



Effect of hypnosis before general anesthesia on postoperative outcomes in patients undergoing minor surgery for breast cancer: a systematic review and meta-analysis

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Background: Preoperative anxiety is a common phenomenon in breast cancer, causing pain and tension, which is not conducive to the effective surgical treatment and postoperative recovery. It is believed that hypnosis can change the patient's perception of pain, thereby improving the patient's ability to control pain. However, the results of studies for this topic were controversy. In order to explore the effect of hypnosis in breast cancer surgery we included randomized controlled trials (RCTs) and conducted a meta analysis.

Methods: PubMed, Web of Science, Wiley online library, Elsevier, and Clinicaltrials.gov databases were searched by computer with the keywords "hypnosis/hypnotherapy" and "breast cancer" and "oncologic surgery/surgery/biopsy". After screening, the meta-analysis was performed using RevMan 5.4 software, and the evidence was rated using GRADE profiler 3.6 software.

Results: A total of 1,242 patients were included in 8 studies, including 630 patients who received preoperative hypnosis and 612 patients who did not receive hypnosis. Meta-analysis showed that hypnosis before general anesthesia reduced the degree of preoperative anxiety (MD = -2.79, 95% CI: -3.93, -1.65, $P < 0.00001$) and postoperative pain (MD = -1.25, 95% CI: -1.64, -0.86, $P < 0.00001$) in patients undergoing breast cancer surgery, but had no effect on the operation time (MD = -6.30, 95% CI: -15.38, 2.78, $P = 0.17$) and the incidence of postoperative nausea and vomiting (OR = 0.68, 95% CI: 0.22, 2.07, $P = 0.49$).

Discussion: The application of hypnosis before general anesthesia for breast cancer surgery can reduce the degree of anxiety of patients, also reducing postoperative pain.

Keywords: Breast cancer; general anesthesia; hypnosis; meta-analysis

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Introduction

Breast cancer is a phenomenon in which uncontrolled proliferation of breast epithelial cells occurs under the action of a variety of carcinogenic factors. It is often characterized by symptoms such as breast lumps, nipple discharge, and axillary lymphadenopathy in the early stage,

and distant metastasis with multiple organ lesions may occur due to cancer cells in the late stage, which directly threatens the patient's life (1,2). Breast cancer has become one of the most common cancers with the highest mortality rate in women worldwide (3). Surgical treatment is still the treatment of choice for patients with breast cancer,

but surgery usually elevates neuroendocrine, metabolic, and inflammation levels in patients, so that patients in the perioperative period produce physical and psychological stress responses, causing pain and tension, which is not conducive to the effective surgical treatment and postoperative recovery (4). Hypnosis uses direct or indirect cues to change the patient's perception, sensation, emotion, thought, or behavior, so that the patient experiences reduced physiological pain and psychological pain during surgery (5). Hypnosis has been widely used in the medical field, and studies suggest that it can change patients' perceptions of pain, thereby improving their ability to control pain (6), which could be measured by the Visual Analog Scale (VAS), Verbal Rating Scales (VRS) or other scales (7). It has also been suggested (8) that hypnosis may help reduce the incidence rate of chemotherapy-related side effects such as anticipatory nausea and vomiting by lowering the degree of treatment-related distress. In recent years, a number of controlled clinical studies have applied hypnosis before breast cancer surgery. However, due to the minimally invasive surgical technique of minor breast cancer surgery and the multimodal analgesic strategy (using several analgesic drugs together to containing the pain), the postoperative pain induced by the surgery was limited, which may weaken the effect of hypnosis (9). A study by Amraoui *et al.* (10) concluded that although patients received hypnosis had significantly lower degree of postoperative anxiety, but they had higher postoperative breast pain score. In this meta-analysis, 8 studies were included, all of which used hypnosis for about 15 minutes before general anesthesia for breast cancer surgery, and the outcome indicators after surgery were analyzed to provide an evidence-based foundation for the effectiveness of hypnosis as an adjuvant therapy.

We present the following article in accordance with the PRISMA reporting checklist (available at <https://gs.amegroups.com/article/view/10.21037/gS-22-114/rc>).

Methods

Inclusion of studies

We defined the inclusion of related studies according to the PICOS criteria (Participants, Interventions, Control, Outcomes, Study). (I) Study type: we only included randomized controlled trials (RCTs); (II) participants: all subjects were female breast cancer patients, aged over 18 years, and patients underwent diagnostic breast biopsy

or early lumpectomy; (III) intervention methods: there was a comparison of 2 groups of intervention methods in the study, namely hypnosis or no hypnosis before general anesthesia, and we did not include combined intervention methods (such as hypnosis + music therapy, hypnosis + mindfulness therapy, hypnosis + preoperative education, hypnosis + group psychotherapy); (IV) control: the control method was not limited when the study was included. If some studies used blinding, the experimental group and the control group were hypnotized by different therapists (the control group did not implement real hypnosis, but a dialogue similar to hypnosis, so that the patients could not distinguish whether they were hypnotized), while some studies did not have any blind control at all, meaning that patients knew whether they belonged to the hypnosis group. We then assessed patients for quality of intervention delivery after inclusion in the study. We preferred the inclusion of a hypnotic intervention guided by a professional psychotherapist rather than hypnosis guided by an anesthesiologist. We did not limit the hypnotist's method of hypnosis, which can involve different tools and verbal cues, but the purpose of hypnosis was to guide the patient into a comfortable, safe, and relaxed state. In the experimental group, preoperative education and pain intervention remained consistent with the control group except for hypnosis before general anesthesia; (V) outcomes: we used the degree of postoperative pain, anxiety, operation time, and nausea and vomiting as the primary outcome indicators, while the degree of postoperative fatigue, anesthesiologist stay, hospital stay, anesthetic dosage, analgesic dosage, and satisfaction were the secondary outcome indicators. In order to contain the heterogeneity between studies, we only extracted the pain data measured by VAS, which was from 0 to 10. Also, all of the pain degree data was collected on the day after surgery.

Literature search strategy

From Dec 2021 to Jan 2022, PubMed, Web of Science, Wiley online library, Elsevier databases, CNKI (the China national knowledge infrastructure), Wanfang Data were searched by computer, and to include the latest clinical studies, we also searched the literature on this topic in Clinicaltrials.gov. The input keywords were: "hypnosis/hypnotherapy" and "breast cancer" and "oncologic surgery/surgery/biopsy". We did not limit the time of literature publication. The starting time of the above databases was the initial time of database establishment.

Literature selection and data extraction

During Dec 2021 to Jan 2022, two of our co-workers independently completed the inclusion screening of the literature. In this process, if any of the inconsistency happened, a 3rd person was introduced to help reaching an agreement. Excel 2020 (published by Microsoft Corp) was used to extract the data. The extracted data included: (I) basic information: the author names, and region of the study, publication date; (II) basic characteristics of the participants: age, gender, disease type, surgical category, education level, preoperative pain level, occupation, and anxiety level; (III) literature intervention methods: specific implementation method of hypnosis, implementation time length, and number of cases grouped; (IV) outcome data: data for the outcome indicators. If there was no data provided in the article, we tried to contact the original author of the article for it. We extracted mean value (plus standard deviation) for the continuous variables. For the graphical representation of data, unless there was specified data number appeared on the graphical, the data could not be counted.

Risk of bias, heterogeneity and sensitivity analysis

We used the tool Cochrane RoB 2.0 for the risk of bias assessment, which covered 5 aspects: (I) randomization process, (II) deviations from intended interventions, (III) missing outcome data, (IV) measurement of the outcome, (V) selection of the reported result. If there was heterogeneity in the statistical process, we tried to use subgroup analysis for investigation. If the source of heterogeneity could not be identified and confirmed, we only generally describe the situation. Sensitivity analysis was performed by comparing the results of the fixed effects model with the random effects model.

Statistical methods

I^2 test analysis and the Q test were used to assess heterogeneity between different studies. $I^2 < 50\%$ or $P \geq 0.1$ indicated no statistically significant heterogeneity. Mean difference (MD) was used for continuous variables (Postoperative pain, Postoperative anxiety, operation time etc.), odd ratio (OR) was used for binary variables (incidence of postoperative nausea and vomiting), and 95% CI was used as the confidence interval. For each outcome indicator, the results of studies reporting the indicator were pooled

for statistics. The fixed effects model was applied if no statistical heterogeneity among studies, or else the random effects model was applied. RevMan 5.4 software provided by the Cochrane Collaboration was used as the analysis tool in this study to present the analysis results in the form of forest plots. Publication bias was depicted in funnel plots and was assessed by Egger's test quantitatively. GRADE profiler 3.6 software was used for evaluation of the quality of evidence. All of the above were considered two-sided statistically significant when $P < 0.05$.

Results

Literature screening results

This study initially retrieved 502 articles and finally included 8 studies (10-17). The selection flow chart is shown in *Figure 1*. In the study by Elkins *et al.* (18), the effect of preoperative hypnosis on postoperative hot flashes was investigated and the study was excluded as lacking of identified outcome indicators. In the study by Lew *et al.* (19), the authors only had an experimental group, but no control group, and was therefore excluded. The intervention method in study by Sánchez-Jáuregui *et al.* (20) was hypnosis + music therapy and was excluded. The study by Grégoire *et al.* (21) focused on overall psychological intervention before surgery, rather than preoperative hypnosis, and was therefore excluded. The type of study by Potié *et al.* (22) was a systematic review rather than a clinical control study, and was also excluded. We did not list all the excluded articles, but only listed 5 representative articles.

Basic characteristics of the studies

A total of 1,242 patients were included in this study, including 630 patients who received preoperative hypnosis and 612 patients who did not receive hypnosis. All patients underwent breast cancer surgery. The surgical types included breast lumpectomy and breast tissue biopsy. The youngest subject was 18 years old and the oldest was 92 years old. The shortest preoperative hypnosis time was 2 minutes and the longest was 20 minutes, as shown in *Table 1*.

Risk of bias assessment of the included studies

The risk of bias assessment of the included studies using RevMan 5.4 is shown in *Figures 2,3*. One study (11) only divided patients into the experimental group and control

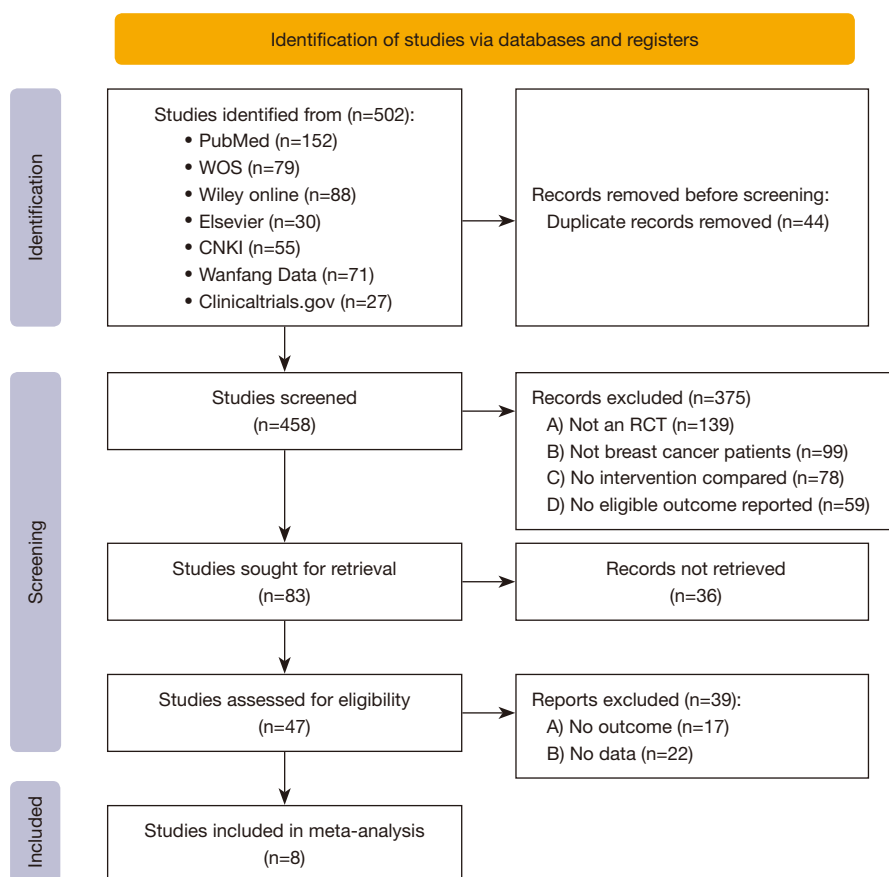


Figure 1 The study selection flow chart. WOS, Web of Science; CNKI, China national knowledge infrastructure; RCT, randomized controlled trials.

group according to the treatment method, without the random allocation method. There was a large selection bias. Allocation concealment was not described in 4 studies (10,11,12,17), which may introduce significant bias. All studies described the blinding method, and only one study (15) did not describe the dropout cases, which may lead to incomplete data. No selective reporting bias or other biases were found.

Meta-analysis results

Postoperative pain

Seven studies (10,12-17) reported the effect of hypnosis before general anesthesia on postoperative pain after breast cancer surgery, with statistical heterogeneity between the studies ($I^2=93\%$, $P<0.00001$). Hypnosis before general anesthesia reduced the postoperative pain of patients undergoing breast cancer surgery (MD = -1.25, 95% CI:

-1.64, -0.86, $P<0.00001$) performed by random effects model, as shown in *Figure 4*.

Preoperative anxiety

Six studies (10,11,13,14,16,17) reported the degree of preoperative anxiety, with the number of 499 and 480 for both the groups, respectively. There was statistical heterogeneity between the studies ($I^2=96\%$, $P<0.00001$), Hypnosis before general anesthesia reduced the degree of anxiety before breast cancer surgery (MD = -2.79, 95% CI: -3.93, -1.65, $P<0.00001$) performed by random effects model, as shown in *Figure 5*.

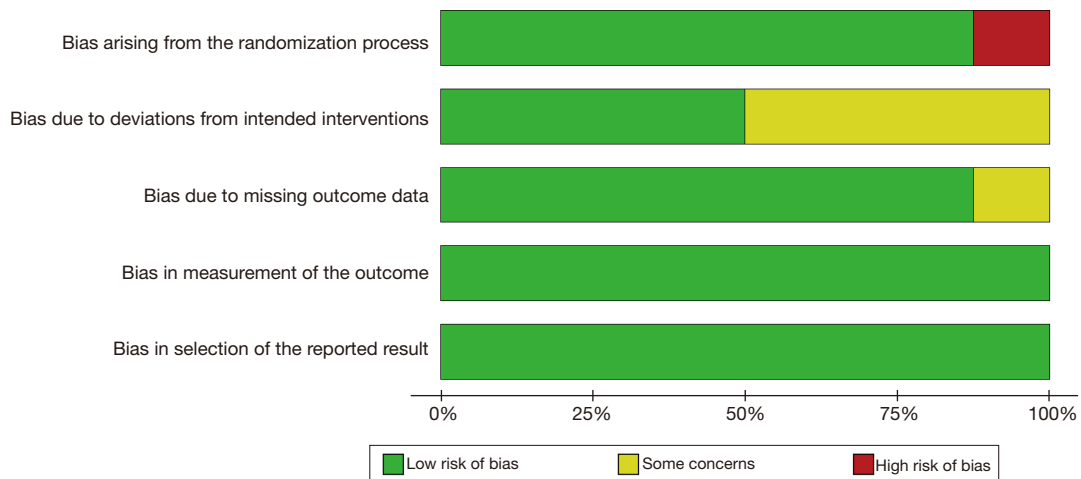
Operation time (minutes)

Three studies (10,11,13) performed comparisons of operation time between the 2 intervention methods. There was statistical heterogeneity between the studies ($I^2=88\%$, $P=0.0002$). Hypnosis before general anesthesia had no effect

Table 1 Basic characteristics, intervention measures, and outcome indicators of the included studies

| Author | Year of publication | Procedure type | Mean age (years) | Population (E/C) | Experimental group | Hypnosis time (min) | Control group | Outcome indicators | Jadad Score |
|-------------------------------|---------------------|-------------------------------|------------------|------------------|---|---------------------|---------------|--------------------------------|-------------|
| Amraoui <i>et al.</i> (10) | 2018 | Tumorectomy or quadrantectomy | 57 (33–79) | 77/73 | Short session before anesthesia induction | 6 (2–15) | Standard care | (a)(b)(c)(d)(e)(f)(g)(h)(i)(j) | 3 |
| Berlière <i>et al.</i> (11) | 2018 | Lumpectomy or mastectomy | 58 | 150/150 | Session before anesthesia induction | N/A | Standard care | (e)(f)(g) | 2 |
| Berliere <i>et al.</i> (12) | 2021 | Oncologic surgery | 53 | 31/32 | Session before anesthesia induction | 20 | Standard care | (a) | 2 |
| Lang <i>et al.</i> (13) | 2000 | Breast biopsy | 57 (18–92) | 82/79 | Self-hypnotic relaxation exercise | N/A | Standard care | (a)(b)(e)(g) | 3 |
| Butler <i>et al.</i> (14) | 2009 | Breast biopsy | 53.1 (30–80) | 63/61 | Self-relaxation hypnotic exercise | N/A | Standard care | (a)(b)(e) | 2 |
| Montgomery <i>et al.</i> (15) | 2010 | Breast cancer surgery | 48.5 | 100/100 | Short session before anesthesia induction | 15 | Standard care | (a)(b)(c) | 2 |
| Schnur <i>et al.</i> (16) | 2008 | Excisional breast biopsy | 45.0 | 49/41 | 15-minute pre-surgery hypnosis session | 15 | Standard care | (a)(e) | 3 |
| Lang <i>et al.</i> (17) | 2006 | Breast biopsy | 50 (18–82) | 78/76 | Self-hypnotic relaxation exercise | N/A | Standard care | (a)(e) | 3 |

Outcome indicators: (a) VAS postsurgical pain; (b) postsurgical nausea/vomiting; (c) fatigue; (d) comfort/well-being; (e) anxiety; (f) PACU length of stay; (g) operative time; (h) use and dose of antiemetics; (i) analgesic consumption; (j) satisfaction. E represents experimental group, C represents control group. VAS, visual Analog scale; PACU, post anesthesia care unit; N/A, not applicable.

**Figure 2** Summary chart of the risk of bias assessment of the included studies.

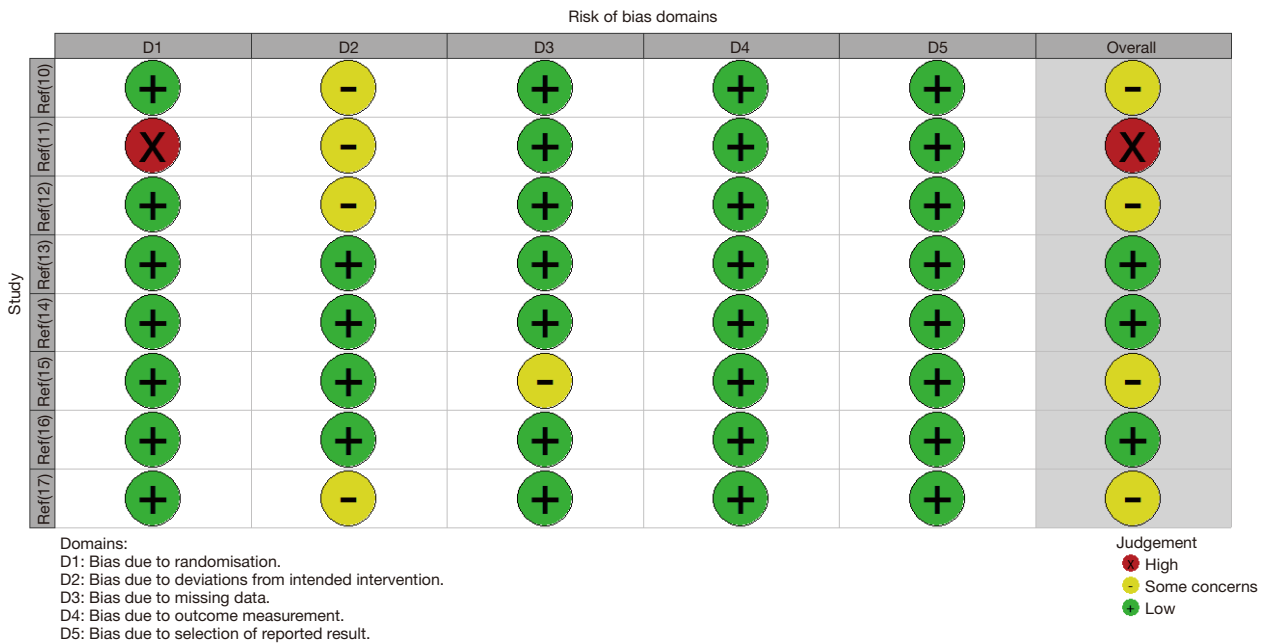


Figure 3 Risk of bias assessment chart of the included studies.

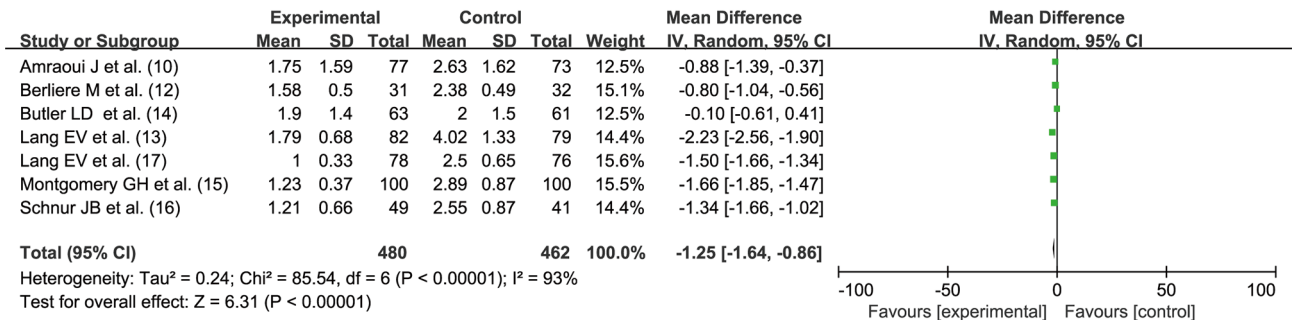


Figure 4 Effect of hypnosis before general anesthesia on postoperative pain after breast cancer surgery. SD, standard deviation; IV, inverse variance; CI, confidence interval.

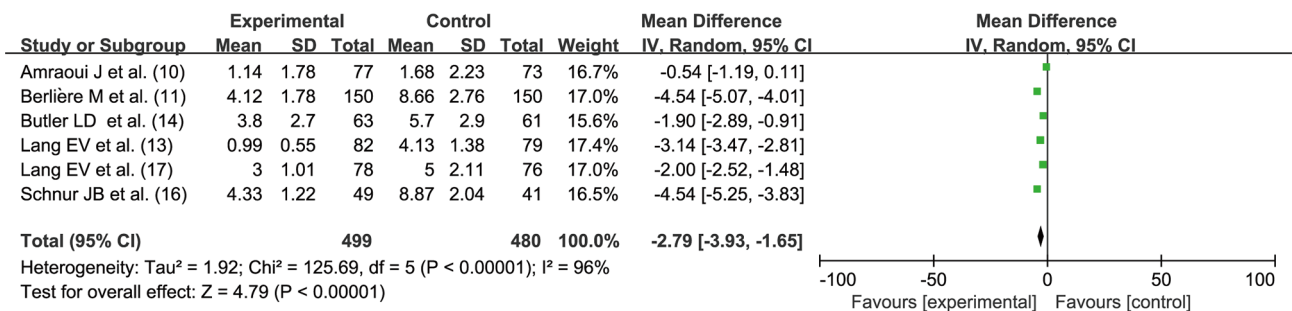


Figure 5 Effect of hypnosis before general anesthesia on postoperative anxiety after breast cancer surgery. SD, standard deviation; IV, inverse variance; CI, confidence interval.

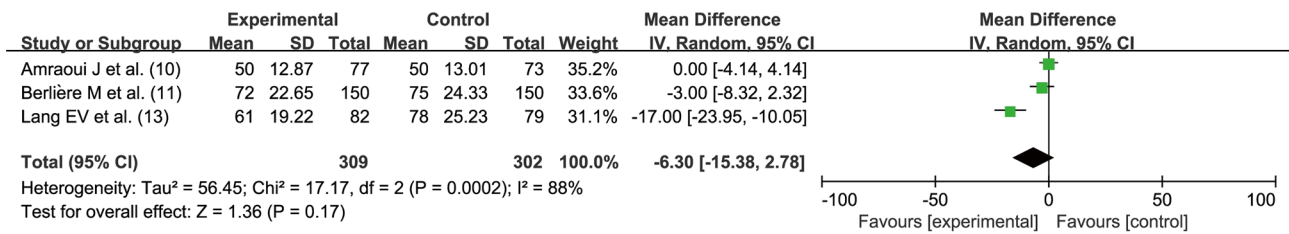


Figure 6 Effect of hypnosis before general anesthesia on the operation time of breast cancer surgery. SD, standard deviation; IV, inverse variance; CI, confidence interval.

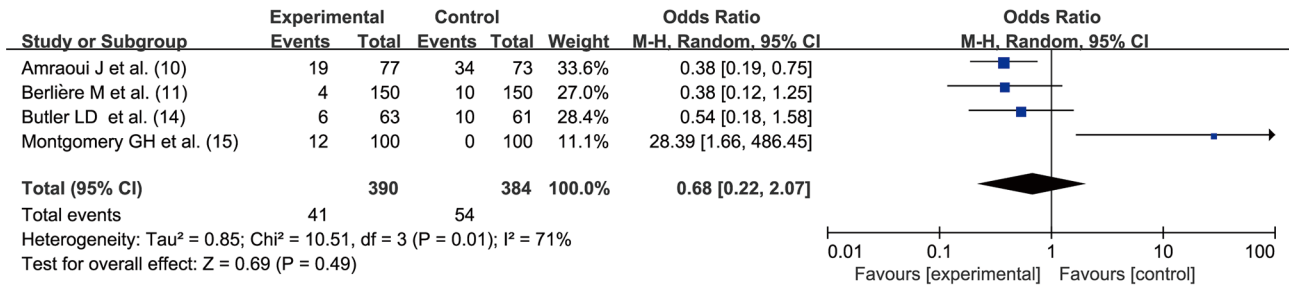


Figure 7 Effect of hypnosis before general anesthesia on the incidence of postoperative nausea and vomiting after breast cancer surgery. SD, standard deviation; M-H, Mantel Haenszel; CI, confidence interval.

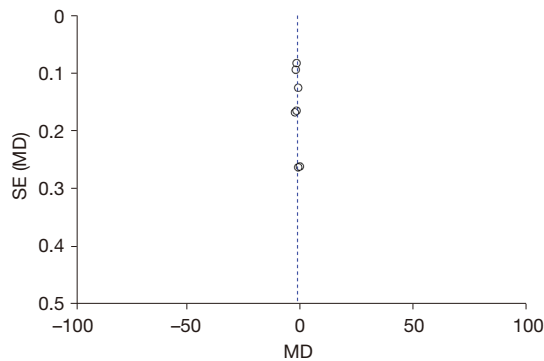


Figure 8 Funnel plot for the analysis of hypnosis before general anesthesia for postoperative pain after breast cancer surgery. MD, mean difference, SE, standard error.

on the operation time (MD = -6.30, 95% CI: -15.38, 2.78, P=0.17) performed by random effects model, as shown in Figure 6.

Incidence of postoperative nausea and vomiting

Four studies (10,11,14,15) reported postoperative nausea and vomiting adverse reactions. There was statistical heterogeneity between the studies (I²=71%, P=0.01).

Hypnosis before general anesthesia had no effect on the incidence rate of postoperative nausea and vomiting (OR =0.68, 95% CI: 0.22, 2.07, P=0.49) performed by random effects model, as shown in Figure 7.

Heterogeneity investigation and sensitivity analysis

Significant heterogeneity among the studies occurred in the case of meta analysing all the 4 indicators. The source of heterogeneity may be from the different types of surgery for patients. However, some studies included multiple surgery types, while some studies did not describe surgery type, we could not perform a subgroup analysis by the type of surgery. Patient age stratification may also be a source of heterogeneity. In addition, different evaluation criteria for outcome indicators were also sources of heterogeneity. The random effects model results were consistent with the fixed effects model results, indicating that the results were stable.

Analysis of publication bias

In the analysis of postoperative pain outcome, the funnel plot showed a evenly distribution for both sides, suggesting that there was little publication bias, as shown in Figure 8.

The P value of Egger’s test was 0.280, which showed that

there was little publication bias, as shown in *Figure 9*.

GRADE evidence quality analysis

GRADE was used to evaluate the quality of the evidence, and the 4 outcome indicators were all graded as moderate, as shown in *Table 2*.

Discussion

The diagnosis of breast cancer places great pressure on patients, and surgery causes changes to a patient’s appearance, which will impact gender identity in female patients and may cause anxiety and depression (23). In addition, fear of surgery, fear of pain during surgery, inability to wake up from anesthesia, and postoperative discomfort increase the patient’s anxiety. Clinical study (24) has shown that preoperative mental health (positive affect, optimism) can predict postoperative acute pain and is a protective factor for postoperative chronic pain, and this protection can even continue until 4 months after

surgery. The effect of hypnotherapy on anxiety reduction has been demonstrated by several studies and applied in different surgeries. The study by Hirzli *et al.* (25) applied hypnotherapy for 10 minutes before ultrasound-guided needle biopsy in patients with prostate cancer to relax patients and reduce tension, and the results showed that both tension and pain were reduced in patients. A study by Hemmerling *et al.* (26) showed that patients who underwent hypnosis before surgery had a better sense of pain control than those who did not, which reduced the amount of analgesia required. The use of hypnosis in breast cancer surgery was first seen in a controlled clinical study published by Spiegel and Bloom *et al.* (27), which showed for the first time that hypnosis can reduce pain in patients undergoing breast cancer surgery. Since then, the effectiveness of hypnotic oncological therapy has expanded from initial pain control to improvement in a variety of outcome indicators.

In this meta-analysis, 8 controlled clinical studies were included. The intervention measure was hypnosis before general anesthesia for surgery. The pooled effect size showed that the implementation of hypnotic surgery was beneficial for reducing the degree of postoperative pain and anxiety. However, in this analysis, it did not improve the operation time and postoperative nausea and vomiting side effects. Jackson *et al.* (28) showed that anxiety prior to surgery was strongly associated with multiple outcome indicators of surgery, such as pain intensity, pain medication use, and functional impairment. From a neurocognitive and neuroscientific point of view, hypnosis is thought to be mediated by the right cerebral hemisphere, while from a neuroanatomical point of view, it has been possible to find local gray matter related to hypnotic cues in some regions of the frontal, temporal, and occipital cortices. Although the neurobiological basis of hypnosis has not been elucidated, the results suggest that the attention skills involved in hypnosis may be related to central dopaminergic activity, and hypnotic cues

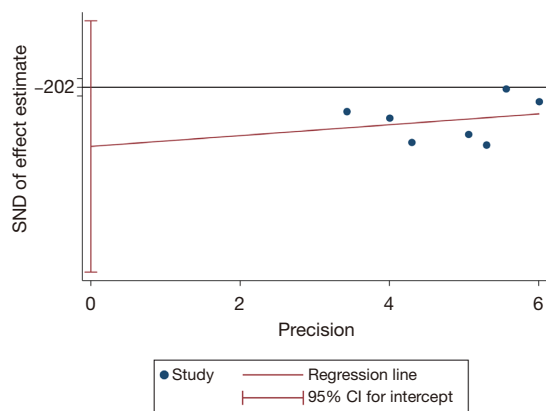


Figure 9 Egger’ test result for the analysis of hypnosis before general anesthesia for postoperative pain after breast cancer surgery. SND, standard normal deviate; CI, confidence interval.

Table 2 Grading of evidence for 4 outcome indicators

| Outcomes | Number of studies | Number of participants | Relative effect (95%CI) | Quality of the evidence |
|-----------------------|-------------------|------------------------|--------------------------|-------------------------|
| Post surgical pain | 7 | 942 | MD =-1.25 (-1.64, -0.86) | Moderate |
| Post surgical anxiety | 6 | 979 | MD =-2.79 (-3.93, -1.65) | Moderate |
| Operating time | 3 | 611 | MD =-6.30 (-15.38, 2.78) | Moderate |
| Post nausea rate | 4 | 774 | OR =0.68 (0.22, 2.07) | Moderate |

MD, mean difference; CI, confidence interval.

cause changes in the brain's perception and interpretation of input elements, accompanied by changes in neural connection (29). After hypnosis, the patient's perception of pain changes and their threshold is increased, so the degree of pain decreases (30).

In addition to reducing pain perception, several studies have shown that hypnosis can be applied in the treatment of hot flashes in breast cancer patients, improving symptoms and the quality of life of patients (31). The study by Lang *et al.* (17) compared the medical costs of hypnosis with 2 other interventions (standard care versus structured empathic attention) and concluded that hypnosis provides more powerful anxiety relief without excessive costs and is therefore more attractive for outpatient pain management. The study (32) has explored the applicable population for hypnosis, concluding that elderly patients are also able to be hypnotized and that the role of hypnotic analgesia does not appear to diminish with age during invasive medical procedures.

In this study, GRADE evidence quality analysis showed that the evidence grading of the 4 outcome indicators was moderate. The funnel plot showed that both sides were evenly distributed, indicating no significant publication bias, which was proved by the Egger's test results. Sensitivity analysis showed that the results were stable. However, there were studies that did not use the random allocation method, which may cause randomization bias. In addition, in this meta-analysis, there was significant heterogeneity among studies, and we found no improvement in operation time and postoperative nausea and vomiting after hypnosis. More controlled clinical studies using the same evaluation method with the same case characteristics are needed for deeper investigations in the future due to the risk of bias.

Conclusions

In this meta-analysis, 8 studies were included. Meta-analysis showed that the application of hypnosis before general anesthesia for breast cancer surgery could reduce the degree of anxiety of patients, thereby reducing postoperative pain.

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Footnote

Reporting Checklist: The authors have completed the

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://gs.amegroups.com/article/view/10.21037/gc-22-114/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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