Clinical Trial/Experimental Study

Medicine

OPEN

Hydromorphone combined with ropivacaine for erector spinae plane block in patients undergoing modified radical mastectomy

A prospective randomized controlled trial

Xue Cao, MM[a,b], Malian Bao, MM[c], Yuhua Ma, BM[b], Jie Ren, BM[b], Weiwei Ma, BM[b], Yongli Bao, BM[b], Changfei Ma, BM[b], Xin Sui, BM[b], Yongzhen Nie, BM[d,*]

Abstract

Background: Combining hydromorphone with ropivacaine in ultrasound-guided erector spinae plane blocks enhances postoperative analgesia and reduces interleukin-6 expression in breast surgery patients.

Methods: In this study, breast cancer patients undergoing modified radical mastectomy were randomized into 3 groups for anesthesia (30 patients in each group): standard general (group C), Erector Spinae Plane Block (ESPB) with ropivacaine (group R), and ESPB with ropivacaine plus hydromorphone (group HR). Diagnosis: Breast cancer patients. Postsurgery, pain levels, IL-6, anesthetic doses, additional analgesia needs, and recovery milestones were compared to evaluate the efficacy of the ESPB enhancements.

Results: The 3 groups were not significantly different in baseline characteristics, operation time, number of cases with postoperative nausea, and serum IL-6 concentrations at T1 (the time of being returned to the ward after surgery). At T2 (at 6:00 in the next morning after surgery), the serum IL-6 concentration in group HR was significantly lower than that in groups R and C ($P < .05$); the intraoperative doses of remifentanil, sufentanil, and propofol were significantly lower in groups HR and R than those in group C ($P < .05$); Groups HR and R had significantly lower visual analog scale scores at T3 (4 hours postoperatively), T4 (12 hours postoperatively), and T5 (24 hours postoperatively) than those in group C ($P < .05$); the proportions of patients receiving postoperative remedial analgesia were significantly lower in groups HR and R than in group C ($P < .05$); groups HR and R had significantly lower proportions of patients with postoperative nausea than group C ($P < .05$); the time to the first anal exhaust and the time to the first ambulation after surgery were significantly shorter in groups HR and R than those in group C ($P < .05$).

Conclusion: Hydromorphone combined with ropivacaine for ESPB achieved a greater postoperative analgesic effect for patients receiving MRM under general anesthesia. The combined analgesia caused fewer adverse reactions and inhibited the expression level of the inflammatory factor IL-6 more effectively, thereby facilitating postoperative recovery. ESPB using hydromorphone with ropivacaine improved pain control post-MRM, reduced adverse effects, and more effectively suppressed IL-6, enhancing recovery.

Abbreviations: ASA = American society of anesthesiologist, BIS = bispectral index, BMI = body mass index, ERAS = enhanced recovery after surgery, ESPB = Erector Spinae Plane Block, HM = hydromorphone, IL-6 = Interleukin-6, MRM = modified radical mastectomy, PACU = post-anesthesia care unit, PCIA = patient-controlled intravenous analgesia, PONV = postoperative nausea and vomiting, TCI = target controlled infusion, VAS = visual analog scale.

Keywords: erector spinae plane block, hydromorphone, interleukin-6, modified radical mastectomy, ropivacaine

1. Introduction

Breast cancer is one of the most common cancer types in Chinese females, and surgical resection remains the primary treatment. Relentless explorations have been conducted into the minimally invasive surgeries for breast cancer to relieve intraoperative and postoperative pain. Optimizing the type and the administration pathway of the anesthetics is an

XC and MB contributed equally to this work.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Graduate School of Inner Mongolia Medical University, Hohhot, China,
[b] Department of Anesthesiology, Xing'anmeng People's Hospital, Ulanhot, China,
[c] Department of Anesthesiology, Inner Mongolia Forth Hospital, Hohhot, China,
[d] Department of Anesthesiology, Peking University Cancer Hospital Inner Mongolia Hospital, Hohhot, China.

** Correspondence: Yongzhen Nie, Department of Anesthesiology, Peking University Cancer Hospital Inner Mongolia Hospital, Hohhot 010010, China (e-mail: nyz1@163.com).*

How to cite this article: Cao X, Bao M, Ma Y, Ren J, Ma W, Bao Y, Ma C, Sui X, Nie Y. Hydromorphone combined with ropivacaine for erector spinae plane block in patients undergoing modified radical mastectomy: A prospective randomized controlled trial. Medicine 2024;103:26(e38758).

Received: 5 March 2024 / Received in final form: 28 May 2024 / Accepted: 7 June 2024

http://dx.doi.org/10.1097/MD.0000000000038758

important mission for anesthesiologists to reduce the pain in women receiving breast cancer surgery. For modified radical mastectomy (MRM), general anesthesia is typically administered using inhaled anesthetics and opioids. Postoperative nausea and vomiting (PONV) is one of the most common adverse effects of opioids, with an incidence of about 80%.[1] As complained by numerous patients with a history of PONV, PONV is even more unbearable than postoperative pain. A great number of studies have been recently carried out on how to relieve postoperative pain and reduce the side effects of opioids, typically PONV. To date, ultrasound-guided regional nerve block has become an integral part of multimodal analgesia.

Ultrasound-guided erector spinae plane block (ESPB) is an adjunctive analgesic technique that may possess noticeable clinical benefits. ESPB is easy to operate, causes fewer complications, and achieves definite analgesic effects. Consequently, ESPB has demonstrated an increasing range of applications as an adjuvant analgesic in patients undergoing MRM. However, given the limited number of local anesthetics available, the combined utilization of different types of adjuvants and ropivacaine for ESPB to prolong the analgesic effects has become a research hotspot in recent years. In the present study, hydromorphone was used as an analgesic adjuvant due to its strong and prolonged analgesic effect. Pain is mainly accompanied by the increased expression levels of pro-inflammatory factors, including interleukin-6 (IL-6).[2] The IL-6 concentration was found to have a significant correlation with patients' symptoms and quality of life.[3] The present study assumed that hydromorphone combined with ropivacaine for ESPB could achieve a better postoperative analgesic effect for patients receiving MRM under general anesthesia. Moreover, the combined utilization of hydromorphone and ropivacaine might cause fewer adverse reactions and inhibit the serum IL-6 level more effectively.

2. Materials and methods

This single-center, prospective, double-blind controlled study was approved by the Medical Ethics Committee of Xing'anmeng People's Hospital (Ulanhot, China; Approval No. YJXM2021QN8) and registered in the Chinese Clinical Trial Registry database (Registration No. ChiCTR2100052700).

Patients who received elective MRM under general anesthesia from October 2021 to September 2022 at Xing'anmeng People's Hospital were randomly divided into 3 groups, including 30 patients in each group. Patients' baseline characteristics were not significantly different among the 3 groups ($P > .05$). Inclusion criteria were summarized as follows: Patients with grades I and II according to the American Society of Anesthesiologists (ASA) physical status classification; patients who aged 45 to 65 years old, with body mass index (BMI) ≤ 30 kg/m^2; expected operation time of 1 to 3 hours; voluntary participation in the study and signing the informed consent form. Exclusion criteria were summarized as follows: failure of ESPB; suffering from perioperative cardiovascular and cerebrovascular events or other severe complications; unable to understand or cooperate with pain assessment using the visual analog scale (VAS) score; dropping out of the postoperative follow-up.

2.1. Blinding scheme and randomization method

Prior to the inclusion of each participant in this study, the researchers introduced the objective, procedures, and potential risks of this study to the participants or their representative in details. They signed a written informed consent form, and the participants were informed that they had the right to withdraw from the study at any time. The informed consent was kept as clinical research document for future reference.

After patients signed the written informed consent form, they were randomized into different treatment groups using a random number table. An opaque sealed envelope was opened by a nurse after the patient was wheeled into an operating room, and the patient received any of the 3 anesthetic regimens: conventional general anesthesia group (group C), general anesthesia following ESPB using 30 mL of 0.5% ropivacaine (group R), and general anesthesia following ESPB using 30 mL of 0.5% ropivacaine and 0.5 mg hydromorphone (group HR). However, this nurse was not involved in patient care and postoperative follow-up. The nurse documented the anesthetic regimen designated for the specific patient and sealed the document in an envelope. This envelope was then handed over to an anesthesiologist who was not involved in postoperative follow-up and statistical analysis. Principal researchers, patients, and postoperative care team were also blinded about randomization. The anesthesiologist responsible for the anesthesia in MRM did not participate in the data analysis. During the research, the privacy and data confidentiality of the participants were protected.

2.2. Anesthetic methods

Patients receiving MRM under general anesthesia were first assessed for their eligibility for inclusion. Three patients with BMI > 30 kg/m^2 and 3 patients who dropped out of postoperative follow-up were excluded. Thus, a total of 90 patients were finally included in the analysis, and they were randomly divided into groups C, R, and HR (n = 30 patients in each group).

Group C: Conventional general anesthetic induction using the following agents: 0.03 mg/kg imidazole, 0.2 mg/kg etomidate, 0.3 μg/kg sufentanil, and 0.15 mg/kg cisatracurium. Maintenance anesthesia: target controlled infusion (TCI) to deliver propofol at 5 to 8 mg/kg/h and remifentanil at 0.1 to 0.3 μg/kg/min.

Group HR: ESPB was performed at 30 minutes before surgery. An injection of 0.5% ropivacaine + 0.5 mg hydromorphone, a total of 30 mL, was conducted under ultrasound guidance above the T5 transverse process in the deep surface of erector spinae. After 20 to 30 minutes, the block plane and range were determined by acupuncture. If the hypoesthesia plane was in line with the range of operation, it was indicated that it was effective; if not, the ESPB was ineffective, and the case should be excluded, followed by conventional general anesthesia.

For group R, ESPB was performed at 30 minutes before surgery. An injection of 0.5% ropivacaine + 0.5 mg hydromorphone, totaling 30 mL, was carried out under ultrasound guidance above the T5 transverse process in the deep surface of erector spinae. After 20 to 30 minutes, the block plane and range were determined by acupuncture. If the hypesthesia plane was in line with the range of operation, it was indicated that it was effective; if not, the ESPB was ineffective, and the case should be excluded, followed by conventional general anesthesia.

Group C was the blank control group, which did not receive ESPB except for general anesthesia. Group R received general anesthesia following ESPB using 30 mL of 0.5% ropivacaine. Group HR received ESPB using 0.5% ropivacaine + 0.5 mg hydromorphone, totally accounting for 30 mL, followed by general anesthesia. Both groups HR and R received ESPB at 30 minutes before surgery. Under the guidance of a convex array ultrasound probe, the needle was inserted using an out-of-plane approach, with the tip reaching above the T5 transverse process. The anesthetics were injected into the deep surface of erector spinae. The plane of block was detected within 20 to 30 minutes. General anesthesia with endotracheal intubation was performed after ESPB for groups HR and R. However, general anesthesia was conducted without ESPB in group C. General anesthesia was induced using the

Table 1

Visual analog scale (VAS).

Score	Pain intensity	Subjective experience
1 to 3	Mild pain	Painful but tolerable, living a normal life, with sleep undisturbed
4 to 6	Moderate pain	Obvious pain and intolerable, required to take analgesic drugs, with sleep disturbed
7 to 10	Severe pain	Intense pain and intolerable, indicated for analgesic drugs, with severe disturbance of sleep, possible autonomic dysregulation or passive position

following agents: 0.03 mg/kg imidazole, 0.2 mg/kg etomidate, 0.3 μg/kg sufentanil, and 0.15 mg/kg cisatracurium. Intraoperative maintenance anesthesia: TCI was utilized to deliver propofol at 5 to 8 mg/kg/h and remifentanil at 0.1 to 0.3 μg/kg/min. The intraoperative dosage of the anesthetics was adjusted to maintain the bispectral index (BIS) within the range of 36 to 60 and based on changes in blood pressure and heart rate. Additional anesthetics, such as 0.03 mg/kg cisatracurium and 5 to 10 μg sufentanil, were used, if necessary. TCI was terminated 5 minutes prior to the completion of suturing, and the patient was subsequently connected to a patient-controlled intravenous analgesia (PCIA) device (PCIA mixture: 100 μg sufentanil + 4 mg tropisetron + 0.9% NaCl, totaling 98 mL; flow rate of continuous infusion was 2 mL/h, loading dose was 3 mL per time, and lock-out time was 15 minutes). After the surgery, the endotracheal tube was removed if there was an indication. Patients were subsequently sent back to inpatient wards from PACI after assessment for about 30 minutes. Despite using BIS to monitor the intraoperative depth of anesthesia, patients were asked about intraoperative sleep after resuscitation from general anesthesia, including whether they were asleep and had intraoperative memories. If the patient answered that he/she was asleep and did not remember the intraoperative situation, it was considered that general anesthesia was effective; otherwise, general anesthesia was ineffective, and the case should be excluded. The patient's intraoperative dosage and the VAS scores at 4, 12, and 24 hours after the operation were recorded. IL-6 was detected when returning to the ward after operation and at 6 AM on the first day after operation, respectively.

2.3. Data collection

2.3.1. Primary indicators.

(1) Changes in serum IL-6 concentrations were measured by electrochemiluminescence immunoassay at 2 time points for the 3 groups of patients, namely, the time of being returned to the ward after surgery (T1) and at 6:00 in the next morning after surgery (T2).
(2) VAS scores were calculated at different postoperative time points for the 2 groups, namely, at 4 hours postoperatively (T3), at 12 hours postoperatively (T4), and at 24 hours postoperatively (T5). Further details are presented in Table 1.

2.3.2. Secondary indicators.

(1) Intraoperative doses of anesthetics were recorded in the 3 groups, including remifentanil, sufentanil, and propofol.
(2) The incidence of postoperative adverse reactions (nausea and vomiting) and prevalence of remedial analgesia (sufentanil supplementation) were recorded in the 3 groups.
(3) The time to the first anal exhaust and the time to the first ambulation after surgery were recorded in the 3 groups.

2.4. Detection of IL-6 by electrochemiluminescence

2.4.1. Detection principle. Double antibody sandwich method, with a total detection time of 18 minutes. Primary incubation: 30 μL of specimens were co-incubated with biotinylated IL-6 specific monoclonal antibody, forming an antigen–antibody complex. Secondary incubation: the ruthenium (Ru) labeled IL-6 specific monoclonal antibody was co-incubated with streptavidin-coated magnetic beads, and the antigen–antibody sandwich complex was combined with the magnetic beads through the action of biotin and streptavidin. The reaction solution was sucked into the measuring pool, and the magnetic beads were adsorbed on the surface of the electrode through electromagnetic action. Substances not bound to the magnetic beads were removed by ProCell. A certain voltage was applied to the electrode to make the complex chemiluminescent, and the luminescence intensity was detected by a photomultiplier. The detection results were automatically calculated through the 2-point calibration curve method, and the calibration curve was obtained by reading the barcode/electronic barcode of the reagent. (Note: a represents Tris (2,2′-bipyridyl) ruthenium (II)-complex (Ru (bpy))2 + 3 tris-bipyridyl ruthenium.))

2.4.2. Instrument. Roche automatic electrochemiluminescence immunoassay analyzer.

2.4.3. Reagents and their main components. M streptavidin-coated magnetic bead particles, 6.5 mL/bottle: streptavidin-coated magnetic bead particles, 0.72 mg/mL; R1 biotinylated IL-6 antibody, 9 mL/vial: biotinylated anti-IL-6 monoclonal antibody (mouse) 0.9 μg/mL, phosphate buffer 95 mmol/L, pH 7.3; R2 ruthenium labeled anti-IL-6 antibody, 9 mL/bottle: ruthenium complex labeled anti-IL-6 monoclonal antibody (mouse) 1.5 μg/mL, phosphate buffer 95 mmol/L, pH 7.3.

2.4.4. Specimen.

(1) Specimen type: Serum.
(2) Specimen collection and preparation: When the patient was fasting, a BD biochemical collection tube was used to collect 3 mL of venous blood, and the serum was separated after the specimen was coagulated to avoid hemolysis, jaundice or chyle. Serum specimens were collected with a vacuum tube containing separation gel.
(3) Specimen transportation: Transport under room temperature.
(4) Specimen processing and storage: It can be stored for 5 hours at 20–25 °C, 1 day at 2–8 °C, and 3 months at –20 °C (±5 °C). One freeze-thaw cycle.
(5) Calibration and quality control: Specimen with precipitation must be centrifuged before detection. Avoid using heat-inactivated specimens. Specimen and quality controls with added azide should not be used. The specimen, calibration solution and quality controls must be equilibrated at 20 to 25 °C prior to detection. The specimen detection, calibration solution, and quality controls on the analyzer must be completed within 2 hours due to the influence of evaporation.

2.4.5. Detection. (1) Reagent processing: The kits (M, R1, and R2) were ready-to-use and cannot be used separately. Reagent related information was obtained by reading the reagent barcode. (2) Detection: Before using the reagent, the analyzer automatically stirred the magnetic bead particles to keep suspension. Reagent related information was automatically read through the barcode. The refrigerated reagent was balanced to about 20 °C at room temperature, and then placed in the reagent disk of the analyzer (20 °C) (avoid foaming). The analyzer can automatically adjust the temperature of the reagent, and open and close the cap of each kit.

Table 2

Patients' baseline characteristics among the 3 groups (n = 30).

Group	Age (years old)	Body weight (kg)	Body height (cm)	Operation time (min)
Group HR	53.23 ± 1.85	61.93 ± 1.98	159.86 ± 4.55	97.5 (75.00, 115.75)
Group R	58.07 ± 1.68	62.53 ± 1.84	158.77 ± 6.65	98.00 (80.00, 119.75)
Group C	52.50 ± 2.14	63.73 ± 1.49	158.87 ± 6.24	107.50 (85.00, 142.25)
F/Wallis χ^2	3.731	0.264	0.320	4.273
P	.058	.768	.727	.118

Table 3

Serum Il-6 concentrations in resting state at different time points after surgery among the 3 groups (pg/mL, M (P25, P75), n = 30).

Group	T1	T2
Group HR	19.87 (10.83, 24.72)*	12.77 (9.24, 22.22)*
Group R	21.84 (15.67, 32.56)	22.23 (11.61, 36.89)
Group C	22.76 (18.15, 33.16)	23.54 (18.97, 32.78)
Wallis χ^2	5.525	11.246
P	.063	.004

*$P < .001$, compared with group C.

2.4.6. Calculation. The analyzer automatically computed the analyte concentration in each specimen, with the unit being pg/mL (reference range: 0–7 pg/mL).

2.5. Statistical analysis

Statistical analysis was performed using SPSS 26.0 software (IBM, Armonk, NYs). Normally distributed data were expressed as mean ± standard deviation. Intergroup comparison was conducted using 1-way analysis of variance (ANOVA). Enumeration data were expressed as rate and ratio and compared between the groups using the χ^2 test. Abnormally distributed data were expressed as median (interquartile range [M (P25, P75)]) and compared between the groups using the rank-sum test. $P < .05$ was considered statistically significant.

3. Results

3.1. Patients' baseline characteristics

The 3 groups were not significantly different in age, body height, body weight, and operation time ($P > .05$) (Table 2).

3.2. Serum IL-6 concentrations at different time points in the 3 groups

Serum IL-6 concentrations of the 3 groups were compared at T1 and T2, respectively. At T2, and the results showed the 3 groups were significantly different in the serum IL-6 concentration (Wallis $\chi^2 = 11.246$, $P = .004$). However, the serum IL-6 concentration in group HR was significantly lower than that in group C (Wallis $\chi^2 = 217.00$, $P = .001$) (Table 3).

3.3. Intraoperative doses of maintenance anesthetics in the 3 groups

A comparison of the intraoperative doses of maintenance anesthetics indicated no significant differences among the 3 groups. The intraoperative dose of remifentanil was significantly lower in groups HR and R than that in group C (Wallis $\chi^2 = 105.0$, $P < .001$; Wallis $\chi^2 = 118.4$, $P < .001$); the intraoperative dose of sufentanil was significantly lower in groups HR and R than that in group C (Wallis $\chi^2 = 117.0$, $P < .001$; Wallis $\chi^2 = 128.5$, $P < .001$). The intraoperative dose of propofol was also significantly lower in groups HR and R than that in group C (Wallis $\chi^2 = 215.0$, $P < .001$; Wallis $\chi^2 = 123.5$, $P < .001$; Wallis $\chi^2 = 123.5$, $P < .001$) (Table 4).

Table 4

Intraoperative doses of anesthetics among the 3 groups (n = 30).

Group	Intraoperative dose of remifentanil (mg, M (P25, P75))	Intraoperative dose of sufentanil (μg, M (P25, P75))	Intraoperative dose of propofol (g, M (P25, P75))
Group HR	0.886 (0.737, 1.131)*	20 (17.500, 20.000)*	0.581 (0.501, 0.670)*
Group R	0.931 (0.807, 1.398)*	20 (20.000, 22.750)*	0.556 (0.490, 0.725)*
Group C	1.510 (1.128, 1.873)	30 (29.000, 32.000)	0.784 (0.639, 0.968)
Wallis χ^2	31.523	41.431	15.001
P	<.001	<.001	.001

*$P < .001$, compared with group C.

Table 5

Postoperative VAS scores in resting state at different time points among the 3 groups (M (P25, P75), n = 30).

Group	4 h (postoperative)	12 h (postoperative)	24 h (postoperative)
Group HR	1 (1,1)*	1 (1,2)*	2 (2,3)*
Group R	1 (1, 1.25)*	1 (1,1)*	2 (1.75, 2)*
Group C	2 (2,3)	2 (2,3)	4 (2,4)
Wallis χ^2	25.632	27.514	10.389
P	.001	.001	.004

*$P < .05$, compared with group C.

3.4. Postoperative VAS scores among the 3 groups

There were significant differences in VAS scores at 4, 12, and 24 hours after surgery among the 3 groups. The VAS scores in groups HR and R at 4, 12, and 24 hours after surgery were significantly lower than those in group C (Wallis $\chi^2 = 106.00$, $P < .001$; Wallis $\chi^2 = 199.00$, $P < .001$; Wallis $\chi^2 = 158.50$, $P < .001$; Wallis $\chi^2 = 152.50$, $P < .001$; Wallis $\chi^2 = 242.00$, $P < .001$; Wallis $\chi^2 = 24.12$, $P < .001$) (Table 5).

3.5. Postoperative recovery among the 3 groups

The 3 groups were significantly different in the time to the first anal exhaust and in the time to the first ambulation after surgery. The time to the first anal exhaust after surgery was earlier in groups HR and R than that in group C (Wallis $\chi^2 = 207.0$, $P = .001$; Wallis $\chi^2 = 300.5$, $P = .027$). The time to the first ambulation after surgery was earlier in groups HR and R than that in group C (Wallis $\chi^2 = 258.5$, $P = .005$; Wallis $\chi^2 = 311.5$, $P = .040$) (Table 6).

Table 6

Postoperative recovery in the 3 groups (n = 30).

Group	Time to the first anal exhaust (h)	Time to the first ambulation (h)
Group HR	17.25 (6.50, 22.00)*	23.50 (21.50, 25.63)*
Group R	21.00 (15.50, 23.00)*	23.54 (22.88, 25.63)*
Group C	22.75 (20.00, 29.00)	25.23 (22.05, 27.13)
Wallis χ^2	13.412	9.162
P	.001	.010

*$P < .05$, compared with group C.

Table 7

Distribution of patients receiving postoperative remedial analgesia and suffering adverse reactions (n = 30).

Group	Remedial analgesia, n (%)	Nausea, n (%)	Vomiting, n (%)
Group HR	1 (3.3)*	8 (26.75)	5 (16,7)*
Group R	2 (6.7)*	7 (23.30)	6 (20,0)*
Group C	8 (26,7)	13 (43.30)	16 (53,3)
χ^2	8.907	3.214	11.746
P	.012	.200	.003

*$P < .05$, compared with group C.

3.6. The prevalence of postoperative remedial analgesia and the incidence of adverse reactions

The incidence of postoperative adverse reactions was compared among the 3 groups. It was found that the percentage of patients with PONV and the percentage of patients receiving sufentanil supplementation were significantly different among the 3 groups ($\chi^2 = 3.370$, $P = .015$, $\chi^2 = 9.407$, $P = .009$, $\chi^2 = 8.907$, $P = .012$). The percentage of patients with PONV and the percentage of patients receiving postoperative remedial analgesia were lower in groups HR and R than those in group C. The percentage of patients having postoperative nausea did not significantly differ among the 3 groups ($P > .05$). Further details are presented in Table 7.

4. Discussion

At present, MRM is a commonly utilized surgery for breast cancer. According to a survey, about 90% of breast cancer patients are worried about deterioration and they suffer from anxiety and depression, further resulting in a remarkable impairment of their quality of life. Appropriate interventions addressing the above-mentioned problems may alleviate negative emotions in breast cancer patients, such as anxiety and depression.[4] Cancer patients' survival is associated with certain physical and psychological problems that may last for lifetime. Further investigations are required to address the following questions: first, whether the relief of postoperative pain to the extent that patients experience only mild discomfort or no pain during the recovery period can genuinely mitigate negative emotions. Second, exploring the possibility of establishing a virtuous cycle between pain relief and positive emotions, potentially enhancing patients' overall quality of life and contributing to improved prognosis. Notably, postoperative pain following MRM primarily emanates from the T2 to T6 intercostal nerves and the anterior and lateral cutaneous branches of the supraclavicular nerve of the cervical plexus.[5] Depending on the approach and scope of MRM, rupture, stretching or spasm of the fascia, and muscles innervated by the medial and lateral pectoral nerves, long thoracic nerve and thoracodorsal nerve are reasons for myofascial pain.[6] About 50% of patients with untreated acute pain develop to chronic pain, which may worsen patients' postoperative conditions.[7] Postoperative pain management for MRM patients is crucial for alleviating chronic pain and promoting early recovery. Besides, effective perioperative pain management is an integral component of enhanced recovery after surgery (ERAS). Selection of an appropriate analgesic method is crucial for reducing postoperative pain and improving MRM patients' prognosis.[8]

In recent years, there has been a notable rise in the prominence of comfort medicine and ERAS, leading to an increased preference for multimodal analgesia in postoperative pain management. The combined utilization of 2 analgesic techniques can achieve effective pain management while reducing the dosage and side effects of opioids. Hence, multimodal analgesia has become a cornerstone of ERAS.[9] ESPB is an indispensable technique constituting the multimodal analgesia. Ultrasound-guided ESPB is the preferred choice for adjunctive analgesia due to its high levels of safety and efficacy. Single-shot ESPB, initially proposed by Forero et al,[10] is a recently invented method for regional nerve block, and it has been widely utilized thereafter. A previous study demonstrated that single-shot ESPB causes fewer side effects, such as hematoma and nerve injury.[11] This adjunctive analgesic method has been proven safe, effective, and easy to administer. As a novel, convenient, and more effective technique for regional nerve block, ESPB can achieve nerve block for trunk fascia in MRM patients. Traditionally, ESPB involved injecting local anesthetics into the myofascial plane of the erector spinae. In the present study, ESPB was modified by delivering the needle tip to the T5 transverse process, followed by an injection of local anesthetics into the deep surface of the erector spinae. This modified technique is expected to achieve a wider dispersion of local anesthetics and a better analgesic effect. The present study indicated that MRM patients receiving ESPB had a better analgesic effect than those receiving simple general anesthesia.

A meta-analysis demonstrated that ESPB performed before general anesthesia was more effective in reducing postoperative opioid use and lowering the VAS score at 24 hours after surgery.[12] The present study highlighted the benefits of ESPB combined with general anesthesia in 65 patients (including 3 patients with BMI above 30 kg/m^2 and 2 patients dropping out of postoperative follow-up), who received modified single-shot ESPB before general anesthesia. These patients all received decreased intraoperative doses of general anesthetics and had lower VAS scores. Besides, no puncture-related complications were found in these patients. When ESPB was utilized as a part of the anesthetic regimen guided by the nociception level index (NOL), the perioperative dose of opioids decreased, and the time to removing the endotracheal tube was shortened. Furthermore, there was no need for vasopressors, and a better postoperative analgesic effect was achieved.[13] Single-shot ESBP is an easy-to-perform technique of interfascial plane block. The success rate of single-shot ESBP, performed by well-trained anesthesiologists, is typically noticeable, and the incidence of complications is desirably low. The distinctive aspect of ESPB lies in its requirement for a single injection, a departure from other regional nerve blocks that typically involve multiple injection sites. Despite the efficiencies associated with ESPB, particularly its streamlined approach, the single-shot nature of this nerve block technique poses limitations due to the relatively short duration of action of local anesthetics. Both domestic and international researchers have endeavored to address this limitation by exploring the co-administration of adjuvants with local anesthetics to prolong the duration of nerve block effects. The frequently utilized adjuvants can be divided into the following 3 types: opioids, glucocorticoids, and α2 receptor agonists.[14]

In the present study, hydromorphone, an opioid analgesic drug, was utilized as an adjuvant for ropivacaine in ESPB. Hydromorphone is suggested for relieving moderate-to-severe acute pain and severe chronic pain. The intramuscular or subcutaneous dose of hydromorphone is generally 1 to 2 mg. For those with hepatic and renal insufficiency, the dose can be cut down by 1/4 to 1/2. However, further attention should be given to explore the synergistic effects of combined analgesia while also addressing the longstanding challenge of mitigating potential side effects.

Although hydromorphone is injected via the interfacial approach, the possibility of absorption into the bloodstream via a vein cannot be completely ruled out. In the present study, hydromorphone was injected as an adjuvant with a low initial dose of 0.5 mg. It was found that ropivacaine combined with 0.5 mg hydromorphone as an adjuvant was more effective in reducing the serum IL-6 concentration than ropivacaine alone and the difference was statistically significant. Although the combination of ropivacaine and hydromorphone also outperformed ropivacaine alone for ESPB in other indicators, the differences were not statistically significant, while the noninferiority of ropivacaine combined with hydromorphone for ESPB was proven. Whether the combined application of ropivacaine and a small dose of hydromorphone (preferably 0.5 mg) for ESPB can result in greater benefits should be further verified. The peripheral analgesic effects of opioids[15] should be discussed more intensively and extensively through clinical trials. This is because the peripheral administration of opioids can relieve the pain without causing adverse reactions in the central nervous system, such as respiratory depression, addiction, nausea, or sedation. Determining the most appropriate administration pathway of anesthetics to maximize their analgesic effects has become a topic of continued discussion.

The present study revealed that subcutaneous analgesia using hydromorphone had satisfactory analgesic effects on relieving cancerous bone pain, which was accompanied by a reduced serum IL-6 concentration.[16] This finding agreed with conclusion of the present study that ropivacaine combined with hydromorphone for ESPB inhibited the serum IL-6 concentration. Inflammatory response is mainly manifested as a rapid rise of IL-6 concentrations, peaking at about 2 hours. The rise of IL-6 concentrations typically occurs earlier than the changes in levels of other cytokines and lasts for a longer period of time. Therefore, the serum IL-6 concentration can assist the early diagnosis of acute infections. Moreover, IL-6 can enhance monocyte procoagulant activity.[17] During treatments for cardiovascular diseases, patients with a greater decrease in IL-6 concentrations might experience a reduction in major cardiac adverse events by about 1/3, with no increase in the infection risk.

Evidently, patients experiencing a more significant decrease in IL-6 concentrations derived greater overall benefits and a more favorable risk ratio. In summary, the reduction of IL-6 concentration proves advantageous for patients undergoing MRM, who commonly exhibit an inflammatory response and an elevation in IL-6 level. In light of these findings, anesthesiologists should prioritize the optimization of analgesic type and administration methods to achieve a reduction in IL-6 concentrations. This comparative analysis revealed that patients undergoing ESPB with combined analgesia exhibited a lower serum IL-6 concentration on the morning after surgery compared with those receiving simple general anesthesia. However, the assessment of whether this translates to a superior prognosis in the former group requires further evaluation using refined indicators.

The present study had the following limitations: this study was conducted only at a single-center and had a small sample size. Whether similar analgesic effects can be achieved in patients from other geographical regions remains elusive; we did not set up groups receiving different doses of hydromorphone or a control group receiving intravenous hydromorphone. It remains largely unknown whether a smaller dose of hydromorphone can further reduce the incidence of adverse reactions and whether an intravenous administration of an equal dose of hydromorphone can provide equivalent analgesic effects; in this study, the serum level of only 1 inflammatory factor, namely, IL-6, was detected, and the detection was repeated twice for each patient. It is worthy to investigate whether the combined analgesia for ESPB had any impact on other inflammatory factors or on the serum IL-6 level at other time points; patients' sleep quality or satisfaction was not assessed. Additional assessment indicators should be included to make the findings more convincing; no long-term follow-up was performed, and whether the specified dose of hydromorphone could affect patients' long-term prognosis should be further elucidated.

5. Conclusion

In conclusion, the administration of ropivacaine, whether combined or not with 0.5 mg of hydromorphone for ESPB, led to a significant reduction in opioid dosage in patients undergoing MRM. Notably, this reduction was achieved without inducing severe adverse reactions or complications. Moreover, the combined analgesia for ESPB in MRM under general anesthesia lowered the serum IL-6 concentration on the first day after surgery, thereby facilitating postoperative recovery.

Author contributions

Writing – original draft: Xue Cao, Malian Bao.
Data curation: Yuhua Ma, Jie Ren.
Project administration: Yuhua Ma, Jie Ren.
Methodology: Weiwei Ma, Yongli Bao.
Software: Changfei Ma, Xin Sui.
Conceptualization: Yongzhen Nie.

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