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Anesthetic effect of ultrasound-guided multiple-nerve blockade in modified radical mastectomy in patients with breast cancer

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Abstract

Introduction: Routine anesthesia modality for modified radical mastectomy (MRM) includes general anesthesia (GA), epidural blockade-combined GA and nerve blockade-combined GA. However, GA has been associated with postoperative adverse effects such as vertigo, postoperative nausea and vomiting and requirement for postoperative analgesia, which hinders recovery and prognosis. Moreover, combined blockade of thoracic paravertebral nerves or intercostal nerves and adjuvant basic sedation for massive lumpectomy provided perfect anesthesia and reduced opioid consumption, whereas the excision coverage did not attain the target of MRM. Regional anesthesia strategies involving supplementation of analgesics in ultrasound-guided multiple nerve blocks have garnered interests of clinicians. Nevertheless, the precise effects of intercostal nerves, brachial plexus and supraclavicular nerves in MRM in patients with breast cancer remain obscure.

Methods: Eighty female patients with breast cancer scheduled for MRM were recruited in the present trial between May, 2019 and Dec., 2019 in our hospital. The patients ranged from 30 to 65 years of age and 18~30 kg/m^2 in body-mass index, with the American Society of Anesthesiologists I or II. The patients were randomized to ultrasound-guided multiple nerve blocks group and GA group. The patients in multiple nerve blocks group underwent ultrasound guided multiple intercostal nerve blocks, interscalene brachial plexus and supraclavicular nerve blocks, (local anesthesia with 0.3% ropivacaine: 5 ml for each intercostal nerve block, 8 ml for brachial plexus block, 7 mL for supraclavicular nerve block) and basic sedation and intraoperative mask oxygen inhalation. The variations of hemodynamic parameters such as mean arterial pressure, heart rate (HR) and pulse oxygen saturation were monitored. The visual analog scale scores were recorded at postoperative 0 hour, 3 hour, 6 hour, 12 hour and 24 hour in resting state. The postoperative adverse effects, including vertigo, postoperative nausea, and vomiting, pruritus, and urinary retention and so on, as well as the analgesic consumption were recorded.

Conclusions: The ultrasound guided multiple intercostal nerve blocks, brachial plexus and supraclavicular nerve blocks could provide favorable anesthesia and analgesia, with noninferiority to GA and the reduced incidence of adverse effects and consumption of postoperative analgesics.

Abbreviations: BCS = breast-conserving surgery, BMI = body-mass index, HR = heart rate, MAP = mean arterial pressure, MNB = multiple nerve blocks, MRM = modified radical mastectomy, PONV = postoperative nausea and vomiting, SpO$_2$ = pulse oxygen saturation, VAS = visual analog scale.

Keywords: general anesthesia, Modified radical mastectomy, ultrasound-guided multiple nerve blocks

1. Introduction

Breast cancer is the most prevalent malignancy among women, with an incidence of over 1.5 million worldwide per annum,[1,2] and ranks as the second leading cause of cancer-related mortality, with breast cancer alone responsible for the death of 626,679 female patients. Surgery is by far the primary and most effective treatment for breast cancer and over 40% female patients with breast cancer underwent the neoplasm resection.[3] Despite the large-scale application of breast-conserving surgery (BCS) and sentinel lymph node biopsy, a number of patients are contra-indicated for BCS or have positive diagnosis of sentinel lymph node biopsy, for which case the modified radical mastectomy (MRM) renders the standard surgical algorithm in clinic. At present, the anesthesia methods for patients undergoing MRM predominantly comprise general anesthesia (GA), epidural block combined with GA, and nerve blocks combined with GA. However, GA is considered to be related to a high incidence of postoperative nausea and vomiting (PONV), which is primarily attributed to inhalation of anesthetics, application of periopera-tive opioids for analgesia and susceptibility of female gender per se, thereby mitigating the patient satisfaction and delaying patient recovery after breast surgery.[4–6]

Recently, BCS has frequently been conducted in short-stay setting, which entails the anesthesia techniques promising prompt recovery without adverse postoperative effects. A technique of regional analgesia extended into the postoperative period offers postoperative analgesia, attenuation of the surgical stress response, reduction of PONV, and early mobilization.[7] Thoracic epidural block, thoracic paravertebral block, multiple intercostal nerve blocks are the main regional anesthesia techniques, which have been employed in breast surgery.[8] Nevertheless, these techniques are disadvantageous for the high risks of pneumothorax, hemorrhage, dural penetration and hypotension.[8] A novel interfascial plane block between the pectoralis major and minor muscles termed as Pecs I block and later, modified Pecs block (or Pecs II) has been introduced, with low incidence of complications, especially with the guidance of ultrasound in breast cancer surgery.[3,9–11] Unfortunately, the dampness of the operating field renders inconvenience to surgeons, and the multiple nerve distribution in the regions of modified radical mastectomy also restrains the performance of complete analgesia. The target nerves involve the brachial plexus, the superficial cervical plexus (the supraclavicular nerve) and the intercostal nerves. However, there is a paucity of data with respect to the anesthetic effects of multiple nerve blocks (MNB) of intercostal nerves, brachial plexus and supraclavicular nerves in patients with breast cancer undergoing MRM.

Herein, we investigated the exact effects of anesthesia with blockade of the intercostal nerves, brachial plexus and supra-clavicular nerves with the guidance of ultrasound in patients with breast cancer who underwent MRM.

2. Materials and methods

2.1. Ethics and patient selection

The present trial was conducted with the approval of the Ethics Committee of The First People's Hospital of Yancheng ([2019] J-003) and the Chinese Clinical Trial Registry (ChiCTR2000029424) in accordance with the Declaration of Helsinki. The written informed consents were provided by all participants prior to enrollment in this investigation. The female

patients with breast cancer scheduled for MRM were recruited by the following inclusion criteria: age between 30 to 65 years, body mass index (BMI) of 18 to 30 kg/m2, and the American Society of Anesthesiologists physical status of I or II grade. The exclusion criteria were as follows:

(1) disease of central nervous system or mental disorders;
(2) homeostatic disturbances and dysfunction of the heart, lungs, liver and kidneys;
(3) severe visual impairments and dysaudia;
(4) contraindications to either anesthetic techniques or presenta-tion with systemic infectious symptoms;
(5) coagulation defects or morbid obesity (BMI $\geq$ 35 kg/m^2);
(6) movement disorder or history of smoking.

Accordingly, 22 patients were excluded, that is, 15 patients owing to other types of surgery rather than modified radical mastectomy; 2 patients due to BMI > 35 kg/m^2; 1 patient due to age of over 65 years; 3 patients owing to the history of smoking; 1 patient owing to mental disorder. Eventually, 80 patients were eligible for the present trial and were randomly allocated to the MNB group and GA group (n = 40 each). A sample size estimate suggested that 36 patients would be required for each group in order to detect a reduction of 31% in the incidence rate of PONV, with a power of 90% at the 0.05 level of significance. Considering an approximately 5% loss to follow-up, we included 38 patients in each group (actually 40 patients in each group).

2.2. Anesthesia procedures

All participants were fasted for 8 to 12 hours without premed-ication prior to the operation. Routine monitoring included electrocardiogram, pulse oxygen saturation (SpO$_2$) and nonin-vasive blood pressure. After intravenous injection of midazolam at a dose of 0.02 to 0.05 mg/kg and intravenous administration of propofol at a dose of 2 to 4 mg/kg per hour, the patients were sedated, with the airway maintained open throughout the operation. The blockade sites in MNB group included the 1 to 7 intercostal nerves in the diseased side, the interscalene brachial plexus, and the supraclavicular nerve. 0.3% ropivacaine was applied to local anesthesia and ultrasonography was employed with LOGIQ P6GE. Intercostal nerve block: patients, with arms folded, took the lateral recumbent position on the affected side to allow for lateral and caudal movement of the scapula and full exposure of the contour of paraspinal ribs.

Prior to routine disinfection, the ultrasound probe was placed at the medial margin of the scapula and 4 to 6 cm proximal to the spinal process of the second thoracic vertebra. The section plane was parallel to the sagittal plane. The anesthesiologist moved the probe to search for the first, second and third ribs. The cross-sectional plane of ribs, intercostal tissues, pleura and lung tissues were distinctly visualized. With in-plane technique, the puncture needle was advanced into the intercostal space from the side. When the needle tip reached the site near the pleura of the inferior border of the upper costal space with no blood backflow, local anesthetics were injected until ultrasound visualization of the liquid dilation of intercostal tissues and the bulge of the dilated parietal pleura, and hence the completion of the first and second intercostal nerve blockade. Thereafter, the probe was gradually moved laterally and caudally to medial margin of scapula until scapular line.

Consistent with the afore-mentioned real-time ultrasound guidance method, the third, fourth, fifth, sixth and seventh

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intercostal nerves were sequentially blocked, with 5 mL local anesthetics injected in each site. The procedures of brachial plexus block: with the patient in supine position, the head turning to the healthy side, the probe was closely adhered to the skin at the clavicle to explore the sections of anterior and medial scalenus muscles, and thereby the section of the brachial plexus in the interscalene groove was clearly visualized, followed by the real-time ultrasound-guided puncture to facilitate injection of local anesthetic at 8 mL around the nerve. The procedures of supraclavicular nerve block of the superficial cervical plexus: with the puncture site located at the midpoint of the lateral margin of the sternocleidomastoid muscle of the affected side, the needle was introduced into the muscular fascia to allow for injection of local anesthetic at 7 mL. All the blocking manipulations were performed in approximately 15 minutes, followed by a duration of 15 minute for testing of pain and thermal sensation of the operation site. The operation was initiated provided the perfect anesthetic effect was achieved. Propofol TCI was pumped in at 1.5 g/ml, and the *Observer's Assessment of Alertness/Sedation* score was maintained at 2–3 points. In case of the score higher than 3 points, GA with laryngeal mask was employed instead. Anesthesia induction in group G: patients received propofol 2 mg/kg, cisatracurium 0.15 mg/kg and fentanyl 2~2.5 g/kg for anesthesia induction, 0.8% to 1.0% sevoflurane and $1\,\mu g\cdot kg^{-1}\cdot h^{-1}$ remifentanil for anesthesia maintenance, coupled with intraoperative adjustment of sevoflurane concentration, addition of fentanyl and intermittent addition of muscle relaxant as appropriate. If necessary, vasoactive drugs were administered so as to maintain the hemodynamic stability, that is, BIS 40~60. All patients received dolasetron (12.5 mg) as a routine medication 15 min prior to the end of surgery to prevent PONV. No analgesic pump was employed postoperatively in either group, and analgesic drugs were given according to the visual analog scale (VAS) scores, with the dose recorded. The administration of analgesics adopted a step-wise approach, that is, commencement with non-steroidal analgesics and gradual transition to opioids. In the event of VAS scores > 3, flurbiprofen was offered at a dose of 50 mg and the patients were evaluated at an interval of 30 min. In the case of insignificant pain relief, oxycodone (4–6 mg) was supplied for remediation.

Finally, the general information of the patients was collected, with the intraoperative and postoperative hemodynamic parameters including MAP, HR and SpO_2 recorded. The resting VAS scores, analgesic consumption were recorded at 0, 3, 6, 12, and 24 hours after surgery, and the incidence of postoperative adverse effects was also recorded. For the consistency of anesthesia, an experienced anesthesiologist performed all the manipulations. Meanwhile, the surgical operations were performed by the same team. Anesthesia was aimed to meet the operation requirements, and the corresponding depth of sedation was maintained during the operation, with the data recorded by the anesthetist nurse. After each operation, follow-up was conducted by another anesthesiologist (single blind, unaware of the patient grouping), and the data statistics was conducted by an assigned technician.

2.3. Statistical analysis

All statistical assessments were conducted by means of SPSS 20.0 (SPSS Inc., Chicago, IL). The numerical variables with normal distribution were presented as mean ± SD. The between-group comparison involved independent sample t-test for normal distribution or medial and interquartile range for abnormal distribution, with sum rank test adopted for comparisons. Chi-square test was employed for enumeration data. Differences at $P < .05$ were considered statistically significant.

3. Results

3.1. Demographic and clinical data

Eighty patients were eligible for the recruitment of the present study and were equally randomized to the MNB and GA groups. As shown in Table 1, the common characteristics of patients in both groups were well matched for demographic data and no significant difference was noted between the two groups with respect to age, American Society of Anesthesiologists stage, BMI, operation duration and blood loss volume ($P > .05$).

3.2. Postoperative pain and hemodynamic variation

To investigate the exact effect of MNB on the patients with breast cancer scheduled for MRM, the VAS scores were recorded at postoperative 0 hours, 3 hours, 6 hours, 12 hours, and 24 hours in resting state in MNB and GA groups. As displayed in Table 2, the VAS scores of patients in MNB group were significantly reduced at postoperative 0 hours, 3 hours, 6 hours, 12 hours, and 24 hours versus those in GA group ($P < .05$). These findings indicated that the anesthetic effect of MNB is superior to GA within 24 hours postoperatively in patient with breast cancer undergoing MRM. Furthermore, we also observed the hemodynamic parameters, that is, MAP, HR, and SpO_2 preoperatively, at intraoperative 30 minutes and postoperatively. Despite the modest elevation of MAP and HR in MNB group as compared with the GA group intraoperatively, the statistical difference was insignificant ($P > .05$) for all the time points of testing (Table 3).

Table 1

Demographic features of eligible participants.

Groups	MNB group (n = 40)	GA group (n = 40)	P values
Age (yr)	53.1 ± 8.1	51.7 ± 8.3	.441
ASA status (I/II)	24/16	23/17	.820
BMI (kg/m2)	24.6 ± 2.5	23.7 ± 3.3	.205
Operative duration (min)	140.4 ± 18.3	142.4 ± 15.0	.591
Blood loss (mL)	191.3 ± 22.9	198.5 ± 17.7	.120

The results are presented as mean ± SD (independent-samples t test). $P < .05$ was considered statistically significant.
ASA = American Society of Anesthesiologists, BMI = body-mass index VAS, GA = general anesthesia, MNB = ultrasound-guided multiple nerve blocks.

Table 2

The VAS scores in the time course in MNB and GA groups.

Groups	MNB group	GA group	P values
0h	1 (0–1)[***]	3 (0–4)	.000
3h	1 (0–2)[***]	3 (2–5)	.000
6h	1 (0–4)[***]	3 (2–5)	.000
12h	1 (1–5)[***]	3 (1–5)	.000
24h	2 (1–5)[***]	3 (1–5)	.000

Medial and interquartile range for abnormal distribution, with sum rank test adopted for comparisons.
GA = general anesthesia, MNB = ultrasound-guided multiple nerve blocks, VAS = visual analog scale.
[***] represents significant differences at $P < .001$.

Table 3

Comparisons of MAP, HR, and SpO$_2$ in the time course in MNB and GA groups.

	Groups	Preoperative	Intraoperative 30 min	Postoperative
MAP	MNB	81.6±9.1	82.6±11.3	83.4±11.0
	GA	82.8±8.2	80.6±9.0	82.4±5.6
	P value	.572	.728	.612
HR	MNB	72.2±8.7	69.4±10.3	72.2±7.7
	GA	73.8±8.1	68.3±5.9	72.6±6.5
	P value	.39	.586	.791
SpO$_2$	MNB	98.2±1.5	99.7±0.8	98.1±1.5
	GA	98.4±1.4	99.9±0.4	97.5±1.9
	P value	.588	.156	.103

The results are presented as mean±SD (independent-samples *t* test).
GA = general anesthesia, HR = heart rate, MAP = mean arterial pressure, MNB = ultrasound-guided multiple nerve blocks, SpO$_2$ = pulse oxygen saturation.

3.3. Adverse effects and the analgesics consumption

Subsequently, in case of the VAS scores exceeding 3 points, the number of patients who received supplementation of analgesic drugs was recorded at postoperative 0 hours, 3 hours, 6 hours, 12 hours, and 24 hours, in 2 groups. As illustrated in Table 4, the number of patients who received the analgesic drugs was significantly reduced in MNB group versus the GA group at postoperative 0 hours, 3 hours, and 12 hours ($P < .05$). Furthermore, the adverse effects such as vertigo, PONV, pruritus, and urinary retention were compared in MNB and GA groups. The incidence of vertigo and PONV was markedly decreased in MNB group versus the GA group, whereas pruritus and urinary retention were only present in GA group (Table 5).

4. Discussion

GA in patients with breast cancer undergoing MRM has been described to be responsible for a higher incidence of postoperative pain and PONV. Despite the accumulating evidence that diverse nerve blocks combined with GA for MRM could decrease the consumption of opioids, mitigate the postoperative pain and improve patient recovery, the incidence of adverse effects still remains high.[12–14] Potential strategies aimed to further reduce the opioid consumption and minimize postoperative adverse effects under the premise of improving perioperative analgesia still remain a challenge.

Sato et al[15] described that thoracic paravertebral nerve block assisted with basic sedation was effective for simple mastectomy and exhibited good postoperative analgesia and low the incidence of adverse effects. Albeit this *anesthesia* technique reached the surgical excision range of axillary lymph nodes and sentinel

lymph nodes, it did not well meet the requirements for MRM. Moreover, spread of local anesthetics under thoracic paravertebral nerve block is reportedly unsatisfactory, due to the anesthetic diffusion in the epidural space, anterior and contralateral regions of vertebrae, resulting in indefinite anesthetic effect.[16] Furthermore, paravertebral nerve block has been reported to evoke the total spinal *anesthesia*.[17] *The feasibility and repeatability of simple thoracic paravertebral nerve blockade in MRM still invite further verification, but this blocking approach provides a novel notion to minimize the dose of opioids and reduce the incidence of adverse reactions after MRM.*

MRM does not require muscle relaxation, and surgery can be performed while retaining the spontaneous respiration in the patients. The range of free flaps for MRM is based on the extent of anatomical breast glands, which are generally considered to be appropriate boundaries from the clavicle, down to the rib arch, medial to the parasternal, and lateral to anterior latissimus dorsi. The surgery also includes axillary lymph node dissection.[18] From the perspective of neuroanatomical distribution, blockade of the ipsilateral 1 to 7 intercostal nerve branch, brachial plexus and supraclavicular nerve, supplemented by moderate sedative hypnosis to eliminate the patient's tension and discomfort, may agree with the MRM in patients with breast cancer, with fewer incidences of adverse reactions. Based on the aforementioned findings, we investigated the feasibility and the effect of multiple nerve blocks, including intercostal nerve, brachial plexus in the interscalene groove and supraclavicular nerve, with the guidance of ultrasound in patients with breast cancer scheduled for MRM.

In the present study, all patients underwent the MRM under the MNB, with small doses of propofol to maintain sedative hypnosis. Compared with the technique of nerve block combined

Table 4

The postoperative supplementation of analgesics in MNB and GA groups.

Groups	MNB group	GA group	P values
0h	0*	6	.034
3h	0**	10	.001
6h	2	6	.264
12h	3**	13	.005
24h	5	12	.056

The results are shown as frequency (chi-square tests).
GA = general anesthesia, MNB = ultrasound-guided multiple nerve blocks.
* *P* < .05 was considered statistically significant.
** represents significant differences at *P* < .01.

Table 5

The incidence of adverse effects in MNB and GA groups.

Adverse events	MNB group	GA group	P values
Vertigo	2*	8	.043
PONV	1***	16	.000
Pruritus	0	1	1.000
Urinary retention	0	5	.055

The results are shown as frequency (chi-square tests).
GA = general anesthesia, MNB = ultrasound-guided multiple nerve blocks, PONV = postoperative nausea and vomiting.
* *P* < .05 was considered statistically significant.
*** represents significant differences at *P* < .001.

with GA, no opioids were used during our operation and no substitute for GA or no supplementation of analgesics occurred due to insufficient anesthesia. Intraoperative respiration and circulation of patients were stable in MNB group and hemodynamic parameters were insignificantly different from those in GA group. Patients who underwent anesthesia via multiple nerve blocks had lower VAS scores at 0–24 h after surgery, and the postoperative analgesic effects were more satisfactory versus GA. Meanwhile, there were lower reparation rates for postoperative analgesic drugs and had lower adverse reactions with flurbiprofen in MNB group. In addition, postoperative follow-up validated significantly earlier recovery of postoperative gastrointestinal motility and better dynamic pain scores in MNB group than in GA group, with higher subjective comfort. Breast mass resection under simple nerve block was reported to be conducted during pregnancy.[19] In our trial, no opioids were applied and a wider range of surgery was offered, which might provide a novel and safe anesthesia modality for pregnant patients. With respect to anesthesia procedures and related complications, the patient undergoing multiple nerve blocks under ultrasound guidance effectively precluded the complications such as puncture injury, pneumothorax and other anesthesia manipulations, hence the absence of adverse events as pneumothorax, local anesthetic poisoning or respiratory depression in our operations. Generally, it takes approximately 15 minutes for a skilled ultrasound-guided puncture operator to conduct the block anesthesia, unless in the obese patients, wherein block duration would be significantly prolonged.

Our study had limitations. One limitation was the involvement of more puncture sites in modality, which may increase the complexity and proficiency requirement to anesthetists. There are reports in which the nerve block of anterior serratus and the modified pectoral nerve block can be used in the postoperative analgesia of modified radical mastectomy.[20,21] Accordingly, compared with the GA, anterior serratus nerve block or modified pectoral nerve block is superior with respect to the analgesic effect, owing to the less involvement of the puncture points, and less discomfort in the patients. Nonetheless, there is no report on the use of anterior serratus nerve block or modified thoracic nerve block alone for modified radical mastectomy. Moreover, other auxiliary techniques may be needed to complete the operation, which brings prospect for our subsequent research. Another limitation was relatively larger dosage of local anesthetics for nerve block, which however, was still within the safe range, since ineligible patients with underlying diseases had been excluded in our study. Otherwise, the possibility of local anesthetic poisoning would have increased, and the dosage should be reduced as appropriate. Anyway, relatively larger dosage of local anesthetics would generally increase the proficiency requirement on the part of the medical practitioners, albeit this regimen remains advantageous. Hence, further investigations are required into the optimal concentrations of blocking agents and the minimum dosage of anesthetics at each block site to reduce the risk of potential toxicity. In addition, as well acknowledged, pain is an unpleasant physical and emotional experience associated with actual or potential tissue injury, which emphasizes the unity of pain and emotion. At present, incremental studies have shown that pain and emotional disorders are mutually attributable. Emotional disorders include depression, anxiety, etc., and the increment of pain can lead to the exacerbation of depression or anxiety.[22] With respect to the scoring systems of such emotional disorders, such as the Amsterdam pre-operative anxiety and information scale[23] and the Patient Health Questionnaire-9 score,[24] psychological evaluation will surely benefit clinical trials with more accuracy and reliability.

5. Conclusion

Collectively, MNB of intercostal nerves, interscalene brachial plexus and supraclavicular nerves, supplemented with mild sedation can drastically meet the needs of MRM, with better postoperative analgesia and fewer postoperative adverse effects.

Author contributions

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