

Acute postoperative pain predicts chronic pain and long-term analgesic requirements after breast surgery for cancer

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Abstract : Postoperative pain and analgesic requirements may be associated with chronic pain. The aim of the study was to investigate this association. We studied 98 patients who had cancer breast surgery and served as controls in four previous studies, receiving placebo. We compared the pain and analgesic requirements 0-9 h and 1-6 days postoperatively : a) between patients with chronic pain 3 months postoperatively versus patients without and b) between those patients who consumed analgesics at home versus those who did not. Patients with chronic pain had experienced higher intensity pain at rest the first 9 postoperative hours (VAS-rest $p = 0.033$). Patients requiring analgesics at home had consumed postoperatively more opioids ($p = 0.005$) and more paracetamol ($p = 0.037$). These patients had experienced pain of higher intensity the first 9 postoperative hours (VAS-rest $p = 0.022$, VAS-movement $p = 0.009$) as well as during the six postoperative days (VAS-rest $p = 0.013$, VAS-movement $p = 0.001$). Higher intensities of acute postoperative pain are associated with chronic pain development. Higher analgesic needs and higher acute postoperatively pain intensity are associated with long-term analgesic consumption.

Key words : Postoperative pain ; analgesic requirements ; chronic pain ; cancer breast surgery.

INTRODUCTION

Nowadays patients having surgery and other treatments for cancer in general and for breast cancer in particular live longer than in the past or even are cured. So adverse outcomes such as postsurgical chronic pain may affect the patient's quality of life.

Postoperative chronic pain after breast surgery for cancer presents as suffering due to pricking (needles and pins) sensation, burning or stabbing and involving the chest wound area and/or the ipsilateral axilla and arm, and may influence seriously patient's life. The pain has the characteristics of neuropathic pain and an impact on the professional and/or domestic activities of the patient.

Several studies as well as review papers that focus on the chronic pain as result of surgery also include postmastectomy pain (3, 8, 12, 13). The

incidence of chronic pain after cancer breast surgery between several studies varies considerably. MACDONALD *et al.* in a long-term outcome at 7-12 years after surgery reported that 52% of the women interviewed in 1996 continued to experience postmastectomy pain in 2002, while in the remaining 48% of this population symptoms were subsided (11).

Important risk factors predisposing to chronic pain after cancer breast surgery are patient characteristics (11), the type of operation (1), radiotherapy and/or chemotherapy (16), and inadequate pain treatment during the immediate postoperative period (16). In fact unrelieved or inadequately treated acute postoperative pain is considered as the major factor for persistent pain development after surgery (10, 13).

The aim of the present study was to investigate the impact of acute postoperative pain and of analgesics consumed during the immediate postoperative period on the presence of chronic pain and long-term need for analgesics 3 months after breast surgery for cancer.

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METHODS

After obtaining approval from the Local Ethics Committee we analyzed the data for acute and chronic postoperative pain obtained from patients served as controls in four previous randomized controlled double-blind trials, with a sample size determined by power analysis (studies A to D) (4-7). In these studies we investigated different modalities to treat acute postoperative pain after breast surgery for cancer aiming to prevent or attenuate the chronic postoperative pain.

Data Collection

Ninety-eight patients were recruited for data analysis having origin from the following studies :

Study A (4) : Twenty-three patients comprised the control group of study A. These patients received placebo cream around the wound area (mastectomy or lumpectomy plus ipsilateral axilla) versus the treatment group who received EMLA cream. Treatment with cream started the day of surgery and continued for another four days postoperatively. One of these patients developed allergy to the membrane (Tegaderm™) covering the cream, and the treatment was discontinued. Thus 22 patients were studied for acute and chronic postoperative pain.

Study B (5) : Twenty-five patients served as controls to receive placebo capsules twice per day, identical to mexiletine capsules consumed by the treatment groups of the study. Intraoperatively the brachial plexus and the fourth to sixth intercostal spaces were infiltrated with 12 and 6 mL of normal saline respectively. Treatment groups received ropivacaine 0.75% solution instead. One patient failed to complete the protocol as she could not swallow the capsules and another patient was not available for chronic follow up. Therefore, data for postoperative analgesic requirements and acute pain were collected from 24 patients and for chronic pain from 23 patients.

Study C (6) : Twenty-five patients received placebo capsules identical to mexiletine and gabapentin three times per day. One patient after being recruited decided to discontinue participation in the study. So the control group in study C included 24 patients for assessment of acute and chronic postoperative pain.

Study D (7) : Twenty-five patients were assigned to receive placebo capsules for gabapentin 6 hourly. The study protocol also included intraoperatively irrigation of the axilla and the third to

fifth intercostal spaces with 10 and 3 mL of normal saline respectively, as well placebo cream in the wound area from the day of surgery and the following three days. Two patients received by themselves postoperatively also NSAIDs and were eliminated from data analysis. For one patient contact was not possible three months postoperatively. Thus the control group in the study D included 23 patients for acute and 22 for chronic pain assessment.

Anaesthetic technique

The anaesthetic technique was standardized in all four studies. All patients received the same antiemetics (droperidol plus metoclopramide), thiopental and propofol for induction, rocuronium to facilitate tracheal intubation and for maintenance of anaesthesia 2% sevoflurane in an oxygen/nitrous oxide mixture.

The placebo cream we used was a quickly absorbed white, odorless, non-greasy, hypoallergenic moisturizing skin cream (E45 Cream, Reckitt Benckiser, Berkshire, UK).

Postoperative analgesia and assessment of pain

During the first 24 hours analgesics given to the patients of studies A, B, and C consisted of IM paracetamol 600 mg and propoxyphene 75 mg on request. Subsequently, the following postoperative days Lonarid-N™ tablets (Boehringer Ingelheim) were given on request. The tablets contain 400 mg of paracetamol and 10 mg of codeine. Patients of study D received for postoperative pain on request 1200 mg of paracetamol IM in the PACU and Lonalgal™ tablets (500 mg of paracetamol and 30 mg of codeine) in the ward.

We calculated in each patient the total paracetamol consumed intramuscularly and by mouth as plain tablets or in combination with codeine. To facilitate comparisons of analgesics, propoxyphene and codeine are expressed as parenteral morphine equivalent dose, and added into cumulative dose for each subject (Mean equivalent dose conversion table, Regional Palliative Care Program, Edmonton, Alberta, Canada, available at : <http://www.palliative.org>). Thus postoperative analgesics were expressed and compared as cumulative morphine equivalent and cumulative paracetamol.

Acute postoperative pain was scored using the visual analogue scale (VAS, 0 mm = no pain and 100 mm = intolerable pain) at rest and after movement. Movement consisted of the ipsilateral arm abduction by 90°. We analyzed data of acute post-

operative pain at 0, 3, 6, and 9 hours postoperatively and thereafter from the first to the sixth day. We averaged VAS scores at rest and with movement during the first 9 postoperative hours and during postoperative days 1 to 6.

Before discharge from the hospital patients were instructed to record while at home if they were in pain due to surgery and if they consumed analgesics for post-surgical pain.

Chronic pain in our 4 prospective studies was based on : nature of pain, thus, pricking sensation, burning, and numbness or stabbing ; location on the chest wall and/or the axilla and/or the ipsilateral arm. Timing for interview was scheduled at three months period after surgery.

Three months later patients were interviewed by phone and were asked to report if they still experienced pain due to surgery and whether they consumed analgesics for this pain. According to our instructions analgesics were paracetamol, Lonarid-N™ or Lonalgal™ tablets. In case of unrelieved pain patients were instructed to contact us.

We compared the following :

1. The opioid and the paracetamol consumption for the first five postoperatively days between patients who developed chronic pain and those who did not.
2. The postoperative pain from 0 to 9 hours as well as from the first to the sixth postoperative day at rest and after movement between patients who still experienced pain three months after surgery and patients who did not.
3. The opioid and the paracetamol consumption for the first five postoperative days between patients who required analgesics at home and those who did not.
4. The postoperative pain from 0 to 9 hours as well as from the first to the sixth postoperative day at rest and after movement between patients who needed analgesics at home and patients who did not.

The primary outcome of the study was the impact of postoperative analgesic requirements and immediate postoperative pain in patients who developed chronic pain and/or required long-term analgesics versus patients who did not.

Statistics

Patient characteristics, postoperative analgesic requirements and VAS scores were compared between those patients, who experienced chronic pain, or those who needed analgesia at home,

versus those who did not experience chronic pain, or did not need long-term analgesia, using unpaired student's t-tests.

Crosstabulation χ^2 tests or Fisher's exact tests, whenever appropriate, were used to compare the incidence of chronic pain or the need of long-term analgesia between patients : a) who had modified radical mastectomy versus lumpectomy, and b) who received radiotherapy versus the patients who did not.

The SPSS Version 11.0.4 for Mac OS X 9 (Chicago, IL) statistical software was used for statistical analysis, and the Prism 4 for Macintosh, Graphpad software (San Diego, CA), for rendering the figures.

RESULTS

Of the 98 patients who served as the control groups five were excluded from the analysis for acute pain. One patient developed allergy to Tegaderm, two patients received NSAIDs postoperatively, one discontinued participation herself, and one failed to complete the protocol. Of the 93 remaining patients two were excluded from the analysis for chronic pain as contact was not possible.

Characteristics with regard to patient grouping

Table I gives a summary of the studies A, B, C and D.

The patients grouped for chronic pain development and analgesic requirements at home did not differ with regard to age, body weight or height (Table II).

For the same groupings we found no differences regarding the type of surgery, lumpectomy plus axillary lymph node dissection versus modified radical mastectomy, the use of radiotherapy and the use of chemotherapy, except that fewer patients having radiotherapy required analgesics at home versus patients who had not radiotherapy ($p = 0.007$) (Table III).

Chronic versus no chronic pain development

Overall there was no difference in opioid drug consumption during the first five postoperative days between the patients who reported chronic pain three months postoperatively and those who did not (20 ± 11.9 vs 20 ± 14.0 mg of opioid respectively, $p = 0.782$). Similarly, there was no difference in

Table I

Age, body weight (BW), height, analgesic consumption during the first five postoperative days, VAS at rest (VAS_R) and with movement (VAS_M) during the first nine postoperative hours and six postoperative days, as well as chronic pain development and analgesic needs three months after surgery

Study	Age (yrs)	BW (kg)	Height (cm)	Morphine (mg)	Paracetamol (mg)	VAS _R (0-9 h)	VAS _M (0-9 h)	VAS _R (1-6 d)	VAS _M (1-6 d)	Chronic Pain (patients %)	Analgesics at home (patients %)
A, n = 22	49 ± 8.4	71 ± 10.7	160 ± 5.0	22 ± 12.5	3868 ± 3208	14 ± 1.7	34 ± 18.2	7 ± 10.9	23 ± 22.3	20/22 (90.9%)	6/22 (27.3%)
B, n = 23	44 ± 6.6	64 ± 15.2	163 ± 5	26 ± 11.9	4443 ± 1810.7	20 ± 11.2	38 ± 17.7	7 ± 7.4	26 ± 16.1	14/23 (61%)	12/23 (52.2%)
C, n = 24	45 ± 8.5	62 ± 7	163 ± 6	25 ± 11.8	5833 ± 3584.7	18 ± 11.3	36 ± 16.7	10 ± 7.5	28 ± 14.7	14/24 (58%)	6/24 (25.0%)
D, n = 22	48 ± 8.2	63 ± 5.9	163 ± 3.7	7 ± 7.5	3332 ± 2669.8	18 ± 12.5	34 ± 20.1	7 ± 9.3	17 ± 17.1	18/22 (81.8%)	5/22 (22.7%)

Table II

Characteristics for patients who developed chronic pain versus those who did not and for patients who consumed analgesics at home versus those who did not

	Chronic pain	n	Mean	SD	Statistics
Age (years)	Chronic pain	66	46.4	8.2	p = 0.464
	No pain	25	47.8	7.8	
Weight (kg)	Chronic pain	66	64.0	11.7	p = 0.868
	No pain	25	64.5	10.8	
Height (cm)	Chronic pain	66	159.1	20.3	p = 0.312
	No pain	25	161.9	5.9	

	Analgesics at home	n	Mean	SD	Statistics
Age (years)	Analgesics	29	47	9	p = 0.97
	No analgesics	62	47	8	
Weight (kg)	Analgesics	29	63	13	p = 0.46
	No analgesics	62	65	11	
Height (cm)	Analgesics	29	156	30	p = 0.36
	No analgesics	62	161	5	

paracetamol consumption during the period of first five postoperative days between the chronic and non-chronic pain groups (4517 ± 2929 mg versus 4100 ± 3250 mg respectively, p = 0.578) (Fig. 1).

The 66 patients with persisting pain three months postoperatively had significantly more pain at rest during the first 9 postoperative hours when compared with the 25 patients who reported no pain (VAS 19 ± 12.1 mm versus 14 ± 9.8 mm respectively, p = 0.033). The VAS scores after movement though higher in the chronic pain group did not differ significantly between the chronic versus no chronic pain (VAS 37 ± 18.4 mm versus 31 ± 16.4 mm respectively, p = 0.104) (Fig. 2). The VAS values at rest and after movement during the first six postoperative days did not differ between the chronic-pain and no chronic pain groups. These values were 9 ± 9.5 mm and 5 ± 6.6 mm at rest (p = 0.08) and 25 ± 18.7 and 21 ± 15.6 mm after

movement (p = 0.265) for the chronic-pain and no chronic pain groups respectively (Fig. 2).

Longterm use of analgesics versus no use

During the first three months postoperatively 29 of the 91 patients used analgesics at home and 62 did not. Patients who required analgesics at home consumed more opioids during the first five postoperative days (26 ± 13 mg) compared to those patients who did not consume analgesics at home (17 ± 13 mg) (p = 0.005). Similarly for the same time period, these patients consumed more paracetamol (5252 ± 2254 mg) versus the patients who did not need analgesics at home (4005 ± 3242 mg) (p = 0.037) (Fig. 3).

Patients who required analgesics at home had experienced more acute pain at rest and after movement (22 ± 13 and 43 ± 18 mm respectively) during

Table III

Type of surgery (lumpectomy plus axillary node dissection versus modified radical mastectomy), use of radiotherapy or/and chemotherapy in patients who developed chronic pain and required analgesics at home

		Type of surgery		
	n = 91	Lumpectomy 62/91 (68%)	Mastectomy 29/91 (32%)	Statistics
Chronic pain	66	46/62 (74%)	20/29 (69%)	p = 0.788
No chronic pain	25	16/62 (26%)	9/29 (31%)	
Analgesics at home	29	19/62 (31%)	10/29 (34%)	p = 0.446
No analgesics at home	62	43/62 (69%)	19/29 (66%)	
Radiotherapy				
	n = 91	Yes 39/91 (43%)	No 52/91(57%)	Statistics
Chronic pain	66	25/39 (64%)	41/52 (79%)	p = 0.186
No chronic pain	25	14/39 (36%)	11/52 (21%)	
Analgesics at home	29	6/39 (15%)	23/52 (44%)	p = 0.007
No analgesics at home	62	33/39 (85%)	29/52 (56%)	
Chemotherapy				
	n = 90	Yes n = 73/90 (81%)	No n = 17/90 (19%)	Statistics
Chronic pain	66	52/73 (71%)	14/17 (82%)	p = 0.529
No chronic pain	24	21/73 (29%)	3/17 (18%)	
Analgesics at home	29	26/73 (36%)	3/17 (18%)	p = 0.249
No analgesics at home	61	47/73 (64%)	14/17 (82%)	

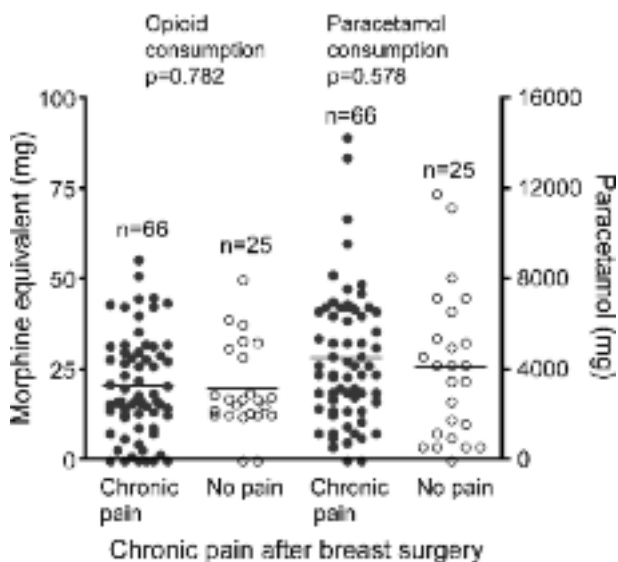


Fig. 1. — Analgesic requirements for acute postoperative pain in patients who developed chronic pain versus patients who did not develop chronic pain. Horizontal lines represent mean values and circles actual data points.

the first 9 postoperative hours versus those patients who did not consume analgesics at home (16 ± 10 and 32 ± 17 mm respectively) ($p = 0.022$ at rest and $p = 0.009$ after movement). The cumulative VAS

scores over the first six postoperative days (12 ± 11.4 mm at rest and 33 ± 17.5 mm after movement) of patients who consumed analgesics at home were significantly higher than the VAS scores of patients who did not consume analgesics at home (6 ± 6.6 mm at rest, $p = 0.013$ and 20 ± 17 mm after movement, $p = 0.001$) (Fig. 4).

DISCUSSION

The characteristics of our patients who developed chronic pain, or those who consumed analgesics at home did not differ from the characteristics of the patients who did not develop chronic pain and/or did not need analgesics at home.

Younger age patients are of higher risk to develop chronic postsurgical breast pain (14). Another study examining long-term survivors after breast cancer surgery showed that risk factors for development and persisting chronic pain included younger age and heavier weight patients (11). However, the most striking factor to develop chronic postoperative pain is unrelieved acute pain after surgery. Kehlet et al have reported recently that persistent postoperative pain development correlates

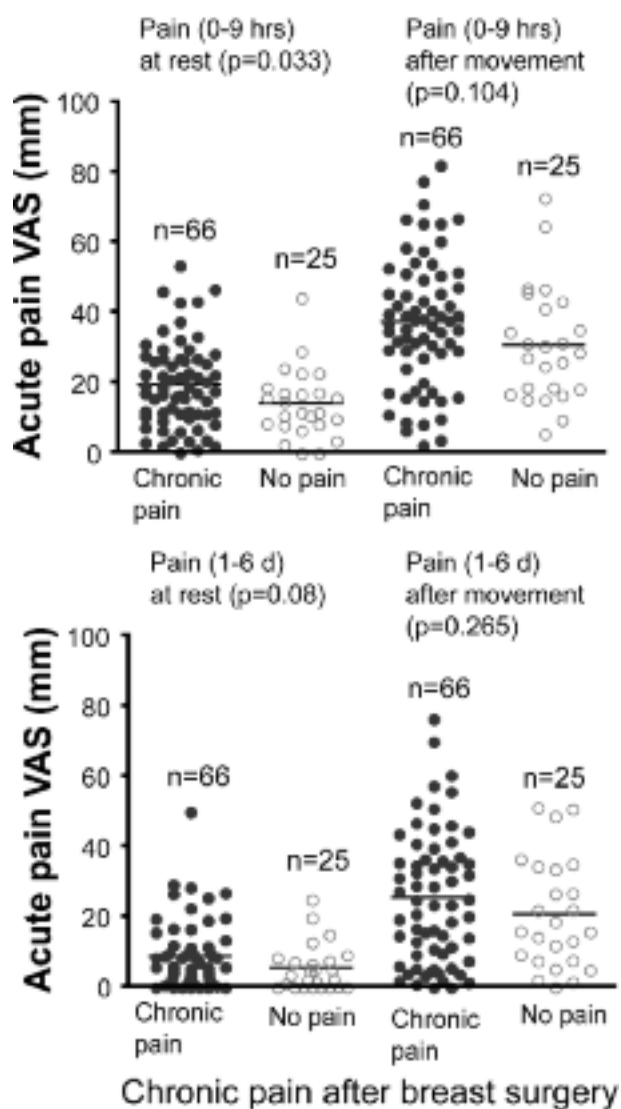


Fig. 2. — Acute pain (VAS mm) during the first 9 h and the first six days postoperatively in patients who developed chronic pain versus patients who did not develop chronic pain. Horizontal lines represent mean values and circles actual data points.

well with the intensity of acute postoperative pain. Therefore early and adequate treatment may be important in preventing or ameliorating the development of chronic postoperative pain (10, 13).

Data analysis of the four control groups originating from four prospective randomized controlled trials indicate that amounts of opioids and paracetamol consumed during the first five postoperative days had no effect on chronic pain incidence. However, those patients who reported chronic pain three months after surgery had experienced significantly more pain during the first nine hours postoperatively at rest. This difference was not significant for the first six postoperative days, though there

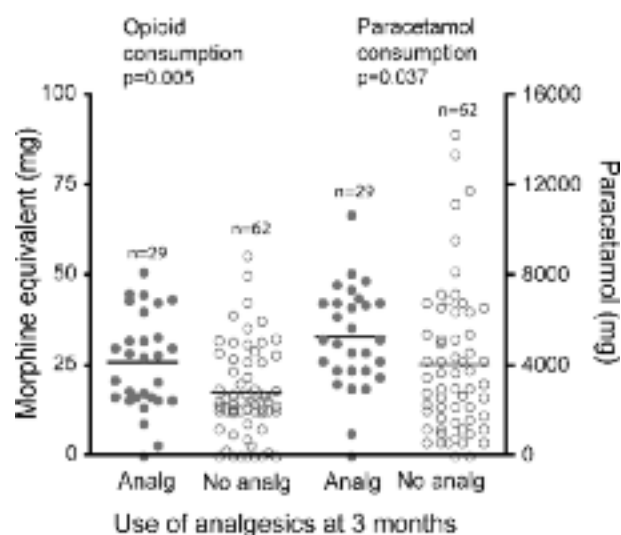


Fig. 3. — Analgesic requirements for acute postoperative pain in patients who required analgesic at home versus patients who did not require analgesics at home. Horizontal lines represent mean values and circles actual data points.

was a trend for higher intensity of acute pain in patients who subsequently developed chronic pain.

Several reports correlate postsurgical chronic pain with insufficient treatment or relief of the acute postoperative pain. In a prospective study, women who had surgery for breast cancer and developed chronic pain remembered also more severe postoperative pain than women who did not develop chronic pain. These investigators did not measure the actual postoperative pain (15). In a series of 509 patients assessment of the factors associated with chronic pain development after breast surgery for cancer showed that the intensity of acute postoperative pain is included among the most important factors (16). A recent prospective study investigating the risk factors after surgery for breast cancer showed that acute postoperative pain is an important prediction factor for stronger chronic pain three months postoperatively (14).

The occurrence of the very early intense postoperative pain during recovery from general anaesthesia can be predicted by assessing the preoperative anxiety and patient's need to be informed about the whole procedure. These variables consist the Amsterdam Preoperative Anxiety and Information Scale (APAIS), can be evaluated during the preoperative visit and be handled accordingly (9).

Other predictive factors for severe pain after surgery in the postanesthesia care unit were found to be the preoperative consumption of analgesics, a higher intraoperative dose of sufentanil during surgery and general anaesthesia (2).

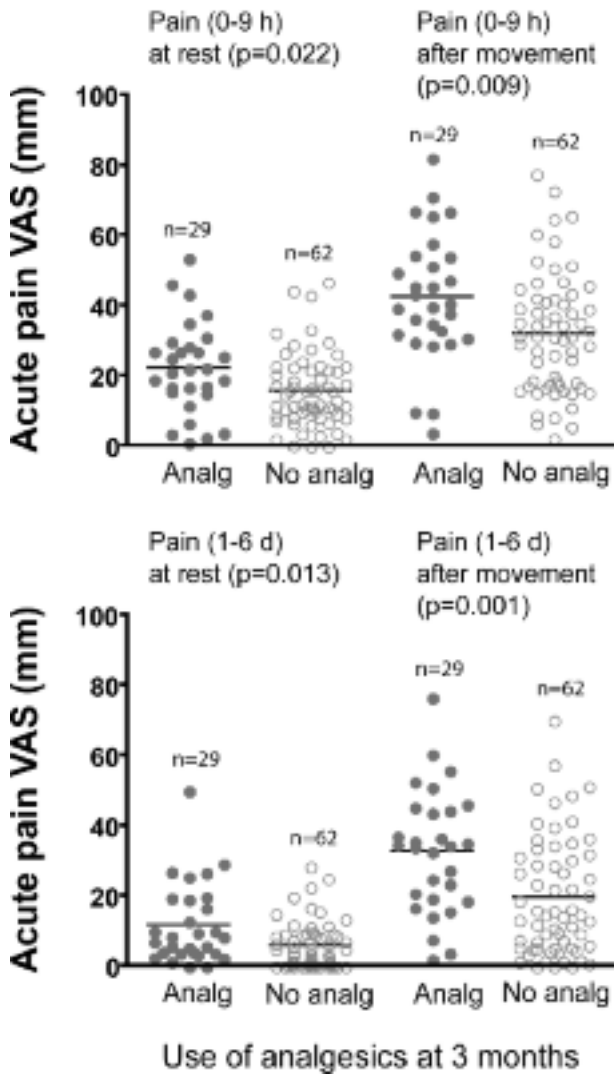


Fig. 4. — Acute pain (VAS mm) during the first 9 h and the first six days postoperatively in patients who required analgesic at home versus patients who did not require analgesics at home. Horizontal lines represent mean values and circles actual data points.

To our knowledge the fact that pain during the first postoperative hours may be an important risk factor for chronic pain has not been reported before. Studies investigating the chronic postoperative pain do not consider a time response to acute postoperative pain and a possible impact of the most important period for further central sensitization and chronic pain development.

Most of the studies investigate the acute postoperative pain as predictor for chronic pain after breast surgery. Nevertheless, data available regarding the analgesic consumption during the first postoperative days are limited. A correlation between the number of doses of opioids and NSAIDs during the first two days after surgery and the intensity of

remembered postoperative pain has been reported (15).

Our results are not in agreement as we found no difference in cumulative opioid requirements and in paracetamol requirements between the patients who reported pain 3 months postoperatively and those who did not. However, we recorded the analgesic consumption every 3 hours during the first 9 hours and every morning during the first five postoperative days, and not by checking the patient's records in a later time. Another difference is that we collected data on analgesic consumption for a longer period of time, thus five days instead of two days in the previous study. As analgesic needs are decreased the days after surgery our data collected for longer period may have skewed a possible relationship between the postoperative analgesic consumption and chronic pain.

Patients who required analgesics at home had consumed more opioids and paracetamol during the first five postoperative days and experienced higher intensity of pain during the first six postoperative days.

None of our patients was treated by antidepressants or analgesics preoperatively as defined by the four study protocols, which had as primary outcome the prevention of persistent pain development after breast surgery for cancer by applying perioperatively several analgesic regimes. However, psychological factors may influence the development of persistent pain after breast surgery for cancer, and this issue was ignored in this retrospective study. The lack of the psychological assessment of our patients is a limitation of our study. Also, our results come from a retrospective analysis, therefore should be interpreted with caution.

In conclusion, under the four studies design, higher intensity of pain during the first postoperative hours was associated with higher incidence of chronic pain after cancer breast surgery. Greater analgesic requirements during the first five postoperative days and higher intensity of acute pain were associated with greater consumption of analgesics at home.

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