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Impact of Perioperative Hypnosedation on Postmastectomy Chronic Pain: Preliminary Results

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Abstract

Objectives: The main aim of this prospective nonrandomized study was to evaluate if mastectomy performed with perioperative hypnosedation led to a lower incidence of chronic pain compared with mastectomy under general anesthesia. **Methods:** Forty-two breast cancer patients who underwent mastectomy either under GA (GA group, n = 21) or HYP (HYP group, n = 21) associated with local and/or regional anesthesia were included. The type of adjuvant therapy as well as the number of reconstructive surgical procedures were well balanced between the 2 groups. The average age of the patients and the type of axillary surgery were also equivalent. Incidence of postmastectomy chronic pain, lymphedema, and shoulder range of motion (ROM) were evaluated after a mean 4-year follow-up. **Results:** The study shows a statistically significant lower incidence of postmastectomy chronic pain in HYP group (1/21, 1 patient out of 21 experiencing pain) compared with GA group (9/21) with 9 patients out of 21 experiencing pain (P = .008). ROM for shoulder was also less frequently affected in the hypnosedation group, as only 1 patient had decreased ROM, instead of 7 in the other group (P = .04). **Conclusions:** Our study is the first to hint at the potential benefits of hypnosedation on postmastectomy chronic pain. Despite the limitations of this study (nonrandomized, small sample), preliminary results merit further study of hypnosedation.

Keywords

breast cancer, hypnoanalgesia, mastectomy, postmastectomy pain syndrome, benefits of hypnosis

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Introduction

Surgical removal of the tumor is one of the mainstays of breast cancer treatment, but chronic pain remains one of the major side effects of mastectomy, severely affecting patients' quality of life. Reduced range of motion (ROM) of the shoulder and lymphedema are also frequently reported as complications of surgery. In the United States and in Europe, between 30% and 40% of early-stage breast cancer patients undergo a mastectomy.[1]

The postmastectomy pain syndrome (PMPS) is recognized as a distinct medical entity. Its incidence has been estimated to be ranging from 20% to 60%.[2-6] As there is no standard definition of PMPS, this wide interval can be explained by the variation of definitions used in the studies and the methods of pain assessment performed. In any case, it remains a substantial health care problem greatly affecting women's quality of life.

As an increasing number of patients are surviving breast cancer (due in large part to improved treatments), it is of

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major importance to preserve the best quality of life and thus aim to avert, or at least attenuate, therapy-induced chronic pain. Furthermore, chronic pain is a significant medical problem. Its management is complicated and remains a burden not only for patients but also for clinicians. Because of the limitations of therapeutic options, this medical entity remains undertreated. Hence, it would be more beneficial to focus on developing preventive strategies to reduce the occurrence of chronic postsurgical pain rather than trying to manage it once established.

One of the factors influencing the onset of chronic pain is the intensity of acute postoperative pain. The perioperative period appears as a key time point to influence postsurgical pain. Some procedures, or anesthetic interventions, like regional blocks, EMLA (Eutectic Mixture of Local Anesthetics) application, or intravenous lidocaine infusion,[7-9] have been considered and seem to be effective to prevent PMPS. However, even if these methods have reduced surgery-related pain, they could lead to significant side effects and their implementation is not devoid of risks.

Hypnosis performed during breast surgery has already been shown to induce benefits during the acute postoperative period, decreasing analgesic medication consumption, anxiety, hospitalization duration, asthenia, lymphocele, and also adjuvant treatments side effects.[10] Its impact on postmastectomy chronic pain has not been investigated yet. As performing endocrine cervical surgery with hypnosedation instead of general anesthesia was shown to reduce postoperative pain,[11,12] we hypothesized that hypnosis could also have positive effects in the prevention of PMPS.

The main aim of this study was to investigate if mastectomy performed with hypnosedation led to a lower incidence of chronic pain compared with mastectomy performed under general anesthesia.

Material and Methods

Study Design

Patients were recruited from 2 studies performed in our Breast Clinic (King Albert II Cancer Institute, Cliniques universitaires Saint-Luc, Université catholique de Louvain) and conducted to evaluate the benefits of HYP in breast cancer patients undergoing oncologic surgery.

Those studies were nonrandomized trials approved by our local ethics committee and registered on ClinicalTrials.gov with NCT 03003611 and NCT 03330717. The first study was a case-control study performed between 2010 and 2015, which included 300 patients (150 patients in a group of surgery under general anesthesia and 150 patients in a group with hypnosedation). Eleven patients underwent a mastectomy in each group. Only patients with mastectomy + axillary sample (sentinel lymph node biopsy [SLNB] or axillary dissection) were studied in the context of mastectomy pain syndrome. The second study was a prospective study initiated in 2016 and still in progress. Out of a total of 150 patients, already included, 10 underwent mastectomy + axillary sample in the group of general anesthesia and 10 in the group of hypnosedation. A written informed consent was obtained for all patients. In the first study, a second informed consent was required and obtained to evaluate chronic pain perception.[10,13]

Population and Data Collection

Eligible individuals were breast cancer patients included in the 2 previous studies and having undergone mastectomy + axillary sample under general anesthesia (GA) or hypnosedation (HYP) between 2010 and 2017 at our Breast Clinic. Thus, a total of 42 patients were evaluated. Half of the patients underwent surgery under GA (GA Group, n = 21), while the other half were operated with HYP (HYP Group, n = 21).

Clinical data such as medical and surgical factors were gathered from medical record reviews by trained research assistants. In our institution, all patients are evaluated for acute pain in the postoperative period in an attempt to evaluate and to adequately treat acute postoperative pain. Evaluations are performed by Numerical Pain Rating Scales and Visual Analog Scales on days 0 and 1. This evaluation is independently performed by nurses. In our studies, an additional evaluation was performed on day 8. In the context of our treating clinic, which is known for its studies of hypnosedation, randomization was not possible for patients because highly motivated patients who want to undergo surgery (mastectomy) while on hypnosedation refuse to be included in a blinded study with the risk to be operated while on general anesthesia.

One of the patients was a man, while all the others were women (Table 1). The mean follow-up after surgery was 4.1 years in the GA group and 4.5 years in the HYP group (Table 3).

The average age of patients included in the study was 58 years in the reference group, GA group (range = 39-75 years), and 60.1 years in HYP group (range = 36-79 years; Table 1). This well-balanced age distribution in both groups is important to point out, as young age is known to be a risk factor for developing chronic pain.[2,3] Patients with prior medical history of other cancer, rheumatologic disorders (polyarthritis), neurologic problems (polysclerosis), or depression could be included in this study.

Table 1 summarizes the demographical and tumor characteristics of the study population. These characteristics were well balanced between the 2 groups, as shown in Tables 1 and 2. In the reference GA group, 12 SLNBs and 9 axillary lymph node dissections (ALNDs) were performed in addition to mastectomy. Ten SLNBs and 11 ALNDs were carried out in the HYP group (Table 2). There were no

Table 1. Demographical and Tumor Characteristics of the Sample.

	GA Group (Number of Patients)	HYP Group (Number of Patients)	*P*	95% Confidence Interval
Tumor characteristics				
DCIS	2	1	1.0	
LCIS	0	1	1.0	
IDC	9	8	1.0	
ILC	2	3	1.0	
Mixed (IDC + ILC)	2	3	1.0	
Other subtypes	6	5	1.0	
ER and/or PR+	18	17	1.0	
HER 2 (FISH+)	0	5	.0478	0-0.98
T1	13	11	.7552	0.37-6.02
T2	4	7	.4841	0.1-130.2
T3	2	1	1.0	
T4	0	0	1.0	
Tis	2	2	1.0	
Patient characteristics				
Age				
Median	58	60.14	.5376	
Standard deviation	10.99	11.34		
Men	0	1	1.0	
Women	21	20	1.0	
Medical history of				
Polyarthritis	1	2		
Other cancer	1	1		
Depression	2	2		
Neurological disorder	0	2		

Abbreviations: GA, general anesthesia; HYP, hypnosedation; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; HER2, human epithelial growth factor receptor 2; FISH, fluorescent in situ hybridization; T1, T2, T3, T4, Tis, TNM classification.

Table 2. Type of Surgery and Anesthesia Performed.

	GA Group (Number of Patients)	HYP Group (Number of Patients)	*P*	95% Confidence Interval
Type of surgery				
Mastectomy + SLNB	12	10	.7573	0.37-5.87
Mastectomy + ALND	9	11	.7573	0.18-2.7
Type of anesthesia				
Local anesthesia				
Administered	3	21	7.52e-09	0-0.06
Not administered	18	0	7.52e-09	16.65-inf
Block				
Administered	15	19	.2379	0.02-1.81
Pectoralis nerve blocks I and 2	15	15	1.0	0.21-4.72
Paravertebral block	0	4	.1069	0-1.42
Not administered	6	2	.2379	0.55-42.4
Local and/or locoregional anesthesia	18	21	.2317	0-2.35

Abbreviations: GA, general anesthesia; HYP, hypnosedation; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

Table 3. Adjuvant Treatments Administered and Mean Duration of Follow-up.

	GA Group (n = 21)	HYP Group (n = 21)	*P*
Adjuvant treatments			
Radiotherapy			
Administered	9	12	.5
Not administered	12	9	
Chemotherapy			
Administered	10	9	1.0
Not administered	11	12	
Endocrine therapy			
Administered	18	16	.69
Not administered	3	5	
Trastuzumab			
Administered	0	5	.04
Not administered	21	16	
Breast reconstructive surgery	8	6	.74
	13	15	
Mean follow-up (years)	4.14	4.48	.9

Abbreviations: GA, general anesthesia; HYP, hypnosedation.

significant surgical complications in any group. In the HYP group, 15 and 4 patients, respectively, had pectoralis nerve block (PEC) and paravertebral block and all of them had additional local anesthesia. In GA group, 15 patients had a PEC block and 3 received LA (Table 2).

After surgery, 9 patients received radiotherapy in GA group and 12 in HYP group, 10 required chemotherapy in GA group and 9 in HYP group, and endocrine therapy was administered in 17 patients in GA group and 16 in HYP group. Eight patients benefited from breast reconstructive surgery in GA group and 6 in HYP group (Table 3).

To summarize, there were no significant differences between the 2 groups in terms of key features such as patients' age, type of axillary surgery, local and regional anesthesia, tumor characteristics, adjuvant treatment modalities, and breast reconstruction.

Anesthesia and Surgical Procedures

In both groups, patients were evaluated before surgery during a preoperative anesthesiology consultation. In the HYP group, patients received specific explanation about hypnosedation. During this session, the modalities and the course of the procedure were described to patients, and physicians confirmed that they were adequate candidates for this kind of analgesia and anesthetic procedure, that is, they were able to sign an informed consent and able to understand languages proposed in our institution. No patient requesting hypnosedation was refused in these 2 studies. One hour before surgery, premedication with lorazepam (0.5 mg) was proposed to the patient. At the time of the surgical procedure, all the patients were monitored classically (electrocardiography, noninvasive blood pressure measurement, blood oxygen saturation assessment [SpO_2], and capnography), and a paravertebral or PEC 1 and 2 with a combination of levobupivacaine 0.25% and lidocaine 1% was performed. Oxygen was administered to each patient. Once they were comfortably installed on the operating table, the anesthesiologist induced hypnosis as a procedure where indirect suggestions were given on the anesthesiologist's observation of patient's behavior, and on her or his judgement of the patient's needs. The patients were invited to fix a point in front of them while concentrating on their body to achieve total muscle relaxation before finally closing their eyes. Guided by the anesthesiologist, the patients had to focus their attention on a positive recollection. By using a calm and monotonous voice, the anesthesiologist constantly talked to help them relive a dream or experience so that they remained as detached and dissociated as possible from the reality surrounding them. A state of intense well-being and comfort had to be reached and maintained during the whole procedure. The peri-incisional skin is injected with a local anesthetic such as 0.5% lidocaine combined to 0.25% levobupivacaine. A continuous infusion of remifentanil, a μ-opioid agonist, was started at a rate of 0.05 μg/kg/min (a dose about 10 times lower than the one used for general anesthesia) and was modified or stopped as required. If needed, small doses of midazolam were administered, 0.1 mg at a time if an anxiolytic was needed. A preestablished communication system between the anesthesiologist and their patients allowed them to express any discomfort. In such a case, the hypnotic state was strengthened, the surgeon could improve local anesthesia, or the infusion rate of remifentanil could be increased. Once the procedure was completed, the anesthesiologist gave the patients recommendations (posthypnotic suggestions) in order to

preserve their comfort in the postoperative period, to have a correct healing, to keep the wound dry, and to give the patient the opportunity to reuse hypnosis during their cancer treatment.

None of the patients in the HYP group included in the current study required a conversion to general anesthesia. So, in this group, patients maintained consciousness during the whole surgical procedure and avoided pharmacological coma.[14] General anesthesia as well as the mastectomy with ALND or SLNB (modified radical mastectomy according to Patey)[15] were performed following the usual institutional procedures, based on international guidelines.

Premedication with lorazepam was the same in the 2 groups. In an attempt to reduce bias, pre- and postoperative suggestions were given by the anesthetists to patients undergoing surgery while on general anesthesia. In the days after surgery, pain was controlled following the institution's protocol: paracetamol 1 g/6 h and naproxen 500 mg/12 h in case of low pain, tramadol 50 mg/6 h in case of mild pain, and piritramide 20 mg/12 h in case of severe pain. Those medicines were given to patients as required.

Outcomes Assessment

Main Outcome: PMPS. The main aim of the study was to assess postmastectomy chronic pain. Pain was evaluated during the preoperative consultation, in order not to neglect preexisting chest wall pain. The evaluations were repeated postoperatively at day 1, day 8, and then at each follow-up consultation (performed every 3 months during the first 2 years and then every 6 months for the next 3 years). All study participants were asked to respond to a simple pain questionnaire based on the definition of the PMPS proposed by Waltho and Rockwell.[4,5,14] This questionnaire also investigates the location of pain and the neuropathic characteristics of the pain.[16] These authors performed a review of the literature, which highlighted a significant number of discrepancies on how to define PMPS.[17] Therefore, they proposed to establish the International Association for the Study of Pain definition of PMPS and to consensually define it as pain occurring after mastectomy, located in the ipsilateral chest wall, axilla, arm, and/or reconstructed breast, present at least 50% of the time for at least 3 months, with an average intensity superior to 3 on a scale running from 0 to 10 (Numeric Pain Rating Scale) and possessing neuropathic qualities. We considered that patients were suffering from PMPS if the pain was fitting all those conditions of character, location, intensity, and timing. The pain questionnaire used in our institution is available as a supplementary file (available online). It is inspired by the DN4 scale.[16]

Secondary Outcomes:Anxiety Scale, Lymphedema, and Shoulder ROM. The 2 following factors were assessed as patient-reported outcomes. Patients' distress severity was measured with the National Comprehensive Cancer Network distress thermometer. This is a Visual Analog Scale in the form of a thermometer. A score equal to or greater than 5 on the scale should draw attention, and patients should be referred to psychosocial services.

The late outcomes were evaluated by physicians and physiotherapists. We considered that patients suffered from lymphedema when the arms' volumetric measurements fulfilled the following criteria: 8 volumetric measurements performed between the lower and the upper extremity of each arm indicated a difference greater than or equal to 5 volume% (RVC: relative volume change) between the 2 arms of the patients (which corresponds to the Belgian criteria for reimbursement of physiotherapy). In case of abnormalities of circumferences, values were repeated by a physiotherapist and volumetric changes were noted. Measures were performed before the surgery and then at each follow-up visit.

Range of motion was recorded for shoulder flexion, abduction, internal rotation, and external rotation, and measures were performed with a goniometer. A simple composite score was defined as the total of these 4 functions.[14] Shoulder ROM was assessed prior to, and then 3, 6, 9, and 12 months following surgery. In case of abnormal values, patients were referred to a physiotherapist. Measures of ROM were repeated. All measures were included in this study.

Statistical Analysis

Data were analyzed using the R Core Team software, 2017 (https://www.R-project.org). P values <.05 were considered as statistically significant. Welch's 2 sample t test, Fisher's exact test, and χ^2 test (with rates continuity correction) were used to compare PMPS, dose of remifentanil, incidence of lymphedema, and decreased ROM in the 2 groups of patients (general anesthesia vs hypnosis). The distribution in the 2 groups of the other factors potentially influencing PMPS was evaluated with χ^2 tests, Fisher exact tests, or the Welch's 2 sample t test for age.

Results

Primary Outcome

PMPS. Forty-two patients were included in our study. Twenty-one patients had a mastectomy performed with hypnosedation associated to local anesthesia ± regional anesthesia, and 21 were operated under general anesthesia ± regional or local anesthesia. Ten out of the 42 patients (23.8%) in the total patient population experienced postmastectomy chronic pain, which is in the 20% to 60% range reported in the literature. Among the patients who underwent mastectomy with hypnosedation, only 1 out of 21 experienced PMPS (4.8%), compared with 9 out of 21 (42.9%) in the GA group (P = .008; Table 4). Pain characteristics of patients suffering from PMPS are described in

Table 4. Incidence of PMPS, Decreased ROM, Lymphedema and Value of Distress Score.

	GA Group (Number of Patients)	HYP Group (Number of Patients)	*P*	95% Confidence Interval
PMPS[a]	9	1	.008	1.616-1.685
PMPS[b]	6	1	.03	0.968-0.981
Decreased ROM	7	1	.04	1.046-1.400
Lymphedema	3	0	.2	
Distress score day 1 (mean value)	8.81	4.2	2.2e-16	4.43-4.63

Abbreviations: PMPS, postmastectomy pain syndrome; ROM, range of motion; GA, general anesthesia; HYP, hypnosedation.
[a]All patients considered.
[b]Patients with no local and/or locoregional anesthesia in general anesthesia group not taken into consideration.

Table 5. Characteristics of Pain Among Patients Suffering From PMPS.

	GA Group (n = 9)		HYP Group (n = 1)
Preoperative pain			
Yes	1/9		0/1
No	8/9		1/1
Intensity score	3		—
Acute postoperative pain			
Day 1	7 (4-9)		6
Day 8	5 (3-8)		4
PMPS Timing	Number of Patients	Score (m)	Score
3 months	9	7 (5-9)	6
6 months	9	7 (5-9)	5
9 months	9	6 (5-8)	5
12 months	9	6 (4-8)	4
15 months	9	6 (4-8)	4
18 months	9	6 (4-8)	4
21 months	9	6 (4-8)	
24 months	9	6 (4-8)	3
30 months	8	5 (4-7)	3
36 months	7	5 (4-7)	No pain
42 months	6	5 (4-7)	No pain
48 months	5	5 (4-7)	No pain

Abbreviations: PMPS, postmastectomy pain syndrome; GA, general anesthesia; HYP, hypnosedation; m, mean value + range.

Table 5.

The total administered dose of remifentanil was 427.8 ± 20.47 µg (mean value ± standard deviation) in the HYP group and 4135 ± 29.47 µg ($P = 9.7$ e-10) in the GA group.

In GA group, general anesthesia was associated to regional anesthesia (PECs) in 15 cases and to local anesthesia in 3 cases. The difference in PMPS between GA group and HYP group remains highly significant, with a *P* value at .03, if patients included in GA group with no local or regional anesthesia were excluded from the statistical analysis.

In HYP group, perioperative hypnosis was combined in all cases to local anesthesia. In addition, regional anesthesia was performed on 19 patients (4 thoracic paravertebral nerve blocks [TPVBs] and 15 PECs).

We can conclude that the drop in postmastectomy chronic pain in HYP group compared with GA group was due to the perioperative hypnosis and not due to the locoregional anesthesia.

Secondary Outcomes

Distress. Results concerning global distress are going in the same direction, as patients who underwent mastectomy under hypnoanalgesia experience less distress.

Lymphedema. As shown in Table 4, no patient suffered from lymphedema in the HYP group, whereas 3 patients presented arm swelling in the GA group (not statistically significant).

Shoulder ROM. Shoulder ROM was preserved in the HYP group, as only one patient had decreased ROM instead of 7 in the other group (at 1 year). Of note, the patient suffering from decreased ROM in the hypnosis group is the one who developed PMPS, and among the patients of the GA group who had decreased ROM, 6 also suffered from PMPS.

Discussion

Our study shows a statistically significant lower incidence of PMPS in HYP group compared with GA group. Decreased shoulder ROM and anxiety scales were also statistically lowered in group HYP. Incidence of lymphedema was lower but not statistically different. We here demonstrate that hypnosis sedation is associated with reduced development of postmastectomy chronic pain. To our knowledge, the impact of perioperative hypnosedation on the development of postsurgical chronic pain has not been studied yet. Our study seems to be the first one to assess the potential benefits of this procedure on postsurgical chronic pain.

Hypnosis Benefits

This finding is interesting because hypnosis used as a complementary intervention for surgical patients has already shown many advantages.

First, it is a nonpharmacological and noninvasive procedure without any side effects. In addition to being a safe procedure, hypnosis gives patients the opportunity to experience a pleasant experience as it leads them through relaxing and peaceful imagery.[16] Indeed, most patients reported such an experience.

Moreover, the use of hypnosis as an adjunctive approach during breast cancer care seems to generate many benefits.[10,18-21] Used during the perioperative period, it decreases surgical complications such as lymphocele,[10,22,23] postoperative hospitalization duration,[10,22,23] and postoperative distress, and it has a positive impact on adverse effects of adjuvant therapy such as reduction of asthenia during chemotherapy, reduction of hot flashes, joint and muscle pain, and asthenia during endocrine therapy.[10] A presurgical hypnosis intervention before breast cancer surgery or breast biopsy decreases acute postsurgical pain and anxiety.[22-25] Finally, hypnoanalgesia improves the postoperative recovery by avoiding the adverse effects of general anesthesia (nausea, vomiting, asthenia[22,23,25]).

Risk Factors Associated With the Development of Postsurgical Chronic Pain

The pathophysiology of postsurgical chronic pain is explained by a complex interaction between psychosocial and neurobiological factors. Several studies have identified independent risk factors associated with the development of postmastectomy chronic pain.

First, young patient age[3-5,26-28] can explain higher postsurgical pain due to changes in the pain perception system and the ensuing changes in physical activities.[5] The poorer prognosis of breast cancer in younger patients may generate greater anxiety and psychological distress that are known to be closely associated with perception of the intensity of pain.[27] This is an unmodifiable criterion. As already mentioned, mean patient age was well balanced in both groups of our study.

The second risk factor is the type of axillary surgical procedure. ALND compared with SLNB increases the risk to develop postsurgical chronic pain.[3,5,27,29] The minimally invasive surgical technique reduces nerve damages, especially sparing the intercostobrachial nerve. The numbers of ALND and SLNB are also well balanced in the 2 groups.

The third well-known factor is the intensity of the acute postsurgical pain. Severe acute postoperative pain predisposes to the development of postsurgical chronic pain.[16,29-31] Indeed, 10% to 50% of patients experiencing acute postsurgical pain will suffer from persistent pain after common surgery such as breast and thoracic surgery, leg amputation, coronary bypass surgery, and groin hernia repair.[32]

Anxiety, depression, emotional distress, and pain catastrophizing affect intensity of pain perception.[23,33] These factors are associated with greater acute postsurgical pain[5,34] and thus with the development of chronic postsurgical pain.[33] By reducing the occurrence of such feelings, hypnosis results in decreased chronic postsurgical pain.

Acute as a Predictor of Chronic Postsurgical Pain

Postoperative chronic pain is the consequence of ongoing inflammatory processes resulting from tissue damage and is usually due to iatrogenic neuropathic pain arising from tissue and nerve injury. Acute postsurgical pain may cause neuroplastic changes resulting in peripheral sensitization, by reducing the threshold of nociceptors' peripheral terminals, and central sensitization, by increasing the excitability of the spinal cord and brain neurons. These changes contribute to amplify and maintain pain and lead to persistent pain.[26,32,33,35] In this study, in the HYP group, the patient who developed PMPS had acute postoperative pain (score 6 on day 1 and 4 on day 8), and this was also the case for the 9 patients in the AG group (score 7 on day 1 and 5 on day 8; Table 5).

Procedures Proven to Reduce Pain After Breast Surgery

Several perioperative procedures have been studied to minimize acute and/or chronic pain occurring after breast cancer surgery.[36] The most established one is probably the TPVB,

known to significantly reduce PMPS whether in single-dose or continuous infusion,[36,37] as well as the PEC, which reduces acute pain following breast surgery.[36] Local lidocaine injection is the second procedure well known to decrease PMPS.[29,38]

The use of drugs such as gabapentin, venlafaxine, and pregabalin has proven a benefit in acute and chronic postmastectomy pain.[36,38,39] Other methods like EMLA application, ropivacaine infusion, mexiletine administration, wound deposit of liposome bupivacaine, and wound catheter of levobupivacaine placement have also led to significant pain reduction after breast cancer surgery.[36,39,40] The use of multimodal analgesia during the perioperative period has the potential to prevent central sensitization.[32] Although they seem effective, all these pharmacological procedures are rarely completely efficient and most of them are associated with significant side effects.

These considerations are another argument in favor of hypnosedation, as it is devoid of adverse effects. With hypnosedation, the patient maintains consciousness during the whole surgical procedure and this technique permits to avoid pharmacological coma and negative impact on immune functions.[11,12] In our study, we also confirm that the total dose of remifentanil is significantly lower in the HYP group than in the GA group. This result is very significant and represents an important argument in favor of the effectiveness of hypnosedation.

Attention must be drawn to a critical point while discussing our results. In addition to general anesthesia or hypnosedation, many patients were locally anesthetized with local anesthesia or regional anesthesia (TPVBs or PECs) or both in combination. In any case, the drugs used were the same (lidocaine 0.5% and levobupivacaine 0.25%), and the total maximum doses were identical whether only one or both techniques were used simultaneously. The only difference was the injection localization. In the case of local anesthesia, the anesthetics are injected close to the distal nerve terminals, whereas in TPVB and PECs, they are injected at the proximal part of the nerve. TPVB and local anesthesia were both shown to decrease PMPS. To our knowledge, only one prospective double-blind randomized placebo-controlled clinical trial compared these 2 techniques in terms of efficacy on chronic pain following breast cancer surgery.[8] With an unexpectedly low rate of chronic pain at 8%, far from the usual range (between 20% and 65%), this study was not able to statistically assess a difference between PVB and local anesthesia in term of reduction of PMPS occurrence. They, nonetheless, concluded that despite this low percentage, both techniques were most certainly equivalent and that neither was more potent than the other in reducing the burden of PMPS. With this in mind, we decided to consider both these techniques as similar and we will, therefore, speak of complementary anesthesia for all patients who received local anesthesia alone, PVB alone, or both local anesthesia and PVB together. In our study, 18 patients in the GA group and 21 patients in the HYP group further benefited from complementary anesthesia. Since the use of additional anesthesia was well balanced between both groups, we can safely conclude that the decrease of the number of PMPS cases in our comparative study is truly due to hypnosedation.

Limitations

Some limitations must be considered to interpret the current study. First of all, we did not randomize patients between the 2 groups for the simple reason that this was impossible in our clinical context. For patients eager to have hypnosedation, it was absolutely inconceivable to propose a general anesthesia, and conversely, it was impossible to impose hypnosis on patients who are not motivated for this type of analgesia because the collaboration of patients is very important. It was, of course, not possible to conduct a blinded study. In the literature, there are randomized trials focused on preoperative hypnosis session in the context of breast cancer. But, after this session, all patients underwent surgery while on general anesthesia.[19,21,23] Another major limitation is the small study sample that may have hampered the results analysis. Moreover, we considered the 3 locoregional analgesia methods to have the same efficacy. Indeed, the types of drugs and the doses were similar regardless of the technique used. As explained before, the only difference between all these interventions is the localization of the injection. Finally, as already mentioned, studies assessing hypnosis could be distorted by the fact that patients suitable for hypnosis must have a particular psychological mindset, which can be a huge bias for the study results. Other factors may also play an important role: the surgical context as well as patient motivation, collaboration, and confidence with the medical team. To definitively reduce bias, it is crucial to investigate biological parameters allowing us to explain the benefits of hypnosis.

Conclusion

PMPS continues to have a high prevalence and negatively affects the quality of life of breast cancer patients. Because development of PMPS is correlated to psychosocial and neurobiological risk factors, the best preventive strategy may be one that combines multimodal pharmacologic and behavioral approaches.[41,42] The results of our study are promising despite limitations of the design. In our second study, which is still ongoing, some biological parameters such as C-reactive protein blood rate, neutrophils to lymphocytes ratio, endocannabinoids rate, and salivary immunoglobulin A secretions are being evaluated to try specify more precise mechanisms by which hypnosis exerts all its effects. A larger clinical study with investigation of several

laboratory parameters is thus warranted to confirm our preliminary results. In the future, despite the difficulties, it would be appropriate to implement randomized trials of hypnosedation.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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