The Effect of a Combined Modified Pectoral and Stellate Ganglion Block on Stress and Inflammatory Response in Patients Undergoing Modified Radical

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Abstract

Background: Surgical resection is the primary and most effective method for removing breast tumors, but it is associated with significant stress and inflammatory responses. Previous studies have indicated that these responses can be influenced by anesthetic method. While regional anesthesia has been shown to attenuate stress and inflammatory responses associated with surgical procedure, the effectiveness of combined nerve blocks has not been investigated. Therefore, we conducted this study to evaluate whether the combination of a pectoral nerve block (PNB) and stellate ganglion block (SGB) is more effective than a PNB alone in reducing stress and inflammatory responses in women undergoing modified radical mastectomy.

Methods: A total of 50 breast cancer patients with American Society of Anesthesiologists physical status I or II were enrolled and randomly allocated to receive either a (1) preoperative ultrasound-guided PNB (20 mL of 0.375% ropivacaine) only (control group, n = 25) or (2) ultrasound-guided PNB (20 mL of 0.375% ropivacaine) combined with a SGB (5 mL of 0.15% ropivacaine) (SGB group, n = 25). The primary outcome was neuroendocrine levels at different time points during the 72-hour postoperative period. Assessed neuroendocrine variables included cortisol, glucose, interleukin (IL)-6, interleukin (IL)-8, and tumor necrosis factor (TNF)- α . Secondary outcomes included pain scores, hemodynamic variables, sleep quality on the night of surgery, and side effects after surgery.

Results: A total of 50 patients completed the study. Cortisol levels were significantly lower in the SGB group compared to the control group at the end of the surgery. Glucose levels at the time of incision were lower in the SGB group than in the control group. The SGB group exhibited significantly lower IL-6 and TNF- α levels compared to the control group at 24 hours post-surgery. There was no significant difference in perioperative IL-10 levels between the two groups. Pain scores up to 12 hours postoperatively were significantly lower in the SGB group, which also exhibited better perioperative hemodynamic stability. Patients in the SGB group reported a better sleep quality on the night of the operation than those in the control group. No side effects were observed in either group.

Conclusions: In patients undergoing a modified radical mastectomy, the combination of a SGB and PNB can more effectively blunt perioperative stress and inflammatory responses, as well as postoperative acute pain, compared to a PNB alone. A combined block approach also results in more stable perioperative hemodynamics and a better postoperative sleep quality.

Background

Breast cancer is one of the most common carcinomas among women, accounting for approximately 30% of cancers among females in the United States in 2019. Breast cancer is also the deadliest tumor in women, being responsible for an estimated 15% of total cancer mortality [1]. The surgical resection of the primary tumor is currently the most effective treatment for patients with early-stage and operable breast cancer [2]. The most common surgical procedure for breast cancer patients is the modified radical

mastectomy, which involves the removal of the whole breast and a large amount of skin, as well as axillary evacuation [3].

The association between cancer and both stress and inflammatory responses has been well-established [4]. Surgical stimulation and general anesthesia are key variables which affect the surgical stress response and exacerbate perioperative inflammation [5–7]. The stress response is harmful for postoperative recovery and the long-term prognosis of patients with cancer [8]. A wide range of inflammatory factors, such as interleukin (IL)-6 [9], IL-8 [10], and tumor necrosis (TNF)- α [11], have been shown to promote the progression and metastasis of tumors.

The pectoral nerve block (PNB) is a new practicable alternative to both the paravertebral and epidural blockade for anesthesia during breast surgery and postoperative pain management. The stellate ganglion blockade (SGB) involves the injection of local anesthetic around the cervical sympathetic trunk of the stellate ganglion, and can be used to facilitate diagnosis and prognosis prediction. SGB can also be used as a therapeutic intervention for various medical conditions including breast cancer-related lymphedema [12], menopausal symptoms [13], and post-mastectomy neuropathic pain [14]. A previous study reported that a modified PNB (with 1 μ g/kg dexmedetomidine) effectively suppressed postoperative pain and stress response in patients who underwent a modified radical mastectomy [15]. While the individual effects of PNB and SGB have been widely investigated, there is a lack of evidence pertaining to the effectiveness of a combined PNB and SGB in reducing stress and inflammatory responses during and after surgical procedures.

The objective of this study was to evaluate whether the combination of an ultrasound-guided SGB and a modified PNB is more effective than a PNB alone in reducing stress and inflammatory responses in women undergoing modified radical mastectomy.

Methods

Patients and group allocation

This randomized, double-blinded, controlled trial was approved by the Ethics Committee of Jiangyin Hospital (affiliated to Southeast University Medical School), and followed the principles of the Helsinki Declaration. The study was registered prior to patient enrollment at ClinicalTrials.gov (Identifier No: ChiCTR2000030285) (date of first registration 27/02/2020). All patients provided written informed consent before surgery.

The inclusion criteria comprised women with an American Society of Anesthesiologists physical status grade of I–II (i.e., aged 40–70 years and weighing 50–70 kg), who were scheduled to undergo a modified radical mastectomy. Patients were excluded if they refused to participate, or had one or more of the following conditions: bleeding diathesis, immune disease, diabetes mellitus, endocrine system disease, relevant drug allergy, mental disorder, and previous chemotherapy.

A pre-anesthetic interview was conducted by a researcher who was blind to group assignment to evaluate the patients' eligibility before randomization, and to record baseline data. The randomization sequence was created with a computerized random-number generator, and patients were randomly allocated into the SGB group or control group at a ratio of 1:1. The details of the allocated treatments were contained in serially numbered sealed opaque envelopes. Another researcher (not involved in this trial and not blind to group assignment) opened the envelopes to view the patients' group assignment in the surgical theater, prior to block administration and induction of anesthesia. A third anesthetist, who was blind to group allocation, was in charge of collecting intraoperative data and blood samples. Postoperative data and blood samples were collected by the same researcher who visited the patients preoperatively and at 4, 8, 12, 24, 48, and 72 hours after surgery. All surgeries were performed by the same team of surgeons.

Intervention

Upon arrival in the operating room, patients were monitored using standard monitoring equipment (i.e., noninvasive arterial blood pressure, electrocardiogram, pulse oximeter, and capnography). Patients in the SGB group received an ultrasound-guided SGB with 3 mL of 0.15% ropivacaine, and an ultrasound-guided PNB with 20 mL of 0.375% ropivacaine before general anesthesia. Patients in the control group were only administered an ultrasound-guided PNB with 20 mL of 0.375% ropivacaine before general anesthesia; no sham intervention (for the SGB) was provided.

Both the SGB and PNB were conducted by the same anesthesiologist before general anesthesia. The ultrasound-guided right-sided SGB was performed with the patient in a supine position, with a thin pillow under the neck. Under the guidance of ultrasound, the C7 level was determined first. Since there was only one tubercle in the transverse process of C7, the probe was slowly moved upward after determining the C7 level. The C6 level corresponded to the point at which the first transverse process with anterior and posterior tubercles was detected. With a size 7 puncture needle, 5 mL of 0.15% ropivacaine (SGB group) was injected below the fascia of the longus colli muscle at the C6 level. The appearance of Horner's syndrome (miosis, ptosis, enophthalmos, sweating, and flush, and presence of above signs > 3 was considered positive) indicated a successful block.

The PNB was performed on the same side of surgery by the same anesthesiologist who performed the SGB. The patient was placed in the supine position with their arm abducted at approximately 90°. The needle was inserted, from the lateral to the medial direction, into the plane between the serratus anterior and pectoralis minor in the proximity of the third rib; 20 mL of 0.375% ropivacaine was subsequently injected.

General anesthesia was induced in the same manner for both groups: administration of 0.05 mg/kg midazolam, 0.15 mg/kg cisatracurium, 0.5 µg/kg sufentanil, and 1–2 mg/kg propofol; this was followed by maintenance with cisatracurium, propofol, and sufentanil. The depth of anesthesia was monitored with the bispectral index (BIS)-Vista monitor, with the BIS being maintained between 40 and 60 during surgery. A 2 mL blood sample was withdrawn from a peripheral vein and collected in a plasma tube at T₀ (upon patient arrival in the operating theater), T₁ (immediately after incision), and T₂ (at the end of

surgery) for the determination of stress hormone (cortisol and glucose) levels. Another 2 mL blood sample was drawn at T_0 (upon patient arrival in the operating theater, T_3 (24 hours after the surgery), and T_4 (72 hours after the surgery) to determine the levels of inflammatory factors (IL-6, IL-8, and TNF- α). Preoperative and intraoperative blood sampling was carried out in the operating room before the end of the surgery, while postoperative blood sampling was conducted in the ward. The blood samples were sent to the laboratory on the same day, and the results of the sample analysis were submitted to the first author.

Perioperative assessment

The primary outcome was the level of stress hormones and inflammatory factors at different perioperative time points. Secondary outcomes included hemodynamic variables during surgery, pain scores, sleep quality, and complications during the first 2 postoperative days. The heart rate (HR) and mean arterial pressure (MAP) were continuously measured and recorded at the following time points: before anesthesia; before incision; immediately after incision; 1 hour after incision; before the end of the surgery; before tracheal extubation; and 5 min after tracheal extubation. After the operation, the patients reported their pain intensity on a visual analog scale (VAS) (0–10, where 0 indicates no pain and 10 is the maximum pain imaginable). VAS scores were assessed and recorded at 4, 8, 12, 24, and 48 hours after surgery. We used the Athens Insomnia Scale [16] to assess the perioperative sleep quality of the patients; higher scores reflected greater sleep disturbances. The questionnaires were completed upon arrival at the operation room and on the first day after surgery to record the sleep quality on the nights before and after surgery, respectively. We also recorded the incidence of relevant short-term complications during the hospital stay.

Statistical analysis

Statistical analyses were performed with SPSS 18.0. A sample size of 18 participants in each arm was calculated based on pretest data, as well as the following parameters: a power of 80%, an alpha of 0.05, and a group difference in cortisol level. The normal distribution of the data was analyzed with the Shapiro–Wilk test. Data were expressed as mean $\pm$ standard deviation (SD). Comparisons of cortisol, glucose, IL-6, IL-8, TNF- α , VAS pain scores, sleep quality scores, and hemodynamic variables between groups were performed with the repeated-measures analysis of variance. Baseline characteristics were compared between groups with the Student's t-test, followed by the 2-tailed Dunnett test. The level of statistical significance was set at $P < 0.05$.

Results

A total of 52 patients were screened for eligibility between March 2019 and August 2019. Two patients were excluded, as they did not meet the criteria for inclusion into the study. Thus, 50 patients (25 in each group) were included in the final analysis (Fig. 1). There were no significant differences in baseline characteristics between the SGB and control groups (Table 1).

Cortisol and glucose levels were not significantly different between the two groups at baseline (T_0). At the end of surgery (T_2), cortisol levels were significantly lower in the SGB group compared to the control group ($P = 0.004$) (Fig. 2a). Compared with baseline, the plasma levels of cortisol in the control group were significantly higher at T_2 (Fig. 2a). Glucose levels were higher in the control group than in the SGB group immediately after incision (T_1) ($P = 0.036$), while no differences were observed at baseline (T_0) (Fig. 2b). In addition, intraoperative cortisol and glucose levels were more stable in the SGB group compared to the control group.

Plasma levels of IL-6 and TNF- α were not significantly different at baseline (T_0), but were significantly lower in the SGB group at 24 hours postoperatively (T_3) ($P_{IL-6} = 0.023$, $P_{TNF-\alpha} = 0.002$) (Fig. 3a, Fig. 3c). No significant differences in IL-8 levels were found between the two groups at any time point (Fig. 3b). IL-8 levels at T_3 were significantly lower than those at T_0 in both groups.

The VAS pain scores at the different time points are shown in Fig. 4. Patients in the control group had higher VAS pain scores compared to those in the SGB group at 4, 8, and 12 hours postoperatively; no significant differences were observed at 24 or 48 hours postoperatively. Hemodynamic data are shown in Fig. 5. Perioperative HR changes were more stable in the SGB group compared to the control group (Fig. 5a). There were no significant differences in MAP between groups at any time point (Fig. 5b). Sleep quality scores on the night before surgery were not significantly different between groups; however, scores on the night after surgery were significantly higher in the control group (Fig. 6).

Discussion

The perioperative stress response is associated with immunosuppression [17], and several studies have suggested a connection between inflammatory responses and tumor development [18–20]. Therefore, there is a critical need for the development of optimal methods to reduce perioperative stress and inflammatory responses in cancer patients. The modified PNB is a new technique for providing effective perioperative anesthesia and analgesia in patients undergoing breast surgery [21]. It has been shown to provide adequate perioperative pain relief, which is essential for the reduction of stress and inflammatory responses [17]. The SGB has a large range of clinical indications, including vasomotor syndromes, and both sympathetic-maintained and neuropathic pain syndromes [22–24]. Nevertheless, while the individual effects of PNB and SGB have been previously evaluated, few studies have investigated the effectiveness of a combined PNB and SGB. Therefore, this study aimed to determine whether the combination of an ultrasound-guided SGB and a modified PNB is more effective than a PNB alone in reducing stress and inflammatory responses in women undergoing modified radical mastectomy.

The results of this study indicated that the plasma levels of cortisol and glucose during surgery were blunted with the combined SGB and PNB approach. The combined block method also resulted in significantly lower postoperative IL-6 and TNF- α levels compared to the control group; additional advantages included a more stable perioperative HR, more effective relief of acute pain up to 12 hours postoperatively, and better postoperative sleep quality. No serious side effects were detected in either

group. Thus, the combined SGB and PNB approach can be successfully used in conjunction with general anesthesia to suppress stress and inflammatory responses in patients undergoing modified radical mastectomy.

It is well known that changes in neuroendocrine mediators and cytokines through the direct activation of the somatic and sympathetic nervous systems can accurately reflect the perioperative stress response. Cortisol is the major glucocorticoid secreted by the zona fasciculata and zona reticularis [25]. The plasma levels of cortisol and glucose are sensitive indicators of the stress response, and accurately reflect the stimulus intensity [26, 27]. In our study, cortisol levels were significantly lower at the end of the surgery, while glucose levels were significantly lower immediately after incision in the SGB group compared to the control group. Our findings are consistent with those of Chen et al. [28], who reported that SGB reduced stress responses in patients undergoing elective laparoscopic cholecystectomy. In addition, surgical trauma is also likely to enhance a patient's inflammatory response [29], due to the increased incidence of postoperative complications.

IL-6 is highly expressed during inflammatory responses to conditions of stress, and can be used to assess the severity of surgical trauma [30]. The observation of a reduction in IL-6 levels in the SGB group suggests that the combined block approach can attenuate the inflammatory response. This result is supported by a study conducted by Zhu et al. [31], who reported on the ability of the SGB to reduce the inflammatory response in patients undergoing laparoscopic colorectal cancer surgery. TNF- α is one of the most important mediators of systemic inflammation, and is released within a few minutes after local or systemic tissue injury [32]. Therefore, it can be used as an indicator of an early inflammatory reaction [32]. In our trial, the plasma levels of TNF- α were significantly lower in the SGB group at 24 hours postoperatively; this may reflect the alleviation of the inflammatory response by SGB. IL-8 plays an important role in acute inflammation [33]. While there was no significant difference in plasma IL-8 values between the SGB and control groups, we observed a significant reduction of IL-8 from T_0 to T_1 in both groups. We speculate that this reduction may have been related to preoperative anxiety; however, previous studies have suggested that anxiety may not be significantly associated with inflammatory markers such as IL-8 [34, 35]. Therefore, further research is needed to elucidate the relationship between preoperative anxiety and changes in inflammatory markers.

Previous clinical trials have reported that SGB can provide effective analgesia [14, 36]. Our results further confirmed the effectiveness of SGB, as we documented effective analgesia for up to 12 hours. As postoperative analgesia reduces the stress response, the analgesic effect of SGB may partly explain the reduction of cortisol, glucose, and inflammatory factor levels in the present study. Patients in the SGB group also exhibited significantly more stable HR changes compared to the control group; similar results were also reported by Chen et al. [28] In the present study, we also found that postoperative sleep quality was significantly higher in the SGB group; this supports the use of the combined block approach in patients with perioperative sleep disorders.

Limitations

This study was limited by its relatively small sample size, and its inclusion of patients with a specific medical condition. Therefore, the external generalizability of our findings may be limited. Also, the use of sufentanil for analgesia during surgery may have affected our results, due to its intrinsic ability to influence the neuroimmunoendocrine network. Furthermore, we did not assess long-term clinical effects of combined PNB and SGB such as patient prognosis, cancer migration, interference with the immune system, and complications. Therefore, our results are preliminary, and further studies are required to evaluate long-term outcomes after the combined use of the SGB and PNB.

Conclusion

The application of the combination of a SGB and PNB can more effectively alleviate perioperative stress and inflammatory responses, as well as postoperative acute pain, compared to a PNB alone in patients undergoing modified radical mastectomy. A combined block method also results in more stable perioperative HR change and a better postoperative sleep quality.

Abbreviations

PNB: pectoral nerve block; SGB: stellate ganglion block; IL: interleukin; TNF: tumor necrosis factor; C7: Seventh cervical; C6: Sixth cervical; HR: heart rate; MAP: mean arterial pressure; VAS : visual analog scale; SD: standard deviation

Declarations

Ethics approval and consent to participate

This trial was approved by the Ethics Committee of Jiangyin Hospital (affiliated to Southeast University Medical School). All patients provided written informed consent before surgery.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

All data used to support the outcomes of this trial are available from the corresponding author upon request.

Competing interests

The authors declare that they have no competing interest.

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Authors' contributions

Jun Geng wrote the main manuscript text and obtained the funding; Jing Wang and Yaowen Zhang conducted the design of the trial and statistical analysis; Wenxiang collected data; Junjia Zhu prepared all the table and figures; JianQing and Zhen Wu modified the manuscript; All authors reviewed the manuscript.

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Figures

Figure 1

Flow chart. It shows Flow chart of participants in this randomized controlled trial.

A **B**

Figure 2

Plasma concentration of cortisol (a), and glucose (b). SGB: stellate ganglion block. T₀: baseline. T₁: immediately after incision. T₂: at the end of surgery. Data are expressed as mean $\pm$ SD. *: $P < 0.05$ compared with control group; #: $P < 0.05$ compared with baseline.

Figure 3

Plasma concentration of IL-6 (a), IL-8 (b) and TNF-α (c). SGB: stellate ganglion block. T₀: baseline. T₃: 24 hours after the surgery. T₄: 72 hours after the surgery. Data are expressed as mean ± SD. *: P < 0.05 compared with control group.

Figure 4

VAS pain scores at the different time points. Time interval is defined as time between baseline and postoperative time. VAS: visual analog scale. SGB: stellate ganglion block. Data are expressed as mean $\pm$ SD. *: $P < 0.05$ compared with control group.

Figure 5

Hemodynamic changes perioperatively. a heart rate (HR); b mean arterial blood pressure (MAP). SGB: stellate ganglion block. Data are expressed as mean $\pm$ SD. *: $P < 0.05$ compared with control group.

Figure 6

Sleep quality scores. SGB: stellate ganglion block. Data are expressed as mean $\pm$ SD. *: $P < 0.05$ compared with control group.

Supplementary Files

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