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Original article

The advantages of hypnosis intervention on breast cancer surgery and adjuvant therapy

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ABSTRACT

Background: In oncology, hypnosis has been used for pain relief in metastatic patients but rarely for induction of anesthesia.
Material and method: Between January 2010 and October 2015, 300 patients from our Breast Clinic (Cliniques universitaires Saint-Luc, Université catholique de Louvain) were included in an observational, non-randomized study approved by our local ethics committee (ClinicalTrials.gov – NCT03003611). **The hypothesis of our study was that hypnosis intervention could decrease side effects of breast surgery.** 150 consecutive patients underwent breast surgery while on general anesthesia (group I), and 150 consecutive patients underwent the same surgical procedures while on hypnosis sedation (group II).
After surgery, in each group, 32 patients received chemotherapy, radiotherapy was administered to 123 patients, and 115 patients received endocrine therapy.
Results: Duration of hospitalization was statistically significantly reduced in group II versus group I: 3 versus 4.1 days ($p = 0.0000057$) for all surgical procedures. The number of post-mastectomy lymph punctures was reduced in group II (1–3, median value $n = 1.5$) versus group I (2–5, median value $n = 3.1$) ($p = 0.01$), as was the quantity of lymph removed (103 ml versus 462.7 ml) ($p = 0.0297$) in the group of mastectomies.
Anxiety scale was also statistically reduced in the postoperative period among the group of patients undergoing surgery while on hypnosis sedation ($p = 0.0000000000000002$).
The incidence of asthenia during chemotherapy was statistically decreased ($p = 0.01$) in group II. In this group, there was a statistically non-significant trend towards a decrease in the incidence of nausea/vomiting ($p = 0.1$), and the frequency of radiodermitis ($p = 0.002$) and post-radiotherapy asthenia ($p = 0.000000881$) was also reduced. Finally, the incidence of hot flashes ($p = 0.0000000000021$), joint and muscle pain ($p = 0.0000000000021$) and asthenia while on endocrine therapy ($p = 0.000000022$) were statistically significantly decreased in group II.
Discussion: Hypnosis sedation exerts beneficial effects on nearly all modalities of breast cancer treatment.
Conclusion: Benefits of hypnosis sedation on breast cancer treatment are very encouraging and further promote the concept of integrative oncology.

1. Introduction

Breast cancer is the most frequent cancer in women worldwide. Fortunately, there is an increase in survival rates; this survival benefit is essentially due to therapeutic progress, and contribution of screening seems to be less evident [1]. However, anticancer treatment is associated with non-negligible side effects related to the different therapeutic modalities, such as [2,3]:

- Side effects associated with surgery: pain, distress, anxiety.
- Side effects associated with radiotherapy: pain, fatigue, radiodermitis, anxiety.

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- Side effects associated with chemotherapy: nausea, fatigue, muscle pain, vomiting, anxiety.
- Side effects associated with endocrine therapy: pain, muscle and joint pain, hot flashes.

Hypnosis has been used for pain relief in metastatic patients but rarely for induction of anesthesia.

More recently, hypnosis has generated important interest in the management of side effects induced by adjuvant treatments [3].

Numerous studies have highlighted the value of hypnotic procedures in different clinical situations, such as stress or pain management, situations which are very frequent in cancer management [4]. The present study evaluates the effect of hypnosis sedation as a modality of anesthesia for oncologic breast surgery and investigates the effect of hypnosis sedation on different breast cancer treatments.

Some researchers believe that hypnosis is related to an altered state of consciousness while others assume that this phenomenon can be explained by a psychological concept suggested by clinicians'/patients' expectations [5].

Hypnosis has been defined by Liebovici V as "a procedure during which health professional researchers suggest that the patient changes in sensations, perception or behavior". It remains difficult to provide an optimal definition of hypnosis. However, the definition proposed by Montgomery characterizes hypnosis as an "agreement between a person designated as the hypnotist and a person designated as the patient to participate in a psychotherapeutic technique based on the hypnotist providing suggestions for changes in sensation, perception, cognition, affect, mood or behavior". This definition emphasizes the relationship between the hypnotist and his/her patient as a necessary condition for anyone practicing hypnosis.

The present study evaluates the effects of hypnosis sedation as a modality of anesthesia for oncologic breast surgery and investigates the effects of hypnosis sedation on different modalities of breast cancer treatment [6,7]. The hypothesis sustained by our study is that hypnosis intervention is able to decrease side effects of surgery and other cancer therapeutic options.

Table 1
Tumor characteristics.

Histologic subtype	General anesthesia group I	Hypnosis sedation group II
DCIS	23	23
LCIS	9	10
IDC	85	86
ILC	17	20
Mixed (IDC + ILC)	12	15
Other subtypes	5	0
ER and/or PgR (+)	130	131
HER2+ (FISH +)	9	8

DCIS: ductal carcinoma *in situ*.
LCIS: lobular carcinoma *in situ*.
IDC: invasive ductal carcinoma.
ILC: invasive lobular carcinoma.
ER: estrogen receptor.
PgR: progesterone receptor.
HER2: Human Epidermal Growth Factor Receptor-2.
FISH: Fluorescent *in situ* hybridization.

Table 2
Patients' characteristics and treatment modalities.

	General anesthesia group I (150 patients /151 procedures)	Hypnosis sedation group II (150 patients/154 procedures)
Mean age (years)	58	59.5
Menopausal status		
Premenopausal	26	25
Postmenopausal	124	125
Treatment modalities		
Lumpectomy alone	10 (10 patients)	17 (14 patients)
Lumpectomy +	92	94
SLNB or ALND	32	33
Mastectomy alone	1	1
Mastectomy/SLNB or ALND	16	16
Radiotherapy	123	123
Chemotherapy	32	32
Trastuzumab	9	8
Endocrine therapy	115	115

2. Material and method

Between January 2010 and October 2015, 300 patients from our **Breast Clinic** (King Albert II Cancer Institute, Cliniques universitaires Saint-Luc, Université catholique de Louvain) were included in an observational non-randomized study approved by our local ethics committee (clinicaltrials.gov – NCT 03003611).

One hundred and fifty consecutive patients underwent **breast surgery** (lumpectomy or mastectomy) +/− axillary lymph node dissection or sentinel lymph node biopsy while on general anesthesia (group I) and 150 consecutive patients underwent the same surgical procedures while on hypnosis sedation (group II).

The **tumor characteristics** were well balanced between the two groups, as mentioned in Table 1. **Patients' characteristics and treatment modalities** are described in Table 2.

After surgery, 32 patients received chemotherapy in both groups, radiotherapy was administered to 123 patients in both groups and 115 patients in both groups received endocrine therapy.

Hypnosis sedation was performed as follows:

The first and very important step was the preoperative consultation. The anesthesiologists had to explain the modalities and the course of the entire procedure. They also had to check if the patient was a good candidate for hypnosedation.

At the time of the surgical procedure, all patients were classically monitored with ECG, noninvasive blood pressure measurement, blood oxygen saturation (SpO2) assessment and capnography. Lorazepam 0.5 mg was proposed to the patient 1 h before surgery as premedication. Oxygen was given. After obtaining a comfortable position on the operating table, the anesthesiologist induced hypnosis with a technique described by Milton Erickson, inviting her patient to fix her eyes on a point in front of her and to concentrate on her body in order to achieve increasing muscle relaxation and finally closure of the eyes. Progressively, guided by the voice of the anesthesiologist, the patient was invited to focus her attention on a positive memory. Using a calm and monotonous voice, the anesthesiologist continually talked to the patient, guiding her with permissive and indirect suggestions of well-being to relive her dream or experience and remain detached from the reality surrounding her. A state of intense well-being is reached and maintained during all the surgery. A continuous infusion of remifentanil, a micro-opioid drugs, was started at the rate of 0.05 μg/kg/min and modified as required. In some cases, the infusion of remifentanil was stopped. Midazolam was sometimes titrated at 0.1 mg/0.1 mg if needed as an anxiolytic. A signaling system was established between the patient and the anesthesiologist in case of discomfort. If the patient reports such discomfort during the procedure, the anesthesiologist strengthens the hypnotic state, asks the surgeon to give more local anesthesia and can also increase the infusion rate of remifentanil. The goal is to insure a consistent level of comfort. At the end of the surgery, the anesthesiologist gives recommendations to the patient aimed at maintaining comfort in the postoperative period, leading to correct healing, keeping the

wound dry and giving the patient the opportunity to re-use hypnosis during her cancer treatment.

Different **parameters** were studied for each treatment modality.

Concerning the perioperative period, the duration of surgery was investigated in the two groups (Table 4).

One of the aims of this study was to evaluate the duration of hospitalization in the two groups.

We also investigated the effects of hypnosis sedation on lymph production.

Finally, because patients were followed prospectively, we decided to evaluate if hypnosis sedation has an impact on side effects of radiotherapy such as asthenia and incidence of radiodermitis.

Regardless of chemotherapy, effects of hypnosis sedation were studied in the domain of nausea/vomiting induction and asthenia.

Finally, compliance to endocrine therapy, incidence of hot flashes, incidence of joint and muscle pain and asthenia were parameters studied during the administration of endocrine therapy.

Statistical analyses were performed using software R Core Team, 20147 (url: https://www.R-project.org).

Welch-two sample *t*-test and X^2-test (with rates continuity correction) were used to compare the studied parameters in the two groups of patients (general anesthesia and hypnosis).

p-values < 0.05 were considered as statistically significant.

3. Results

3.1. Effects of hypnosis in the surgical field

Duration of hospitalization was statistically significantly reduced in group II versus group I: 3 versus 4.1 days (95%confidence interval: 1.07–1.37; p = 0.00000578) for all surgical procedures.

The same results were observed for mastectomies with axillary exploration: 3 versus 5.2 days (95% confidence interval:1.80–2.31; p = 0.0002) and for lumpectomy associated with axillary dissection, sentinel lymph node biopsy or complementary axillary dissection: 3 versus 4.2 days (95% confidence interval: 1.005–1.202; p = 0.00065).

Since 2010, the duration of hospitalization has decreased in the 2 groups because of economic requirements but significant differences persist between the 2 groups.

The number of post-mastectomy lymph punctures was reduced in group II (1–3) (median value n = 1.6) versus group I (2–5) (median value n = 3.1) (p = 0.01), as was the quantity of lymph removed in each puncture (103 versus 462.7 ml; p = 0.0297) in the group of mastectomies.

The duration of the different surgical procedures was also analyzed and there was no statistical difference observed between the two groups (Table 3).

In group I (general anesthesia), the duration of lumpectomy was globally estimated at 48 min (range between 38 and 60 min).

In group II (hypnosis sedation), the duration was estimated at 47 min (range between 35 and 61 min).

Table 3
Mean duration of surgical procedures.

	General anesthesia group I (minutes)	Hypnosis sedation group II (minutes)
Lumpectomy alone	48 (38–60)	47 (35–61)
Lumpectomy + SLNB	75 (60–88)	72 (55–86)
Lumpectomy + ALND	85 (70–90)	84 (69–90)
Mastectomy alone	80	78
Mastectomy + SLNB	90 (80–94)	88 (78–93)
Mastectomy + ALND	104 (98–110)	102 (97–108)

Table 4
Anxiety scales.

	General anesthesia group I	Hypnosis sedation group II
Anxiety scale D0	N = 150	N = 150
	8.86	8.81
	p-value = 0.2	
	95% confidence interval (−0.003–0.136)	
Anxiety scale DI	N = 150	N = 150
	8.66	4.12
	p-value = $2.2e^{-16}$	
	95% confidence interval (4.43–4.63)	

The duration of lumpectomy associated with sentinel lymph node dissection was 75 min in the general anesthesia group (60–88 min) and 72 min in the hypnosis sedation group (58–86 min).

In the group of mastectomies associated with sentinel lymph node biopsy, the duration was 90 min (80–94) in group I, and 88 min (78–93) in group II. In the group of mastectomies associated with axillary dissection, the duration was 104 min in the general anesthesia group (98–110) and 102 min in the hypnosis sedation group (98–108).

The duration of lumpectomies associated with axillary lymph node dissection was 85 min (80–90) in the general anesthesia group and 84 min (69–90) in the hypnosis sedation group. The incidence of surgical complications such as haematomas and infections was studied and similar in the two groups.

Anxiety scale was measured by NCCNDT (National Comprehensive Cancer Networks Distress Thermometer) labelled with

- No distress at 0.
- Moderate distress at 5.
- Extreme distress at 10.

Anxiety was measured before the surgical procedure (D0) and after the surgical procedure (DI). The results are mentioned and developed in Table 4.

Anxiety decreased significantly in the hypnosis sedation group at DI.

3.2. Effects of hypnosis on adjuvant treatment

The incidence of grade II and III radiodermitis was investigated in the two groups.

This complication was less frequent in the hypnosis sedation group, with a p-value of 0.002: 5 cases of moderate and severe radiodermitis were observed in the general anesthesia group, and only 2 cases in the hypnosis sedation group.

Asthenia observed at the end of radiotherapy was more severe in group I (statistically significant p-value of 0.0000008813) with 50 cases diagnosed with asthenia grade III in the general anesthesia group and 15 cases in the hypnosis sedation group.

Side effects of chemotherapy were also studied.

Grade III asthenia was observed in 12 cases in the general anesthesia group and just 3 cases in the hypnosis sedation group. The X^2 reveals a p-value of 0.01.

The incidence of nausea and vomiting was not statistically different in the two groups with a p-value of 0.13 but the number of patients undergoing chemotherapy was low in the two groups.

Ten patients mentioned important nausea and vomiting in the general anesthesia group and only 4 patients mentioned severe vomiting and nausea in the hypnosis sedation group.

Side effects of endocrine therapy were studied in the two

groups.

The absence of compliance was not different between the two groups with a p-value of 0.44.

On the contrary, the incidence of severe hot flashes was statistically reduced in the hypnosis sedation group, with a p-value of 0.0000000000037.

The incidence of joint or muscle pain was also reduced, with a p-value of 0.0000000000021.

Asthenia observed in the group of patients receiving endocrine therapy was also decreased in the hypnosis sedation group, with a p-value of 0.0000000228.

In terms of follow-up, no differences were currently observed in overall or disease-free survival (Table 4).

4. Discussion

To our knowledge, this is the first large study investigating the effects of hypnosis sedation in place of general anesthesia in the field of oncologic breast surgery and its potential effects on the different treatment options. In the review of randomized controlled trials performed in breast cancer care published by Cramer et al., in 2015 [8], there are a few randomized studies investigating hypnosis induction for breast surgery, but these studies essentially concerned patients undergoing a diagnostic biopsy and not the surgical treatment. Some studies [8–13] demonstrated that hypnosis has positive effects on postoperative pain, distress, fatigue, nausea and vomiting, but there are no studies investigating surgical complications such as hematoma or lymphocele and no data concerning the effect of hypnosis sedation on the duration of hospitalization.

Our study suggests reduced lymph production after hypnosis sedation. While this might be due to an effect on the immune system, these data need to be confirmed. We did not study immune parameters, and a review of the literature shows that it is difficult to find sensitive and reliable immune markers [14]. The most interesting parameter seems to be salivary immunoglobulin A, as observed in the Miller and Cohen review [14]. In future prospective studies, this parameter needs to be investigated to confirm the immune impact of hypnosis.

The reduction in the duration of hospital stays might be partly explained by psychological factors. It is well known that substantial psychological distress is present in 1 out of every 3 breast cancer patients. Those symptoms can prolong hospital stays and thereby increase the cost of medical care. In our study, standardized hypnotic procedures - such as suggestions - were performed, and also suggestions for self hypnosis. These suggestions demonstrated a significant impact on anxiety scales, which significantly decreased.

No deleterious effects of hypnosis sedation were observed on the duration of the surgical procedure and surgical complications such as hematomas or esthetic outcomes. On the contrary, concerning the duration of hospitalization, hypnosis sedation was proved to be beneficial.

One of the weaknesses of this study is the fact that it is a non-randomized study. For patients consulting in our breast clinic to have surgical procedures while on hypnosis sedation, it was totally impossible to impose a general anesthesia. On the contrary, patients not motivated or too stressed for hypnosis sedation are bad candidates to try this kind of procedure. The baseline psychological differences between the patients treated in both arms might therefore partly explain the observed differences. However, there was no difference between the 2 groups' anxiety scales at D0.

In the second part of the study, we explore the potential benefits of hypnosis sedation and self hypnosis on various other modalities of breast cancer treatment, such as radiotherapy, chemotherapy and endocrine therapy [15–18].

Parameters studied in the context of radiotherapy were the incidence of moderate and severe radiodermitis and the incidence of asthenia [8,15,18–20].

Montgomery published results in 2014 demonstrating reduced distress and fatigue associated with radiotherapy after hypnosis combined with cognitive behavioral therapy.

Some randomized trials [11] reported no adverse effect of hypnosis used before radiotherapy but also no significant benefit.

Chemotherapy improves survival outcomes in early breast cancer patients [2,12,13].

Chemotherapy-induced nausea and vomiting is the adverse event that most impacts patients' quality of life (Fernandez-Ortega P). Persistent nausea and vomiting, which occurs in 10–25% of patients receiving chemotherapy, creates a significant burden for patients.

In our study of early breast cancer patients, only 32 patients received chemotherapy in each group.

There is a trend in favor of a reduction of nausea and vomiting in the hypnosis sedation group, but the reduction was not significant, probably because the two groups are small and maybe also because a single hypnosis procedure was performed (hypnosis sedation during breast surgery, including recommendations for self hypnosis).

In the literature, a positive effect of hypnosis on nausea and vomiting was observed in some studies [8,15–17], but in the great majority of the studies, hypnosis was repeated at each course of chemotherapy.

Another important side effect induced by chemotherapy is asthenia. In our study, asthenia was statistically reduced in the hypnosis sedation group versus the general anesthesia group.

Hot flashes and joint pain are a highly prevalent problem associated with menopause and endocrine therapy for breast cancer (essentially aromatase inhibitors).

In a study presented by Elkins and Johnson [21], hypnosis has been demonstrated to be a potentially effective treatment for hot flashes in breast cancer survivors (BMC, 2011).

In a small prospective study, published in 2004 (Journal of Integrative Medicine), Elkins has demonstrated that hypnosis intervention could achieve a reduction of approximately 69% in hot flashes as compared to baseline among breast cancer survivors.

These interesting results were confirmed in other studies which showed approximately the same results, with a reduction of 68% from baseline in the hypnosis arm.

Results were also published by Elkins in the JCO.

Hypnosis has major advantages regardless of the use of antidepressants and other medications sometimes used for hot flashes in breast cancer patients.

It is to be mentioned that these medications can induce adverse reactions including somnolence and anxiety [8,21–25].

In our study, the reduction in hot flashes was very important among breast cancer patients and this reduction was similar for patients using tamoxifen, anti-estrogen therapy or aromatase inhibitors.

Joint pain is another frequent side effect of aromatase inhibitors. This is an effect that unfortunately leads some patients to discontinue their medication. In the hypnosis sedation group, we observed a significant reduction of joint or muscle pain. This side effect was not previously studied with hypnotic procedures in the literature.

In our study, two major side effects of cancer treatment, asthenia and anxiety, dropped significantly with hypnosis intervention. The National Comprehensive Cancer Network (NCCN) has defined the concept of cancer-related fatigue as “a distressing persistent subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual

functioning" [26].

It is one of the most common side effects in patients with cancer.

Fatigue has been shown to be a consequence of active treatment but, unfortunately, it may also persist well into the post-treatment period.

It is estimated that 43% of breast cancer survivors may experience distress and fatigue as a result of cancer treatment. In our study, hypnosis appears very efficient to decrease asthenia and distress.

The mechanism which could potentially explain this positive impact can be related to the absence of general anesthesia, which could explain a decrease in post-surgery asthenia and a better recovery during this period. However, this mechanism would be unable to explain a positive impact on different adjuvant cancer treatments, because in this study patients received only one session of hypnosis therapy.

In the literature, other interventions such as yoga and exercise medicine have demonstrated efficacy to release cancer-related fatigue (CRF) by decreasing inflammatory markers. These findings highlight the importance of biomarker studies for ongoing trials.

Another potential mechanism is the fact that hypnosis is able to decrease distress and anxiety linked to medical procedures, and asthenia and stress are strongly intricated.

5. Conclusion

Emotional distress related to medical procedures not only causes direct suffering but also negative downstream consequences of distress.

In this context, interventions which significantly reduce distress are needed to improve patient experience, especially in the field of oncologic interventions. Hypnosis is a non-pharmacologic intervention with no non-specific side effects which has been shown to be beneficial in reducing distress and fatigue related to medical procedures. This study shows that hypnosis sedation in the context of breast cancer surgery is not only safe but also reduces the length of hospital stay. Its potential benefits as anesthesia for oncologic breast surgery far exceed this single procedure but can induce benefits in all therapeutic modalities used for breast cancer treatment. These encouraging results promote the concept of integrative oncology.

They need to be confirmed in large prospective trials and, in an attempt to explain effects mediated by hypnosis, reliable immune parameters need to be studied.

Conflict of interest statement

None declared.

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