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Incidence of contralateral neurosensitive changes and persistent postoperative pain 6 months after mastectomy

A prospective, observational investigation

Paula Masgoret, MD[a,*], Inés de Soto, MD[b], Ángel Caballero, MD[a], José Ríos, MSc[c], Carmen Gomar, MD, PhD[a]

Abstract

Mirror image sensory dysfunction (MISD) after breast surgery has not yet been studied. This prospective observational study aimed to determine the incidence of MISD, persistent postoperative pain (PPP) and mirror image pain (MIP) during 6 months after total unilateral mastectomy.

Visual analogue scale (VAS), Neuropathic Pain Symptom Inventory (NPSI), Pain Catastrophizing Scale (PCS), Hospital Anxiety and Depression Scale (HADS), Life orientation test (LOT) and Quantitative Sensory Testing (QST) (in ipsi and contralateral breast, axilla and thigh) were recorded. VAS $>$ 3 at 1, 3, and 6 postoperative months was considered PPP. Contralateral changes of QST at any time was considered indicative of MISD and spontaneous contralateral VAS $\geq$ 1 as MIP.

Sixty-four patients were included. PPP at 1, 3 and 6 months was 18.8%, 56.2%, and 21.3%, respectively Ten patients presented MIP. MISD was detected in 79.7% patients in contralateral breast and 62.5% in contralateral axilla. Furthermore, changes in QST were present in 39.1% of patients in thigh. Electronic Von Frey (EVF) changes in both contralateral breast and axilla, and in thigh significantly diminished at all postoperative times. Changes of postoperative EVF $\geq$ 20% in contralateral breast were associated to higher VAS values. NPSI scores were significantly higher at all postoperative times. At 1 month, PCS, depression HADS subscale and LOT scores were significantly worse than all the other periods.

MISD incidence was almost 80%, and 15.6% of patients showed spontaneous contralateral VAS $\geq$ 1. At 6 months 21.3% of patients manifested PPP. The worst alteration of factors related to PPP occurred at 1 postoperative month. Most consistent QST was EVF.

Abbreviations: ASA = American Association of Anesthesiology status, BIS = bispectral index, DNIC = diffuse noxious inhibitory control, EVF = Electronic Von Frey, HADS = Hospital Anxiety and Depression Scale, HADSA = Hospital Anxiety and Depression Scale, anxiety subscale, HADSD = Hospital Anxiety and Depression Scale, depression subscale, LOT = Life Orientation Test, MIP = Mirror Image Pain, MISD = Mirror Image Sensory Dysfunction, NPSI = Neuropathic Pain Symptom Inventory, PCS = Pain Catastrophizing Scale, PPP = Persistent Postoperative Pain, QST = Quantitative Sensory Testing, VAS = Visual Analogue Scale, VFM = Von Frey Monofilaments.

Keywords: Electronic Von Frey, mirror image pain, mirror image sensory dysfunction, persistent postoperative pain, quantitative sensory testing

1. Introduction

The mammalian nervous system shows a high degree of symmetry. Studies in rodents describe sensory changes in the homonymous contralateral zone[1] after unilateral injuries.[2–6] These changes are referred to as "mirror image sensory dysfunction" (MISD).[2,5] There are reports of MISD cases in humans,[7] and its spontaneous painful expression is called "mirror image pain" (MIP).[1,5,8–12] Mechanisms engaged in MISD have not been completely elucidated,[1–4,6] although nervous (at peripheral,[3] spinal,[6] thalamic or cortical[4] level) or humoral[1,13] factors have been considered, involving neurons,[4,13] neural growth factors,[13] glia, microglia,[13] and cytokines.[9] Studying mechanisms implicated in MISD and MIP may be useful in understanding chronic pain aethiopathogenesis, especially persistent postoperative pain (PPP),[11,14] which is considered a potentially preventable major clinical problem. Moreover, it could provide a methodological advance in the design of pain studies.[2,11,15]

When reported, MISD and MIP occurred in patients with severe ipsilateral allodynia.[1,7–10] In addition, contralateral neurosensitive changes are reported as being less intense and of delayed onset with respect to ipsilateral responses.[2,9]

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[a] Department of Anesthesiology, Hospital Clinic, University of Barcelona, [b] Department of Anesthesiology, Consorci Sanitari Parc Taulí de Sabadell, [c] Laboratory of Biostatistics and Epidemiology, Universitat Autonoma de Barcelona, Biostatistics and Data Management Platform, IDIBAPS, Hospital Clinic, Barcelona, Spain.

[*] Correspondence: Paula Masgoret, Department of Anesthesiology, Hospital Clínic de Barcelona, Villarroel 170, 08036 Barcelona, Spain (e-mail: pmasgoret@gmail.com).

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Perceptive attention of patients focusing on the aching side could mean that contralateral sensory changes may go unnoticed. A semi-objective exploration with quantitative sensory testing (QST) would allow detection of MISD.[5] Simplified QST protocols, such as the one previously used by our group[16–18] would permit repeated explorations in postoperative patients.

The surgical injury model presents a unique opportunity to study pain mechanisms as it allows QST explorations before the lesion and eventual PPP initiation. This model also gives information on the injury nervous distribution, limiting interpretation variability and detecting posterior sensory changes. Moreover, factors which favor PPP[19] have been identified as well as the correlation between degree of allodynia/hyperalgesia area around the wound (secondary hyperalgesia) and development of PPP.[19,20]

Features of mastectomies make a good model for PPP research as they have a high PPP incidence (up to 60%)[21–25] and affect a well-defined nervous territory allowing contralateral assessment. QST has been used for PPP exploration after mastectomy in the operated side and also at distant zones for demonstrating influence of central mechanisms such as neural sensitization or lack of diffuse noxious inhibitory control (DNIC).[21–25] Contralateral side has also been used as control zone to detect postmastectomy neurosensitive changes[23] or to assess test-retest agreement of QST.[15] However, up to now, there have been few studies specifically focused on MISD[5] and none have been expressly designed to assess MISD after mastectomy using QST before surgery and until 6 months postoperative.

The primary endpoint was to determine the incidence of MISD, PPP, and MIP during 6 months after total unilateral mastectomy and secondary endopoints were to establish possible relationship between them and with factors previously associated with PPP.

2. Patients and methods

The study was approved by the research committee of the Institution as a prospective cohort study without therapeutic intervention (Registered HCB/2014/0548).

Between January 2012 and December 2016, patients of both sexes older than 18 years who underwent a total unilateral mastectomy in the center, (simple, or radical modified) with or without axillary lymphadenectomy and/or removal of sentinel ganglion due to neoplasia or suspicion of it, were included in the study.

Exclusion criteria included allergy to protocol medication, any previous thoracic surgery or mastectomy, chronic pain, opioid use in the last three months, neuropathy of different origin other than chemotherapy or radiotherapy; drug or enol abuse, mental illness requiring anti-psychotic medication; central neurological disorder, cognitive alterations, emergency surgery, language barriers and prediction of impossibility of immediate extubation after surgery. Those patients who previously received chemo or radiotherapy and presented, as a result, peripheral neuropathy were not excluded from the study since this neuropathy was one of the factors considered in the study.

During the pre-op visit, one or 2 weeks before surgery, eligible patients were informed about the study. The day before surgery the investigation was explained in detail and informed consent was achieved.

The day before surgery, general variables were recorded and patients were instructed about the Visual Analogical Scale (VAS 0–10) and how to report on their sensations in the Quantitative Sensory Testing (QST). Patients had to report as "painful" any "change in perceived stimulation that was disturbing enough to make him/her want it to stop" (QST positive alteration: hyperalgesia/allodynia), and "absence" or "reduction" of their sensation if they did not perceive the stimuli or felt it less in comparison to the other side (QST negative alteration: hypo/anesthesia). Patients were also asked about the presence of previous pain or paresthesia. In addition, the following assessments were carried out: subjective pain scales, psychological tests and neurosensitive exploration with QST (See section "*Variables*" and Table 1).

For all patients we used our own anesthetic/analgesic protocol. Sublingual diazepam 5 to 10 mg and thrombotic prophylaxis with enoxaparin was given the previous night. On arrival to the surgery room midazolam 0.025 to 0.05 $mg.kg^{-1}$ and antibiotic prophylaxis with cefminox and anti-emetic medication with 4 mg dexamethasone were administered. Monitoring consisted of pulse oximeter, Electrocardiogram, non-invasive arterial pressure, capnography, esophageal temperature and bispectral index (BIS, Dublin, Ireland). Anesthesia was induced with fentanyl (1–2 $ug.kg^{-1}$), propofol (1–2 $mg.kg^{-1}$) and rocuronium (0.6 $mg.kg^{-1}$) and maintained with desfluorane 4% to 6% in O_2/Air 60% (to maintain BIS between 40 and 50). Fentanyl (2 $ug.kg^{-1}$) and rocuronium bolus were used intraoperatively if needed. At the end of surgery ondansetron 4 mg and dexketoprofen 50 mg were administered. In case of residual neuromuscular blocking,

Table 1

Variables registered in the different times during 6 months.

	-24 h	2 h	24 h	48 h	5 d	Month 1	Month 3	Month 6
General Variables	x							
VAS	x	x	x	x	x	x	x	x
NPSI and PCS	x			x	x	x	x	X
HADS and LOT	x					x	x	x
Presence of "*glove*-and-stocking" *paraesthesia*	x					x	x	x
Analgesics intake	x					x	x	X
Need of analgesic rescue with methadone		x	x	x	X			
QST	x			x	x	x		X
Treatment variables	x					x	x	X
Adverse effects and complications	x	x	x	x	x	x	x	x

HADS = Hospital anxiety and Depression Scale, LOT = Life orientation test, NPSI = Neuropathic Pain Symptom Inventory Scale, PCS = Pain Catastophizing Scale, QST = Quantitative Sensory Tests, VAS = Visual Analogue Scale.

sugammadex was given previous to extubation in the surgical room. No nerve blocking was performed.

Patients remained in the postsurgery care unit during 2 to 3 hours. Postoperative analgesia consisted of dexketoprofen 50 mg and paracetamol 1 g intravenous alternating every 8 hours and if VAS > 3 methadone 3 to 5 mg/8 hour subcutaneous was used as rescue analgesia.

2.1. Variables

Variables were collected on the day previous to surgery and in the postoperative period as described in Table 1.

After operation, variables were recorded face to face up to postoperative 5th day and at 1 and 6 months post-surgery. A follow-up was done by telephone 3 months after surgery applying the subjective scales of pain and psychological tests.

If at 3 or 6 months any patient presented clinical symptoms of PPP, oral paracetamol with or without codeine was prescribed and the possibility to be transferred to the Pain Clinic of the hospital for follow-up and treatment was offered.

General variables (gender, age, body mass index); ocupational, smoking and American Association of Anesthesiology (ASA) status and benzodiazepine and antidepressant intake were assessed. Treatment variables were evaluated the day before surgery and at 1, 3, and 6 postoperative months. Characteristics of chemotherapy, hormone therapy, biological treatments and radiotherapy were recorded. The duration and type of surgery performed (simple or radical modified mastectomy), axillary node resection (without resection, extraction of sentinel ganglion or radical lymphadenectomy) and reconstruction (insertion or not of expander/prosthesis) were also registered. Hospital length of stay was recorded. During admission emergence of nausea or vomiting, hemodynamic, cognitive or visual alterations, sedation, transfusion or vasoactive drugs requirements were assessed. Surgical complications such as seroma, hematoma, or surgical wound infection were recorded.

2.1.1. Pain assessment and psychological tests. In all the evaluated periods the patients were asked to refer VAS in the ipsilateral and the contralateral side of surgery, in the following zones: breast, lateral thoracic wall, axilla and arm. Values of VAS > 3 were considered as non-controlled pain in the immediate postoperative period and as PPP at month 1 and 6. Based on the criteria used in previous studies,[16,18,26] VAS ≥ 1 values in the ipsilateral side after 1, 3, and 6 months in the above mentioned zones were recorded. Contralateral spontaneous pain (Mirror image pain), which has been reported as less intense[1] was defined as VAS ≥ 1 referred in the same zones but in the contralateral side of the surgery at any moment of the follow-up. In order to detect a neuropathic component of pain the *Neuropathic Pain Symptom Inventory (NPSI)*[27] was applied. The presence and intensity of *glove*-and-stocking *paraesthesia*,[28] use of analgesics in the preoperative period and after hospital discharge up to 6 months, and the need for methadone rescue during admission were recorded.

Pain Catastrophizing Scale (PCS),[29] Hospital anxiety depression scale (HADS)[30]: with its subscales anxiety (HADSA) and depression (HADSD), and Life Orientation Test (LOT)[1,31] were applied.

2.1.2. Quantitative sensory testing (QST). *QST* were applied in the ipsilateral side around the incision, in the contralateral breast and in both axillae (anatomical axillary hollow). The anterior part of the middle third portion of the contralateral thigh was also explored. Positive changes (allodynia/hyperalgesia) and negative ones (hypo/anesthesia) were also recorded as described below

Electronic Von Frey (EVF) was analyzed for its quantitative results. The remainder QST used, Von Frey Monofilaments (VFM), and temperature and vibratory tests were analyzed according to the presence of response to the stimulus and, since the systematics of the exploration and data collection were the same, these were grouped as "Binary QST". In addition, the sizes of the response areas to any binary QST in breast and axilla after surgery were registered as continuous variables analyzing their evolution throughout the study.

Furthermore, "absolute changes", defined as the emergence of alterations or the disappearance of responses previously detected with any of the binary QST, whether positive or negative, were registered.

- Mechanical sensibility was assessed by VFM of 0.1, 0.6, 10, and 60 g (Bioseb, Vitrolles, France). VFM were applied as isolated stimuli as described by Stubhaug,[32] starting at 10 cm from the surgical incision and at a 5 cm distance until completing the radial area around the wound. The procedure continued towards the incision marking the point where the patient expressed a change in his/her perception. The process was repeated with the 4 tested VFM outlining an area of response on the skin for each VFM. As in previous studies from our group[16,17] this information was transferred to planimetry paper in order to calculate the size of the area. On the contralateral breast a line simulating the surgical incision was defined and measurements were done in the same manner. The areas with positive and negative changes to VFM stimuli in the contralateral side (considered as MISD) were registered according to each case. The day before surgery, as the surgical incision was not yet defined as reference, the measurements were taken in the zone of dermatome T4 in the anterior thoracic wall and in the axilla of both sides. Only the presence or absence of positive or negative alterations were registered. The same exploration was done on the thigh at all times.
- Vibratory testing was done using an electronic toothbrush following the same exploration described for VFM in thorax, axilla and thigh.
- Thermal sensibility was tested with 2 probes at 24°C and 40°C (Rolltemp, Sösdala, Sweden) applied following the same methodology for VFM.
- EVF (Electronic Von Frey Aesthesiometer, Woodland Hills, Canada): The day before surgery, as there was no surgical incision, a 10 × 10 cm area in dermatome T4 and axilla in both sides was defined. Measurements on the internal, external, superior, and inferior limits of that area were carried out. After surgery, the exploration was done at 2, 4, and 6 cm over and under the surgical incision in three different areas of the wound (internal and external edge and middle of incision). A total of 18 measurements was completed in each zone and their average was recorded. In the contralateral breast a line was defined simulating the surgical incision and the measurements were done in the same way. A 10 × 10 cm area on the middle third portion of the anterior part of the thigh was defined for all times and the measurements were done. The frequency of EVF changes higher or lower than 20% in all the zones during the postoperative period were also registered.

2.1.3. Statistical analysis. Given the observational characteristics of the general evaluation of this type of casuistic, and considering that among our primary endpoints, MISD was the most important since there is no report of MISD or MIP after mastectomies, the sample size was not formally defined. The size of the sample was fixed by feasibility retrieved from the systematic recording of the clinical activity in a third level hospital during the 5 years of the study.

The binary QST in the preoperative explorations in all the zones and in the thigh at all times were analyzed in a binary manner ("yes" or "not") to the presence of areas of positive or negative changes or alterations. For each binary QST, the mean areas size showing positive or negative changes with respect to the preoperative exploration was calculated. The differences in the areas size through time in comparison with the size of the areas at 6 months adjusted by presence or absence of areas of change in the preoperative period were estimated. The presence of contralateral changes of the binary QST at any time was considered indicative of MISD.

The differential characteristics of patients that presented neurosensitive changes in the contralateral side at any time of the study and the association with the appearance of PPP were analyzed.

The inferential analyses of longitudinal results was performed using *Generalized Estimating Equation* models using an intra-subject correlation matrix of type AR(1). These models have the particularity that they can be applied to different types of dependent variables. In this study these were used for quantitative results (VAS, EVF, areas of VFM, vibratory and temperature tests, NPSI, PCS, HADS, and LOT), as well as for the binary QST (EVF changes superior to 20%, VAS ≥ 1, VAS > 3, presence or absence of response to VFM, vibratory and temperature tests. The statistical analyses were stratified by different explored zones: ipsilateral, contralateral breast, axilla, and thigh.

The description of the results was done based on the characteristics of each variable and how they were obtained. Categorical variables are shown as absolute frequency and percentage, and quantitative variables as mean or median and their dispersion by standard deviation or interquartile range. The kappa concordance index was calculated between the presence of EVF changes superior or inferior to 20% and the rest of QST evaluated in a binary manner in terms of their interpretation. In all analysis a bilateral type I error of 5% was considered. Given the observational nature of the present study and the hypothesis formulated, no correction strategy for multiplicity was performed. SPSS Statistical program v. 20 (IBM) was used for all the statistical analyses.

3. Results

During the inclusion period, 290 patients underwent total mastectomy in the institution. Eighty-three patients fulfilled the inclusion criteria and a total of 64 patients were included. Three patients were evaluated only at 3 months while 61 completed a 6 months follow-up. (Fig. 1). The time for each face-to-face

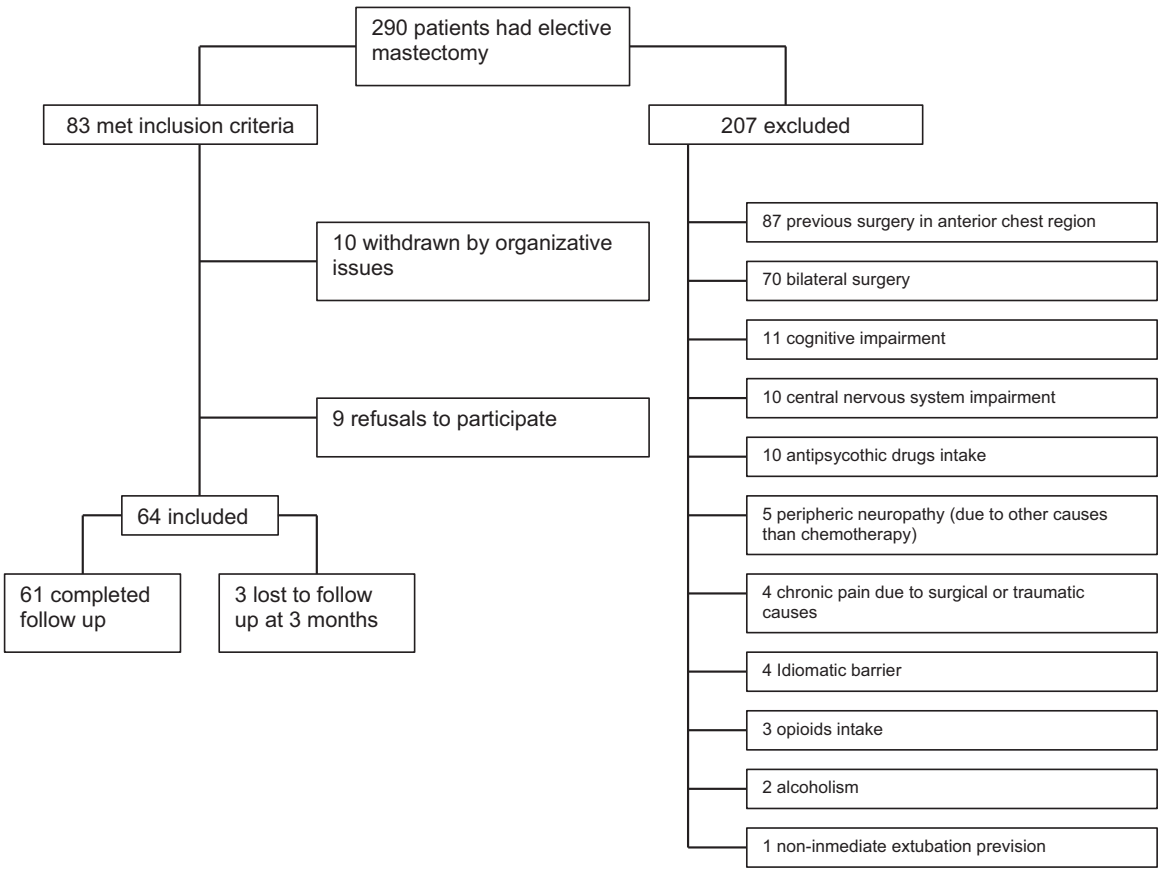

Figure 1. Patients Flow chart. Patients included and excluded and reasons for exclusion.

assessment was approximately 40 minutes. No patient had to be transferred to the Pain Clinic.

Preoperative general, pain and psychological status variables, and surgical and treatment variables during follow-up are shown in Table 2. All patients were female except 2 males. During the preoperative evaluation about one third of patients manifested VAS≥1 and about one sixth VAS > 3 in the affected breast. The percentage of patients taking analgesics preoperatively was similar to that of VAS > 3. About half the patients were consuming benzodiazepines or antidepressants and glove-and-stocking paresthesias we present in 37.5% of patients. The psychological tests did not present clinically significant alterations. Intraoperative Fentanyl consumption did not differ between patients and did exceed in any case 8 ug.kg^{-1}.

3.1. Pain assessment and psychological tests

VAS values in each postoperative period and their differences with respect to preoperative VAS (–24 hours) and VAS at 6 months are shown in Table 3. VAS mean values during the whole study was <3.5 except at month 1 when VAS obtained the highest values (4.08 ± 2.67). At 6 months VAS was significantly higher than in the preoperative assessment.

VAS > 3 was present in 18.8%, 56.2%, and 21.3% at 1, 3, and 6 months, respectively.; VAS ≥ 1 was present in 76.6%, 85.9%, and 57.4% of patients at 1, 3, and 6 months, respectively. (Table 3). The use of analgesics was present in 67.2%, 45.3%, and 28.3% of patients at 1, 3, and 6 postoperative months, respectively.

Ten patients (15.62%) expressed contralateral spontaneous pain with VAS values between 1 and 3 in some of the postoperative periods starting at 1 month until the end of the study. No patient mentioned contralateral spontaneous pain during the first 5 postoperative days.

Postoperative *glove-an*d-stocking *paresthesias were present in* 29 (45.3%), 30 (46.9%) and 26 (41.9%) of patients at 1, 3, and 6 months, respectively. Twenty-one patients (32.8%) required subcutaneous methadone as analgesic rescue during admission.

The NPSI and psychological tests values are shown in Table 4. NPSI scores were significantly higher in all the postoperative times in comparison with the preoperative ones. At month 1, the PCS, HADSD subscale, and LOT scores presented significantly worse values than in the rest of times, expressing a higher degree of catastrophism, depression and pessimism, respectively. The HADSA subscale at 3 and 6 months showed significantly lower scores than in the preoperative, pointing out a lower level of anxiety.

Table 2

Preoperative surgical and treatment variables during follow up.

Preoperative variables	Median and interquartile range or N (%)
Age	56 [45;68]
Women	62 (96.9%)
BMI	24 [23;28]
Occupationally active	36 (56.2%)
Smoking	22 (34.4%)
ASA	
I	14 (21.9%)
II	47 (73.4%)
III	3 (4.7%)
Benzodiazepines intake	29 (45.3%)
Antidepressants intake	10 (15.6%)
Malignancy confirmed	62 (96.9%)
VAS ≥ 1	20 (31.2%)
VAS > 3	10 (15.6%)
Preoperative analgesic intake	9 (14.1%)
NPSI score	0 [0;1.5]
PCS score	0 [0;3.5]
HADSA score	4 [2;8]
HADSD score	3 [1;5]
LOT score	20 [18;22]
Glove-and-stocking paraesthesia	24 (37.5%)
Treatment variables	**Median and interquartile range or N (%)**
Neoadjuvant chemotherapy	36 (56.2%)
Neoadjuvant hormone or biological therapies	23 (35.9%)
Adjuvant chemotherapy	9 (14.1%)
Adjuvant hormone or biological therapies	47 (73.4%)
Adjuvant radiotherapy	34 (53.1%)
Surgical variables	**Median and interquartile range or N (%)**
Simple mastectomy	28 (43.8%)
Radical modified mastectomy	36 (56.2%)
Reconstruction with expander/prosthesis	13 (20.3%)
Radical lymphadenectomy	31 (48.4%)
Sentinel Ganglion extraction	30 (46.9%)
Surgery duration (min)	135 [118;153]
Hospital stay (days)	6 [5;7]

ASA = American Association of Anesthesiologists classification, BMI = body mass index, HADSA = Hospital Anxiety subscale, HADSD = Hospital Depression Subscale, LOT = Life Orientation Test, N = number of patients, NPSI = Neuropathic Pain Symptom Inventory Scale, PCS = Pain Catastrophizing scale, VAS = Visual Analogue Scale.

3.2. QST assessment

For each QST, the preoperative examination (−24 hours) was used as baseline reference in order to evaluate postoperative changes.

Table 3

VAS values in each postoperative period and their differences with respect to preoperative VAS (-24 hours) and VAS at 6 months. Number and percentage of patients presenting with VAS ≥ 1 and VAS > 3 at all times are presented.

	−24 h	2 h	24 h	48 h	5 d	Month 1	Month 3	Month 6
VAS (X ± DS)	1.33 ± 2.25	3.11 ± 2.19	3.42 ± 2.33	3.06 ± 2.17	2.14 ± 2.07	4.08 ± 2.67	2.62 ± 2.26	2.1 ± 2.32
(difference with VAS at -24 h)	(N/A)	(+1.78)*	(+2.09)*	(+1.73)*	(+0.81)*	(+2.75)*	(+1.29)*	(+0.72)*
(difference with VAS at month 6)	(−0.72)*	(+1.05)*	(+1.36)*	(+1.01)*	(+0.085)	(+2.02)*	(+0.57)*	(N/A)
VAS ≥ 1 N (%)	20 (31.2%)	20 (31.2%)	56 (87.5	56 (87.5%)	49 (76.6%)	49 (76.6%)	55 (85.9%)	35 (57.4%)
VAS > 3 N (%)	10 (15.6%)	10 (15.6%)	22 (34.4%)	22 (34.4%)	12 (18.8%)	12 (18.8%)	36 (56.2%)	13 (21.3%)

NA = Not applicable, VAS = Visual Analogue Scale.

* $P < .05$ Statistical significant difference.

N = number of patients, VAS = Visual Analogue Scale, X ± SD = mean ± standard deviation.

Table 4

NPSI and psychological tests applied at all times of the study and their differences with respect to preoperative (−24 hours) scoring.

	−24 h	48 h	5 d	Month 1	Month 3	Month 6
NPSI	2.33 ± 5.12	7.09 ± 8.51 (+4.77)*	7.11 ± 8.39 (+4.78)*	13.89 ± 11.6 (+11.56)*	11.67 ± 10.66 (+9.34)*	9.54 ± 9.85 (+7.12)*
PCS	3.42 ± 6.39	3.17 ± 5.7 (-0.25)	2.83 ± 5.25 (-0.59)	5 ± .74 (+1.58)*	4.13 ± 6.54 (+0.70)	3.95 ± 7.17 (+0.42)
HADSA	5.08 ± 3.81	—	—	4.55 ± 3.72 (-0.53)	4.12 ± 3.36 (-0.95)*	4.07 ± 3.22 (-1)*
HADSD	3.37 ± 3.2	—	—	3.93 ± 3.43 (+0.59)*	3.5 ± 3.49 (+0.13)	3.03 ± 3.37 (-0.38)
LOT	19.42 ± 3.16	—	—	18.52 ± 3.64 (-0.90)*	19.34 ± 3.23 (-0.08)	20.05 ± 3.09 (-0.61)

Values are expressed as x ± SD (mean ± standard deviation). In brackets the magnitude and sense of the changes with respect to −24 h values.

HADSA = Hospital Anxiety and Depression scale, anxiety subscale, HADSD = Hospital Anxiety and Depression scale, depression subscale, LOT = Life orientation test, NPSI = Neuropathic Pain Inventory Scale, PCS = Pain Catastrophizing Scale.

* $P < .05$ statistically significant differences respect −24 h scoring.

Absolute positive or negative changes with any of the "binary" QST in some of the postoperative periods were detected in 51 patients (79.7%) in contralateral breast, in 40 patients (62.5%) in contralateral axilla and in 25 patients (39.1%) in thigh. In the operated side, these changes were registered in 61 patients (95.3%) in the breast and in 53 patients (82.8%) in the axilla. The percentage of patients presenting positive and negative changes with respect to the preoperative period with each "binary" QST through time in the five zoness explored is shown in Figure 2.

The size of the areas with changes in the QST (X ± SD) at 6 months were compared with those at 48 hours, 5 days and 1 month adjusted depending on the presence or absence of changes in the preoperative exploration for all the zones, except thigh. The table with results of area sizes for each explored zone and type of QST in all studied periods and the differences with respect to month 6 for each time can be consulted in Supplemental Digital Content 1, http://links.lww.com/MD/D763, http://links.lww.com/MD/D764.

The areas with positive or negative changes in the binary QST that reached statistically significant differences during the study are as follows:

- In the contralateral breast, the areas were $\leq 30\,cm^2$ (range 0–30 cm^2). The areas with negative changes with 0.1 g, 0.6 g, and 10 g VFM and positive changes with 0,6 g, 10 g, 60 g VFM and positive changes with vibratory and 40° T probe tests, were significantly larger at 6 months than at 48 hours and 5 days. The area with positive changes with 60 g VFM and 40° T probe were significantly larger at 1 month than at 6 months.
- In the contralateral axilla the areas were $\leq 12\,cm^2$ (range 0–12 cm^2). The areas of negative changes with 0.1 g and 0.6 g VFM and positive changes with 10 g and 60 g VFM, vibratory and temperature test were significantly higher at month 6 than at 48 hours and 5 days. The areas of negative changes with 0,1 g VFM and 40° T probe and positive with 10 g and 60 g VFM were significantly larger at 1 month than at 6 months.
- In the ipsilateral breast the areas were $\leq 91\,cm^2$ (range 2–91 cm^2). The areas with negative changes with 0,1 g, 0,6 g, and 10 g VFM and 40°C T probe and with positive changes with 10 g and 60 g VFM, vibratory and 40° T probe tests were significantly larger at 6 months than at 48 hours and 5 days. The area with negative changes with all the tests was significantly larger at 1 month than at 6 months.
- In the ipsilateral axilla the areas were $\leq 22\,cm^2$ (range 1–22 cm^2). The areas with positive changes with 10 g and 60 g VFM, vibratory and 40° T probe tests were significantly larger at 6 months than at 48 hours and 5 days. The area of negative changes was significantly larger at 1 month than at 6 months with all the QST except vibratory test.

Regarding EVF, Figure 3 shows EVF threshold values in the explored zones during the study periods and the comparison with preoperative values and at 6 months. It can be observed that the changes evolution in contralateral breast, axilla and thigh is similar although of different magnitude. In these three zones the EVF values significantly decreased in all the postoperative times with respect to the preoperative ones indicating hyperalgesia/allodynia, being this decrease highest at 1 month.

In the ipsilateral breast, the EVF values significantly increased at 48 hours and 5 days with regard to the preoperative period indicating hypoesthesia/anesthesia. In contralateral breast and axilla as in the ipsilateral breast the EVF values at 6 months were significantly lower than those found in the preoperative, 48 hours and 5 days. In the thigh there was a significant decrease in the EVF at 6 months with respect to the preoperative.

The frequency of EVF changes over and under 20% with respect to preoperative values in the different zones and times are shown in Table 5.

In general, a good concordance between patients that presented changes of EVF above or below 20% and positive or negative changes with the rest of QST was not observed. The highest values of Kappa index were found in breast and ipsilateral axilla, however, in no case did the Kappa index show values higher than 0.5.

3.3. Characteristics of patients with contralateral alterations

Table 6 shows relationship of ipsilateral VAS mean values, VAS ≥ 1, VAS > 3 and EVF threshold values in contralateral axilla, ipsilateral breast, ipsilateral axilla and thigh with presence or absence of EVF changes above or below 20% in contralateral breast at some period of the study with respect to preoperative exploration.

Patients with a 20% decrease of EVF in contralateral breast with respect to the preoperative values at some period manifested VAS values significantly higher at 6 months. No significant

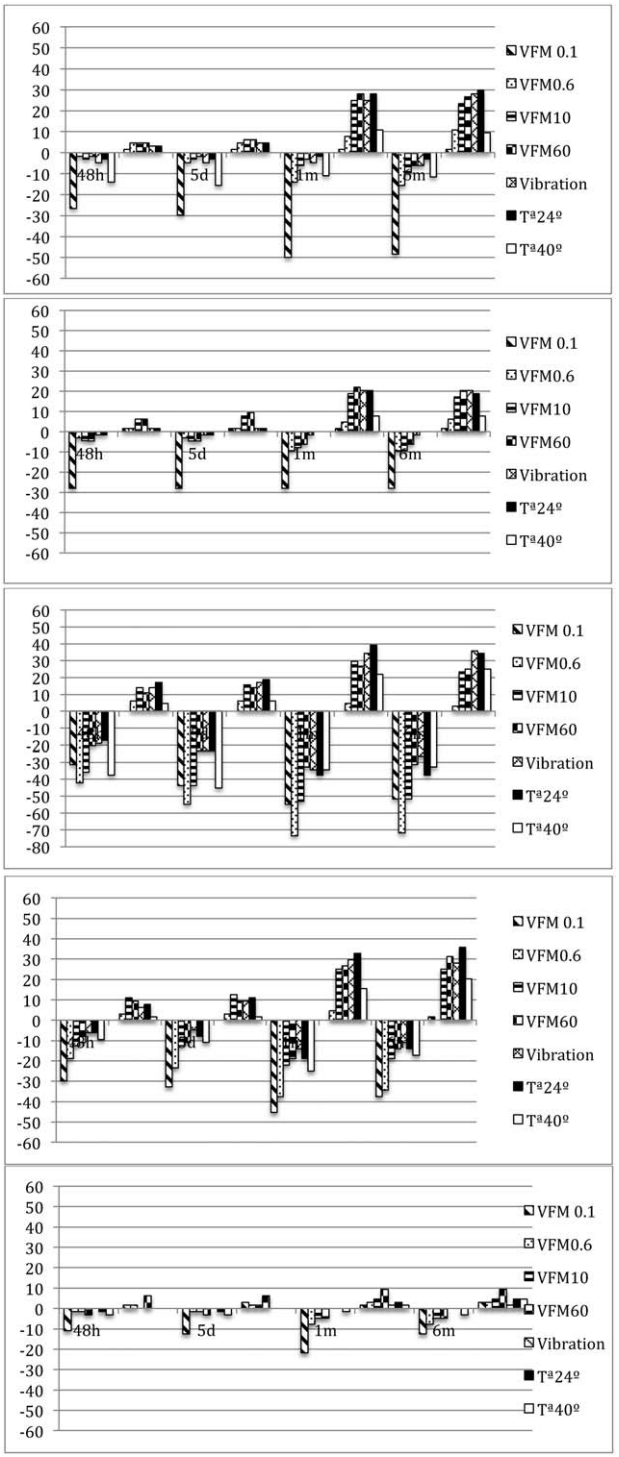

Figure 2. Percentage of patients presenting areas with positive and negative changes with respect to the preoperative period with each "binary" QST through time in the 5 zones explored. Order of zone display: 1. Contralateral breast; 2. Contralateral axilla; 3. Ipsilateral breast; 4. Ipsilateral axilla; 5. Thigh. VFM = Von Frey Monofilament.

correlation of EVF changes with VAS ≥ 1 or VAS >3 values in ipsilateral breast at any time was found. The EVF thresholds in these patients were lower in the contralateral axilla, ipsilateral breast and axilla, and thigh reaching statistically significant values in both axillae at 1 and 6 months.

Patients with a 20% increase of EVF in contralateral breast with respect to the preoperative values at some period showed average VAS values significantly higher at 48 hours and 1 month. A significant correlation existed between increases of 20% of EVF in contralateral breast and VAS ≥ 1 and VAS > 3 in ipsilateral breast up to month 1.

Although there was a trend for patients with absolute "binary" QST changes in contralateral breast at some period to express, at some moment, higher VAS, the difference reached statistical significance only in the preoperative exploration (Fig. 4).

Only 26.6% incidence of nausea and vomiting with an incidence of 26.6% was registered as adverse effect or complication.

4. Discussion

The aim of this study was to assess presence of MISD, MIP, and PPP during the first 6 months after mastectomy. As far as we know, this is the first study which prospectively follows ipsilateral and contralateral neurosensitive changes looking for MISD, from the preoperative period throughout 6 months after mastectomy, including psychological aspects involved in PPP.

Incidence of PPP, defined as VAS > 3 at 6 months was 21.23%, similar to previous studies[21,22]; 57.4% of patients reported VAS ≥ 1 at 6 months, a value that can be considered clinically irrelevant but has been used as threshold to define PPP in previous studies.[16–18,26] The most relevant finding of this study is the high incidence of MISD assessed by QST, which was present in almost 80% of patients. Furthermore, 15.6% of patients referred contralateral spontaneous pain (MIP).

This study applied a brief QST protocol which had been previously used by our group[16,18] as original QST testing is cumbersome, time–consuming and difficult to apply repeatedly in postoperative patients and therefore seldom published after surgery. Reference values for QST around surgical area are scarce.[15,24] Furthermore, QST was designed specifically for neuropathic chronic pain and even in it, the neurological substrate of responses is still of difficult interpretation.[32] Despite those drawbacks, appearance of postoperative QST changes compared to preoperative exploration in the contralateral zone to the surgery (not been injured at all) can be clearly interpreted as MISD.

MISD has been demonstrated in some chronic pain patients[7,8,10–12] but only 2 papers[5,9] have described it in surgical patients, and with already established PPP. Since in these studies preoperative QST assessment had not been made, comparison with baseline pattern is lacking, which limits the definitive attribution of QST alterations to surgery. In our study, contralateral QST changes can be clearly attributed to the surgical process since we had preoperative exploration for each patient as baseline reference.

Information available on MISD development mechanisms is scarce and confusing, and we can only speculate in the interpretation of our findings. Furthermore, the contralateral side to mastectomy, and a distant zone, the thigh, was also explored to assess if neurosensitive changes extended beyond spinal innervation symmetry, suggesting the involvement of supraspinal mechanisms in MISD.[15,24] Interestingly, the incidence of postoperative QST changes at thigh was 39.1%. QST changes in zones distant from each other supports the implication of extensive changes at central nervous level in postoperative pain[15,24,33] and alterations in DNIC has been suggested.[19] It is

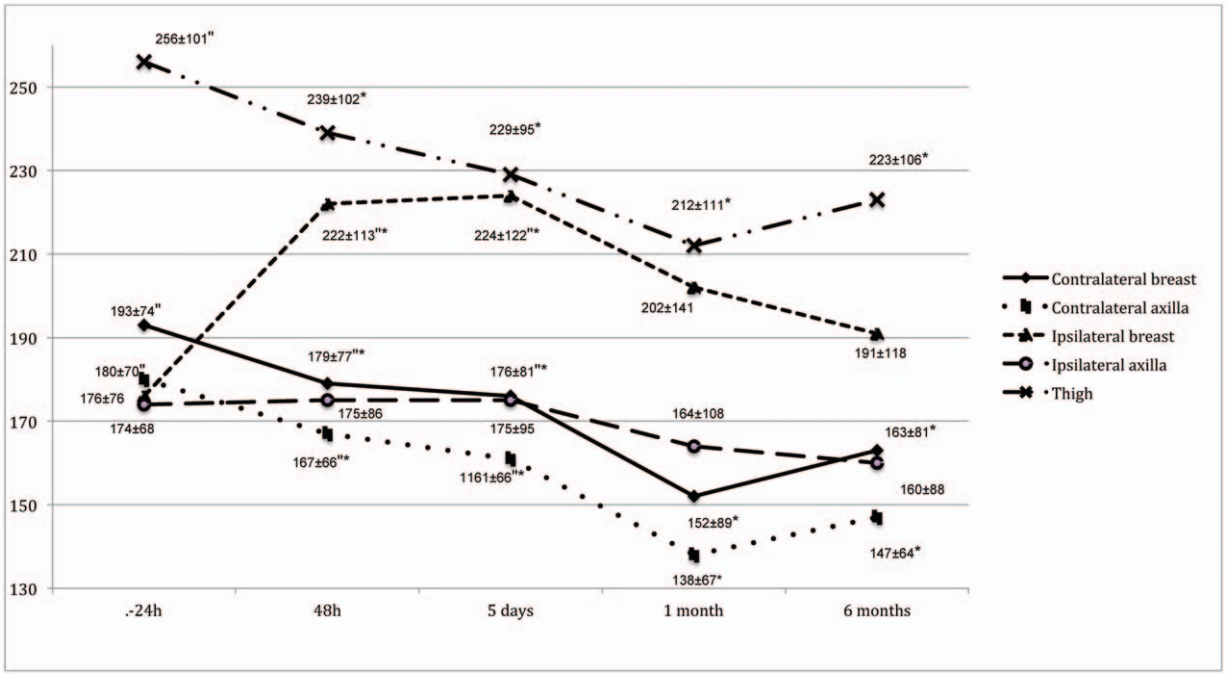

Figure 3. Electronic Von Frey threshold values in the explored zones during the study periods and comparison with preoperative values and at 6 months. Values expressed as x ± DS. *Statistically significant difference with preoperative values ($P < .05$). "Statistically significant difference with 6 months values ($P < .05$).

of note that 15.6% of patients (10 patients) referred MIP evaluated by VAS, starting 1 month after surgery and coinciding with the highest ipsilateral VAS value. This late appearance, with an intensity curve parallel to the contralateral side and thigh QST coincides with previous experimental studies.[2,9] It is believed that MIP is rarely reported by patients since it corresponds in time with intense ipsilateral pain that focuses attention and "masks" contralateral manifestations.[1] Interrogation specifically directed towards MIP allowed us to detect its incidence in the period of maximum pain in the surgical side.

Any significance of the different QST in the perioperative period is not clear[17,23] and we could not corroborate consistency among the different QST and their evolution except for one of them, EVF. It is thought that EVF explores mechanical sensitivity,[34] and is the easiest QST to apply and provides a numeric value, which allows reliable analysis. In this study, EVF showed a concordant evolution between the different explored zones and allowed doing a quantitative follow-up of mechanical sensitivity changes in the postoperative period comparing them with the preoperative evaluation. it has recently been proposed to reduce QST protocols to make them applicable in the clinical setting.[1,28] In light of our results, in the surgical patient the complex protocols can be replaced by a single QST, EVF. By doing so, EVF will detect neurosensitive changes easily and alert about those patients with a higher risk of PPP.

There are no references about what magnitude of EFV change has a neurophysiological meaning but we considered empirically that a 20% change had clinical significance in order to detect changes. More than 1/3 of patients showed 20% changes of EVF in the contralateral side postoperatively, being highest at 1 month. Decrease of 20% contralateral EVF, which means higher sensibility, was more frequent than increase. Contralateral EVF changes ≥20% were associated with changes in the same direction in the other zones explored confirming consistency of this QST.

We assessed the size of the area that presented neurosensitive changes around the surgical incision (secondary hyperalgesia) since it has been associated with PPP onset.[14,20] There are no reference values for the size of these areas. In thoracic and hepatic surgery, our group found areas with changes less frequent and

Table 5

Frequency of Electronic Von Frey changes over and under 20% with respect to preoperative values (−24 hours) in the different zones explored.

	48 h		5 d		1 mo		6 mo	
	Increase	Decrease	Increase	Decrease	Increase	Decrease	Increase	Decrease
Contralateral breast	9 (14.1%)	18 (28.1%)	10 (15.6%)	27 (42.2%)	7 (10.9%)	39 (60.9%)	7 (11.5%)	30 (49.2%)
Contralateral axilla	4 (6.2%)	18 (28.1%)	8 (12.5%)	23 (35.9%)	5 (7.8%)	35 (54.7%)	8 (13.1%)	28 (45.9%)
Ipsilateral breast	24 (37.5%)	14 (21.9%)	29 (45.3%)	17 (26.6%)	22 (34.4%)	25 (39.1%)	20 (32.8%)	23 (37.7%)
Ipsilateral axilla	10 15.6%)	18 (28.1%)	16 (25%)	20 (31.2%)	16 (25%)	35 (54.7%)	14 (23%)	26 (42.6%)
Thigh	9 (14.1%)	19 (29.7%)	7 (10.9%)	21 (32.8%)	5 (7.8%)	31 (48.4%)	8 (13.1%)	23 (37.7%)

Values expressed as N (number of patients) and (%).

Table 6

Relationship of ipsilateral VAS scores, VAS > 1, VAS > 3 and Electronic Von Frey threshold values in contralateral axilla, ipsilateral breast, ipsilateral axilla and thigh with the presence or absence of Electronic Von Frey changes above or below 20% in contralateral breast at some period of the study with respect to preoperative exploration.

	−24 h		2 h		24 h		48 h		5 d		Month 1		Month 3		Month 6	
DECREASE >20% OF EVF IN CONTRALATERAL BREAST AT SOME TIME																
	Yes	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
VAS X ± DS	1.25 ± 2.14	1.5 ± 2.54	3.18 ± 2.43	2.95 ± 1.57	3.36 ± 2.43	3.55 ± 2.14	3.14 ± 2.31	2.9 ± 1.89	2.34 ± 2.24	1.7 ± 1.59	4.18 ± 2.68	3.85 ± 2.72	2.91 ± 2.37	2 ± 1.93	2.45 ± 2.53*	1.32 ± 1.57
VAS≥1 N (%)	14 (31.8)	30 (68.2)	38 (86.4)	6 (13.6)	38 (86.4)	6 (3.6)	38 (86.4)	6 (13.6)	35 (79.5)	9 (20.5)	37 (84.1)	7 (15.9)	34 (77.3)	10 (22.7)	26 (61.9)	16 (38.1)
VAS>3 N (%)	6 (13.3)	38 (86.4)	15 (34.1)	29 (65.9)	18 (40.9)	26 (59.1)	15 (34.1)	29 (65.9)	9 (20.5)	35 (79.5)	27 (61.4)	17 (38.6)	16 (36.4)	28 (63.4)	12 (28.6)	30 (71.4)
EVF contralateral axilla	191 ± 74*	155 ± 55	N/A	N/A	N/A	N/A	164 ± 70	172 ± 57	154 ± 69	177 ± 59	119 ± 51*	180 ± 79	N/A	N/A	127 ± 50*	192 ± 68
EVF Ipsilateral breast	180 ± 75	168 ± 81	N/A	N/A	N/A	N/A	219 ± 115	229 ± 113	220 ± 124	233 ± 121	191 ± 131	225 ± 163	N/A	N/A	176 ± 105	222 ± 140
EVF ipsilateral axilla	178 ± 71	165 ± 59	N/A	N/A	N/A	N/A	165 ± 83	199 ± 89	157 ± 84*	212 ± 106	147 ± 97*	203 ± 122	N/A	N/A	135 ± 66*	215 ± 107
EVF thigh	267 ± 109	232 ± 76	N/A	N/A	N/A	N/A	239 ± 110	240 ± 85	225 ± 101	237 ± 82	201 ± 116	236 ± 96	N/A	N/A	220 ± 117	230 ± 80
Increase >20% of EVF in contralateral breast at some time																
	Yes	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
VAS X ± DS	1.33 ± 2.53	1.33 ± 2.19	3.6 ± 1.3	2.96 ± 2.39	4.47 ± 1.81*	3.1 ± 2.39	3.93 ± 1.94*	2.8 ± 2.19	2.33 ± 1.4	2.08 ± 2.24	5.2 ± 2.6*	3.73 ± 2.63	2.67 ± 1.88	2.61 ± 2.39	1.38 ± 1.71	2.29 ± 2.44
VAS≥1 N (%)	4 (26.7)	11 (73.3)	15 (100)*	0	15 (100)*	0	15 (100)*	0	14 (93.3)	1 (6.7)	15 (100)*	0	12 (80)	3 (20)	6 (46.2)	7 (53.8)
VAS>3 N (%)	2 (13.3)	13 (86.7)	7 (46.7)	8 (53.3)	11 (73.3)*	4 (26.7)	8 (53.3)	7 (46.7)	3 (20)	12 (80)	10 (66.7)	5 (33.3)	4 (26.7)	11 (73.3)	1 (7.7)	12 (92.3)
EVF contralateral axilla	147 ± 49*	190 ± 73	N/A	N/A	N/A	N/A	173 ± 62	165 ± 68	179 ± 69	156 ± 65	175 ± 92*	126 (53)	N/A	N/A	199 ± 76*	133 ± 52
EVF Ipsilateral breast	164 ± 70	180 ± 79	N/A	N/A	N/A	N/A	257 ± 99	211 ± 116	263 ± 104	213 ± 126	231 ± 169	193 ± 132	N/A	N/A	262 ± 141*	171 ± 104
EVF ipsilateral axilla	161 ± 53	178 ± 72	N/A	N/A	N/A	N/A	224 ± 87*	160 ± 80	245 ± 107*	153 ± 80	213 ± 139*	149 ± 93	N/A	N/A	250 ± 108*	136 ± 65
EVF thigh	244 ± 86	259 ± 105	N/A	N/A	N/A	N/A	252 ± 92	235 ± 106	254 ± 85	221 ± 98	228 ± 87	207 ± 118	N/A	N/A	246 ± 88	217 ± 111

EVF = Electronic Von Frey, N/A = not applicable, N = number of patients, VAS = visual analogue scale, X ± DS = mean ± standard deviation.

* $P < .05$.

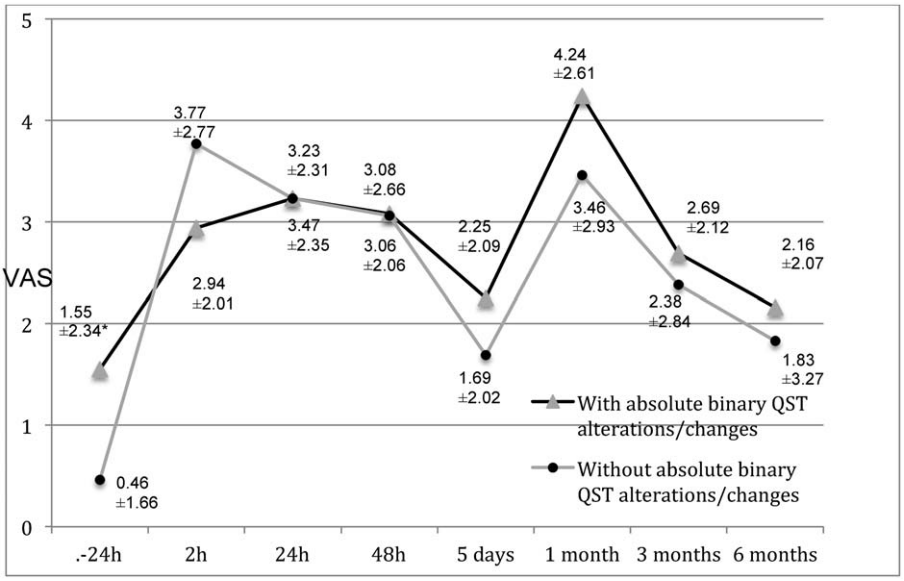

Figure 4. VAS values (X ± SD) in patients with and without absolute "binary" QST changes in the contralateral breast at some period thought the study. VAS is represented in 0-5 scale since no patient showed VAS > 5. *: $P < .05$; QST = Quantitative Sensory Tests, VAS = Visual Analogue Scale.

smaller than those found in the present study in mastectomies.[16,18] The area affected by mastectomy has a more extensive and complex innervation than thoracotomy or hepatectomy and this fact may explain larger areas with neurosensitive changes. We were not able to correlate extension of those areas with PPP.

We looked for association of QST changes in the contralateral side with the other explored zones and with PPP development, since there is evidence about their direct relationship.[14,19,20] The amount of data obtained have made their analysis and interpretation difficult, but we can state that, in this study intensity of postoperative pain correlated with MISD. Decrease of EVF values ≥20% at any time was associated to higher VAS values at 6 months and increases of EVF ≥20% were associated with higher VAS values at 1 month. This confirms certain relationship between intensity of ipsilateral postoperative pain and PPP with neurophysiological changes that affect those zones far from the surgical lesion.

One important contribution of this study is the analysis of psychological tests that influence pain chronification. Applied tests worsened postoperatively, especially at 1 month coinciding with the highest VAS values and with the lowest EVF values in the contralateral side and thigh.

Patients were at their worst at month 1, in which the highest VAS, the worst result of psychological tests and the greatest intensity of QST changes coincided. This finding is important in order to guide postoperative support for these patients. At month 1 also chemotherapy or radiotherapy are frequently initiated and bandages are usually removed making patients aware of the physical sequelae of mastectomy. Those factors, among others,[21,23,25,35] may influence negatively in their well-being. The coincidence of the worsening of all the studied variables supports that changes detected in this study are caused by the surgical process.

The most important drawback of this study is the limited sample size for one of the objectives of the study: PPP incidence. The strict inclusion criteria to limit as much as possible confounding factors in MISD detection, made that only 64 patients met them in a tertiary hospital during a 5-year period with almost 300 patients submitted to mastectomy. To extend the period would entail risk of changes in treatment protocols and to wide inclusion criteria would reduce sample homogeneity.

Strengths of this study are its prospective condition, homogeneous sample of patients, almost complete follow up and exhaustive subjective and semi-objective evaluation of changes related with PPP and MISD during 6 postoperative months having as control the preoperative exploration in each patient.

In conclusion, after mastectomy, MISD incidence was high, almost 80%, with MIP in 15.6% of patients. PPP incidence at 6 months was 21.3%. The greatest alteration in all factors that have been associated with PPP after mastectomy appeared at month 1. EVF is the QST that provides an easier applicability and consistency in order to show contralateral changes after mastectomy.

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Author contributions

Conceptualization: Carmen Gomar, Paula Masgoret.
Data curation: Paula Masgoret, Inés de Soto, Ángel Caballero, Carmen Gomar.
Formal analysis: José Ríos, Paula Masgoret, Carmen Gomar.
Methodology: Paula Masgoret, Carmen Gomar.
Supervision: Carmen Gomar.
Writing: Paula Masgoret, Inés de Soto, Ángel Caballero, José Ríos, Carmen Gomar.

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