 20 mL of 0.25% levobupivacaine, respectively, before skin incision, to minimize technical differences regarding the effect of the nerve block (13, 14).

The dose of remifentanil was adjusted to maintain mean blood pressure within a range of $\pm$ 20% of the pre-anesthesia level. Intraoperatively, bispectral index was maintained between 40 and 60, by adjusting the concentration of sevoflurane administered. Intravenous fentanyl was administered up to a total dose of 4 to 5 $\mu g.kg^{-1}$, during general anesthesia. Rocuronium bromide was used for muscle relaxation during surgery, as needed.

After surgery, loxoprofen 180 $mg.day^{-1}$ per oral (p.o.) with or without acetaminophen 700 $mg.day^{-1}$, intravenously, or 900 $mg.day^{-1}$ p.o. was routinely administered until postoperative day five. A 25-mg diclofenac suppository was used for rescue analgesia.

2.3. Assessments

The same investigator, who performed the general anesthesia, interviewed all the patients to avoid interviewer bias. Preoperative anxiety levels were assessed using the state trait anxiety inventory 1 (STAI-1), and the preoperative depression level was assessed using the self rating questionnaire for depression (SRQ-D), during the preoperative consultation.

Postoperative pain was evaluated using a 0- to 10-point numerical rating scale (NRS) (15) both at rest and during shoulder movement on postoperative days one and six, and three and twelve months after surgery. A value of 0 represented 'no pain' and a value of 10 indicated 'worst imaginable pain'. At three and twelve months after surgery, patients were interviewed by telephone regarding the occurrence and the intensity of CPSP, which was defined using the definition of persistent post-surgical pain i.e. development of postoperative pain three and twelve months after surgery, which was localized around the surgical field without infection or recurring malignancy (16).

The patients' serum concentration of c-reactive protein (CRP) before and one day after surgery were obtained from institutional medical records. The normal range for CRP was below 0.3 $mg.dL^{-1}$ at the institute of the current study.

2.4. Statistical Analysis

All statistical testing was two-sided with a significance level of 5%, and was performed using IBM SPSS Statistics 24 (Chicago, IL, USA). All values are reported as mean $\pm$ SD or median [25 to 75 percentile]. Associations between NRS scores and risk factors for CPSP were assessed using univariate and stepwise multivariate linear regression. Variables that were significant at $P < 0.2$ in univariate analyses were entered using a stepwise method in the multivariate analysis, where variables were significant at $P < 0.05$.

3. Results

Of the 38 patients, who were assessed for eligibility and consented to participate in this study, two patients in the control group were excluded because they did not undergo surgery. Hence, a total of 36 patients were enrolled in this study (Tables 1 and 2).

Table 3 shows the incidence of APSP and CPSP at rest and during shoulder movement. The incidence of CPSP was 25%, three months after surgery and 8.3%, 12 months after surgery (Table 3). However, there were no cases of moderate to severe CPSP (NRS score $\geq$ 4) in the present study (Table 3).

This research performed univariate and multivariate analysis to explore risk factors for CPSP. Univariate analysis was performed using factors of age, BMI, STAI-1, SRQ-D, duration of surgery, axillary lymph node dissection, remifentanil dose, peripheral nerve block, postoperative

Table 1. Patient Demographics[a]

Patient Demographics	Values
Age (y)	55.2 ± 11.6
BMI (kg·m^{-2})	21.7 ± 3.3
ASA physical status (I/II)	8/28
STAI-1	41.0 [33.8 - 45.0]
SRQ-D	16.0 [12.0 - 19.3]

Abbreviations: BMI, body mass index; SRQ-D, self-rating questionnaire for depression; STAI, state trait anxiety index.
[a] Data are expressed as mean ± SD or median [25 - 75 percentile].

Table 2. Perioperative Variables[a]

Variables	Values
Intraoperative variables	
Duration of surgery (min)	149.3 ± 49.7
Duration of anesthesia (min)	214.1 ± 51.0
Axillary lymph node dissection (yes/no)	10/26
Mean continuous dose of remifentanil (μg.kg^{-1}.min^{-1})	0.14 ± 0.04
Total dose of fentanyl (μg.kg^{-1})	4.5 ± 0.9
Peripheral nerve block (yes/no)	19/17
Total urine volume (mL)	192.4 ± 137.5
Total blood loss (mL)	40.9 ± 52.7
Mean BIS	48.3 ± 8.3
Mean rectal temperature (°C)	36.9 ± 0.4
CRP concentration	
Preoperative CRP concentration (mg.dL^{-1})	0.06 ± 0.07
CRP concentration 1 day after surgery (mg.dL^{-1})	0.55 ± 0.57
Radiotherapy/chemotherapy	
Postoperative radiotherapy/chemotherapy (%)	36.1/41.7

Abbreviations: BIS, bispectral index; CRP, C-reactive protein.
[a] Data are expressed as mean ± SD.

CRP concentration, NRS scores for APSP and CPSP, postoperative radiotherapy, and chemotherapy (Table 4). Univariate analysis indicated that body mass index (BMI), duration of surgery, remifentanil dose, peripheral nerve block, postoperative CRP concentration, NRS scores of APSP, and postoperative chemotherapy were selected, and then entered in stepwise multivariate analyses. Multivariate analyses showed that increase in serum CRP concentrations on postoperative day one was significantly associated with NRS scores, three months after surgery during movement, and also 12 months after surgery at rest (Table 5). The NRS score at rest six days after surgery was significantly associated with NRS scores at rest, three months after surgery. Peripheral nerve block was also significantly associated with

Table 3. Incidence of Mild and Moderate to Severe Intensity Post-Mastectomy Pain[a,b]

	Mild Pain	Moderate to Severe Pain
POD 1		
At rest	16 (44.4)	9 (25.0)
During movement	20 (55.6)	12 (33.3)
POD 6		
At rest	12 (33.3)	1 (2.8)
During movement	14 (38.9)	3 (8.3)
3 months after surgery		
At rest	5 (13.9)	0 (0.0)
During movement	9 (25.0)	0 (0.0)
12 months after surgery		
At rest	2 (5.6)	0 (0.0)
During movement	3 (8.3)	0 (0.0)

Abbreviations: POD, postoperative day.
[a] Mild pain = 1 - 3 on the numerical rating scale, moderate to severe pain = 4 - 10 on the numerical rating scale.
[b] Data are expressed as No. (%)

NRS scores during movement, three months after surgery (Table 5). None of the other factors were found to be significant by multivariate analyses.

4. Discussion

Both CRP concentrations on postoperative day one and the intensity of APSP correlated with the increase in pain intensity of CPSP in the present study. Serum concentrations of CRP after surgery, reflecting surgical trauma levels, including extent of surgery and differences in surgical technique, are reportedly associated with acute postoperative pain (11, 12). Given that the extent of surgical trauma plays a key role in the transformation of APSP to CPSP (9), early postoperative phase CRP levels were likely associated with the development of CPSP in the present study.

Several investigators have included persistence of only moderate to severe pain with a score of $\geq$ 4 on a 0- to 10-point NRS in the definition of CPSP after breast surgery (2, 3), and reported that CPSP occurs in 8% to 24% of females after breast cancer surgery (4-7). None of the patients in the current study, however, reported CPSP with an NRS score of $\geq$ 4 (Table 3). The risk factors for CPSP after mastectomy were young age, axillary lymph node dissection, preoperative chronic pain, preoperative breast pain, high BMI, radiotherapy, severe acute postoperative pain, and psychosocial factors (e.g., anxiety, depression, catastrophizing, and somatization) (5, 17-20). The authors believe that the possible reasons for the insignificant occurrence of moderate

Table 4. Univariate Linear Regression Analyses for Associations Between Numerical Rating Scale Scores and Potential Risk Factors for Chronic Post-Mastectomy Pain[a]

Variable	NRS Score 3 Months After Surgery				NRS Score 12 Months After Surgery			
	At Rest		During Movement		At Rest		During Movement	
	β	P	β	P	β	P	β	P
Age	-0.03	0.88	0.02	0.90	0.06	0.74	-0.06	0.75
BMI	0.03	0.87	0.17	0.32	0.28	0.13[b]	0.15	0.44
STAI-1	0.17	0.31	0.14	0.43	0.06	0.76	0.10	0.60
SRQ-D	0.01	0.97	0.03	0.85	-0.04	0.85	-0.03	0.89
Duration of surgery	0.27	0.12[b]	0.15	0.41	0.10	0.62	0.08	0.67
Axillary LN dissection	-0.14	0.42	-0.19	0.28	0.11	0.56	0.02	0.93
Remifentanil dose	-0.07	0.71	-0.12	0.50	-0.17	0.36	-0.25	0.18[b]
Peripheral nerve block	0.28	0.10[b]	0.36	0.04[b]	0.22	0.25	0.27	0.15[b]
Postoperative CRP concentration	0.22	0.20[b]	0.35	0.04[b]	0.44	0.01[b]	0.30	0.11[b]
POD1 NRS at rest	0.32	0.05[b]	0.35	0.03[b]	0.08	0.67	0.10	0.59
POD 1 NRS during movement	0.33	0.05[b]	0.39	0.02[b]	0.13	0.50	0.09	0.64
POD 6 NRS at rest	0.73	0.001[b]	0.54	0.001[b]	0.17	0.36	0.17	0.37
POD 6 NRS during movement	0.68	0.001[b]	0.55	0.001[b]	0.20	0.27	0.15	0.41
Postoperative radiotherapy	-0.13	0.46	0.01	0.94	-0.23	0.21	-0.07	0.72
Postoperative chemotherapy	0.25	0.15[b]	0.18	0.31	0.04	0.85	-0.07	0.72

Abbreviations: BMI, body mass index; CRP, C-reactive protein; LN, lymph node; NRS, numerical rating scale; POD, postoperative day; SRQ-D, self-rating questionnaire for depression; STAI, state trait anxiety index.
[a] Data are presented as standardized beta coefficient (β).
[b] $P < 0.2$ on univariate analysis.

Table 5. Stepwise Multivariate Linear Regression Analyses for the Association Between Numerical Rating Scale Scores and Selected Potential Risk Factors for Persistent Post-Mastectomy Pain[a]

Variable	NRS Score 3 Months After Surgery				NRS Score 12 Months After Surgery			
	At Rest		During Movement		At Rest		During Movement	
	β	P	β	P	β	P	β	P
BMI	-	-	-	-	-	0.33	-	-
Duration of surgery	-	0.24	-	-	-	-	-	-
Remifentanil dose	-	-	-	-	-	-	-	-
Peripheral nerve block	-	0.13	0.39	0.01[b]	-	-	-	-
Postoperative CRP concentration	-	0.09	0.50	0.01[b]	0.44	0.02[b]	-	-
POD1 NRS at rest	-	0.20	-	0.27	-	-	-	-
POD 1 NRS during movement	-	0.38	-	0.21	-	-	-	-
POD 6 NRS at rest	0.53	0.01[b]	-	0.18	-	-	-	-
POD 6 NRS during movement	-	0.46	-	0.10	-	-	-	-
Postoperative chemotherapy	-	0.08	-	-	-	-	-	-

Abbreviations: BMI, body mass index; CRP, C-reactive protein; NRS, numerical rating scale; POD, postoperative day.
[a] Data are presented as standardized beta coefficient (β).
[b] $P < 0.05$ for multivariate analysis.

to severe pain at three and twelve months after mastectomy in the present study were the absence of preoperative chronic pain and preoperative breast pain (17-19), and low patient BMI (17-19).

In a meta-analysis, perioperative systemic dexamethasone, 0.11 to 0.2 mg.kg^{-1}, was reported to reduce postoperative pain (21). On the other hand, perioperative systemic dexamethasone, 4 to 20 mg, was not related to the incidence and severity of CPSP in a cohort study (22). Although a relatively low dose of dexamethasone (3.3 mg) was injected intravenously before induction of anesthesia in the present study, its effects on the reduction of CPSP were unclear.

In conclusion, early postoperative CRP levels were associated with the intensity of CPSP after mastectomy.

Footnotes

Authors' Contribution: Dr. Hashimoto and Tsuji contributed equally to this work.

Funding/Support: This work was supported by a Grant-in-Aid for Scientific Research KAKENHI (#26462375) and MEXT-Supported Program for the Strategic Research Foundation at Private Universities (#S1411041).

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