Cover page

COMPARITIVE STUDY BETWEEN ULTRASOUND GUIDED MID-POINT TRANSVERSE PROCESS TO PLEURA BLOCK AND ERECTOR SPINAE PLANE BLOCK FOR PERIOPERATIVE ANALGESIA IN MODIFIED RADICAL MASTECTOMY IN BREAST CANCER PATIENTS.

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IRB APPROVAL

The institutional review board of the national cancer institute (IRB-NCI) is constitute and operate according to ICH-GCP guidelines, institutional regulations and national regulation. All activities related to human subjects" research is guided by the ethical principles of the declaration Helsinki and Belmoni Report. IRB NCI is in charge with review and approval of all research involving human participants at NCI and other research sites. The Egyptian National Cancer Institute (NCI –Egypt) has a Federal – wide Assurance (FWA) with the Office of Human Research Protection in the Department of Health and Human Services (USA)

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Background and Rationale:

Breast cancer is the most commonly diagnosed malignancy and it is considered the leading cause of cancer-related mortality among women in more than 100 countries [1]. One of the main surgical treatments for breast cancer is Modified Radical Mastectomy (MRM) which accounts for 31% of all breast surgeries [2].Erector Spinae Plane Block (ESPB) is a new regional anesthesia technique which provides regional anesthesia for breast surgeries. Breast surgeries are commonly associated with postoperative pain. Inadequate management of acute postoperative pain may lead to persistent postoperative pain, also known as chronic pain [3] Good postoperative analgesia plays a very important role in patient recovery. The thoracic paravertebral block (TPVB) is the gold standard regional analgesic technique for breast surgery. This block can reduce postoperative pain and opioid consumption [4]. However, the conventional TPVB can be technically difficult in identifying the thoracic paravertebral space (TPVS). This analgesic technique can cause complications, such as pleural puncture, epidural spread, accidental vascular injection of local anesthetic, intrathecal injection, and postural headache [5].

Although recent ultrasound-guided TPVB studies results reported a low incidence rate (0.7%) of complications [6], it is not easy to localize the paravertebral space and the ventral transposition of the pleura cannot be visualized in some patients during injection of the local anesthetic or saline, resulting in increasing the failure rate of Para thoracic nerve block and pleural puncture.In recent years, Erector Spinae Plane Block (ESPB) and mid-point transverse process to pleura (MTP) became new alternatives to thoracic paravertebral nerve block.[7] ESPB is defined as the injection of local anesthetic drugs between the erector spine muscle and the transverse process of vertebra while MTP is defined as injection point midway between the posterior border of the transverse process and the pleura.[8]

Previous studies indicated that both blocks could be easy, safe, and effective analgesic techniques for breast surgery [8-9]. However, which block provides superior analgesia after MRM is still unclear due to lack of enough studies. This randomized study was designed to compare the intra operative and postoperative analgesic effects and adverse events associated with ultrasound-guided ESPB and MTP after MRM.

Hypothesis:

We hypothesize that Ultrasound guided mid-point transverse process to pleura block is going to be as effective as ultrasound guided erector Spinae plane block in reducing post-operative morphine consumption in comparison to control group in cancer patients undergoing MRM.

Objectives:

Primary objectives:

Assessment of post-operative opioid (morphine) consumption in the 1st 24 hours after using

ultrasound guided mid-point transverse process to pleura block compared to ultrasound guided Erector Spinae Plane Block in patients undergoing modified radical mastectomy.

Secondary objectives:

Assessment of:

1 Post-operative Numeric Pain Rating Scale.

2. Effect on hemodynamics: Mean arterial blood pressure and Heart rate.

3. Intraoperative fentanyl consumption.

4.Duration of analgesic effect.

5.Block related complications.

Study Design :

This is randomized controlled trial.

Population of study:

Breast cancer patients who are candidates for MRM.

Study location:

National Cancer Institute Cairo University after approval by the institutional review board.

Inclusion criteria:

- Age starting from 18 to 60 years.
- ASA I-II.
- Undergoing modified radical mastectomy surgery.
- Body mass index (BMI) from 18.5 to 30 kg/m^2

Exclusion criteria:

- Patient refusal.
- Known allergy to local anesthetics.
- Bleeding disorders; platelets count <50,000 , prothrombin concentration < 60% or any coagulopathy disorder.
- Use of any anti-coagulants.
- Inability to provide informed consent.
- ASA III-IV.
- Neurological disorders.
- Patient with psychiatric disorders.

Methodology in details:

Randomization:

The patients will be randomly assigned into three equal comparable groups using computer-generated random numbers in opaque closed envelopes, each of which will include 30 patients. With allocation ratio 1:1:1

Group M (mid-point transverse process to pleura block MTP) N=3o
Patients will receive Ultrasound guided mid-point transverse process to pleura block preoperative with injection of 20 ml bupivacaine 0.25%.Then patients will be transferred to operating room.

Group E (Erector Spinae Plane Block ESB) N=3o
Patients will receive Ultrasound guided erector spinae plane block with injection of 20 ml bupivacaine 0.25%. Patients will be transferred to operating room.

Group C (control group) N=30
Patients will not receive any block, as both blocks are not the gold standard to control post-operative analgesia. Induction will be performed by using a regimen of IV by fentanyl 1 μg/kg, Additional bolus doses of fentanyl 0.5 μg/kg will be given if the mean arterial blood pressure or heart rate rises above 20% of baseline levels.

Randomization will be done by statistician and each group of the patient will revealed only when the included patient is transferred to preanesthetic room.

Study Protocol:

History, physical exam, laboratory and radiological investigations at preoperative assessment clinic National Cancer Institute Cairo University.

Preoperative assessment at night of surgery.

The patients will be instructed how to report pain by means of Numeric Pain Rating Scale, in which 0 = "no pain" and 10 = "worst possible pain".

Informed consent will be obtained.

Preoperative fasting; minimum of 6 hours for food and minimum of 2 hours for water and clear fluids.20G IV is inserted. All patients will be premedicated with IV midazolam 0.05-0.1 mg\kg 30 minutes preoperatively.

Both blocks will be done preoperative with the patients in the lateral position.

The analgesic effect will be evaluated by the skin prick test 20 minutes after the block intervention, from the T3 to T7 nerve distribution segment. A successful ESPB or MTP block must contain at least T4, T5 and T6 segments; otherwise, the block will be considered unsuccessful and will be removed from the study.

After allocation of patient to a study group patient of group M will receive mid-point transverse process to pleura block and patients of group E will receive erector spinae plane block.

- **ESPB**

Group E: The block will be performed preoperatively with full aseptic precautions. The ultrasound probe will be placed on the back in a vertical orientation on the lateral side of the posterior median line to identify the transverse process of the 5^{th} thoracic vertebra and erector spine muscle.

A skin wheal using 3ml of 1% lidocaine will be made 2 to 3 cm superior to the superior aspect of the transducer. The puncture will be performed using the intra-plane needling technique after local anaesthesia infiltration. A 20-gauge Tuohy needle connected to a syringe containing the anesthetic mixture or saline will be advanced. When the puncture needle touch the transverse process, with no blood, gas, or cerebrospinal fluid observed on aspiration, 20 mL of 0.25% bupivacaine will be administered between the erector spine muscle and transverse process.

Local anesthetic diffusion between the transverse process and erector spinae muscle is an indication of a successful puncture.

- **MTP**

Group M: The block will be performed preoperatively with full aseptic precautions. The ultrasound probe will be placed on the back in a vertical orientation on the lateral side of the posterior median line to identify the transverse processes of the 4^{th} and 5^{th} thoracic vertebrae and pleura.

A skin wheal using 3ml of 1% lidocaine will be made 2 to 3 cm superior to the superior aspect of the transducer. Using the in plane needling technique in the space between the transverse processes of the 4^{th} and 5^{th} thoracic vertebrae, the puncture needle needle tip will be placed at the mid-point between the transverse process and pleura, with no blood, gas, or cerebrospinal fluid observed on aspiration, 20 mL of 0.25% bupivacaine will be administered. The local anesthetic spread will be noted in the area midway between the transverse process and pleura is an indication of a successful puncture.

The transverse section and paramedian sagittal paravertebral space will be observed by ultrasound in both groups. All patients included will be anesthetized by the same anesthesiologist and operated on by the same surgeons.

Anesthetic Management:

Monitoring:

all patients will be monitored continuously using electrocardiography, non-invasive blood pressure, peripheral oxygen saturation and end tidal carbon dioxide throughout the duration of the surgical procedure.

Induction:

Induction of general anaesthesia will be performed using a regimen of IV 2 µg/kg fentanyl and propofol IV 2 mg /kg. Tracheal intubation will be facilitated using 0.5 mg/kg IV of rocuronium.

Maintenance:

Anaesthesia will be maintained with inhaled sevoflurane 2-2.5% in oxygen enriched air (FiO2=0.5). Maintenance doses of rocuronium o.1 m\kg will be provided every 30 minutes. Paracetamol 1 gm and IV ketorolac 30mg will be provided as a part of multimodal anelgesia.

Rescue analgesia of fentanyl 1 µg/kg will be given if the mean arterial blood pressure or heart rate rises above 20% of baseline levels.

The patients will be mechanically ventilated at appropriate setting that keep end-tidal CO2 at 30-35 mmHg.

1st reading of mean arterial pressure (MAP) and heart rate (HR) will be taken before induction of general anaesthesia to be defined as a baseline reading another reading will be taken immediately before surgical incision and at 5-minute intervals intraoperatively.

Hypotension ((reduction of more than 20% of baseline reading)) will be treated with 0.9% normal saline and/or 5mg ephedrine in incremental doses to maintain mean blood pressure above 70 mmHg.

The residual neuromuscular blockade will be reversed using neostigmine (0.05 mg/kg) and atropine (0.02 mg/kg), and extubation will be performed after complete recovery of the airway reflexes.

The patients will be transferred to the post-anaesthesia care unit (PACU) where the, Numeric Pain Rating Scale score, MAP and heart rate will be noted immediately on arrival, where they will be observed for 2 hours then discharged to the ward.

Lung ultrasound will be performed once again at PACU looking for signs of pneumothorax.

If the patient indicates Numeric Pain Rating Scale ≥ 4, rescue analgesia will be provided in the form of increments of 3 mg morphine intravenously as needed with a maximum of 0.1 mg/kg in a period of 4 hours. The total amount of morphine given in 24 hours will be recorded for the two groups.

Thereafter, the patients will be transported to their respective ward, Multimodal analgesia will be provided as the following:

IV paracetamol 15 mg/kg /6 hours

IV ketorolac 30mg/12 hours.

There, Numeric Pain Rating Scale score, MAP and heart rate will be noted at 4, 8, 12, 16, 20 and 24 hours postoperatively

Side effects such as nausea, vomiting, sedation, hallucination, respiratory depression (respiratory rate <10/minute) and nightmares will be recorded. Postoperative nausea and vomiting (PONV), as side effects of morphine, will be rated on a four-point verbal scale; (none =no nausea, mild =nausea but no vomiting, moderate=vomiting one attack, severe =vomiting >one attack). 0.1 mg/kg of IV ondansetron will be given to patients with moderate or severe postoperative nausea and vomiting.

Measurement tools:

- ✓ Intraoperative fentanyl consumption.
- ✓ Total amount of fentanyl used by the anaesthetic provider in the operating room will be recorded.

- ✓ Intraoperative hemodynamics heart rate and mean arterial blood pressure every 30 minutes.
- ✓ The total amount of morphine consumption postoperatively.
- ✓ Postoperative hemodynamics heart rate and mean arterial blood pressure taken at 0,4,8.12,16,20 and 24
- ✓ Pain using Numerical rating scale (NRS), both at rest and during movement:
- ✓ Pain scores using NRS will be recorded in the PACU, and for the next 24 hours postoperatively.
- ✓ Presence of side effects such as Nausea, vomiting and local anesthetic toxicity.
- ✓ Time of first rescue analgesia.
- ✓ Presence of side effects of block such as pneumothorax (US check postoperative).

Study outcomes:

Primary outcomes:

post-operative opioid (morphine) consumption in the 1st 24 hours

Secondary outcome parameters:

- Time to first rescue analgesia, starting after extubation.
- Total dose of fentanyl required intraoperative (including induction dose)
- Pain score at 15, 30, 45 and 60 min., 3,6,12 and 24 h after surgery.
- Block failure rate which can be defined by persistence of pain sensation by skin prick test 20 minutes after each block.
- The incidence of side effects.
- Change in heart rate and mean arterial blood pressure intraoperatively at 30 minutes interval in comparison to baseline reading.
- Heart rate, mean arterial blood pressure at 0, 4, 8, 12, 16, 20 and 24 hours postoperatively

Risks:

1. Local anesthetic toxicity.
2. Failure of block.

Sample Size:

A randomized Controlled trial aiming to assess postoperative 24 hours morphine consumption after using ultrasound guided mid-point transverse process to pleura block (Group 1) compared to ultrasound guided Erector Spinae Plane Block (Group 2) and control group receiving IV morphine (Group 3) in patients undergoing modified radical mastectomy. Comparing the previously mentioned block with ratio 1:1:1, based on **(**Mohammed HA **et al, 2023)**(10) **& (**Singh S **et al., 2019)** (11) the average total morphine consumption in the first 24 h is (0, 1.95 and 9.3, in group 1,2 & 3 respectively) with standard deviation (3, 2.01 &2.36 for the three mentioned groups respectively), so we will need to study 24 participant, it will be compensated by 15% due to the use of nonparametric tests, so the final sample size will be **90** subjects (30 per group) to be able to reject the null hypothesis that the population means of opioid consumption in the three groups are equal with probability (power) 0.9999. The Type I error probability associated with test of this null hypothesis is 0.05. Sample size was calculated using G power program (12).

Statistical analysis:

Data will be analyzed using IBM SPSS advanced statistics (Statistical Package for Social Sciences), version 27 (SPSS Inc., Chicago, IL). Numerical data will be described as mean and standard deviation or median and range, as appropriate. Categorical data will be summarized as numbers and percentages. Data will be explored for normality using Kolmogrov-Smirnov test and Shapiro-

Wilk test. Comparisons between the 2 groups for normally distributed numeric variables will be done using the Student t-test while for non-normally distributed numeric variables will be done by Mann-Whitney test. Comparisons between more than 2 groups will be performed by the one analysis of variance (ANOVA) for normally distributed variables (Post Hoc comparison will be done and P value will be adjusted using Bonferroni adjustment) and Kruskal-Wallis for non-normally distributed variables. Comparison between multiple related groups of normally distributed numerical data will be done using Repeated measures ANOVA. Comparison between multiple related groups of non-normally distributed numeric variables will be done using Friedman test. Chi square or Fisher's tests will be used to compare between the groups with respect to categorical data. A p-value less than or equal to 0.05 will be considered statistically significant. All tests will be two tailed.

Sources of funding:

National Cancer Institute Cairo University.

Time plan:

The study will start after the approval of the Ethical Committee.

Ethical committee approval:

- This study will be started after approval of Institutional Review Board and Ethical Research Committee.
- The study protocol will be presented to the Scientific Ethics Committee of the Anaesthesia, Pain Relief, and ICU Department at the National Cancer Institute – Cairo University.
- Patients' data will be presented anonymously with protection of privacy and confidentiality.
- The aim and nature of the study will be explained to each patient before their inclusion in the study. An informed written consent will be obtained from each patient, or a first degree relative before enrolment.

List of Correlative Studies:

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.

2. Garg, R., Bhan, S., & Vig, S. (2018). Newer regional analgesia interventions (Fascial plane blocks) for breast surgeries: Review of literature. Indian Journal of Anaesthesia. https://doi.org/10.4103/ija.IJA_46_18

3. Hickey OT, Burke SM, Hafeez P, Mudrakouski AL, Hayes ID, Shorten GD. Severity of acute pain after breast surgery is associated with the likelihood of subsequently developing persistent pain. Clin J Pain. 2010;26(7):556–60.

4. Terkawi AS, Tsang S, Sessler DI, Terkawi RS, Nunemaker MS, Durieux ME, et al. Improving analgesic efficacy and safety of thoracic paravertebral block for breast surgery: a mixed-effects meta-analysis. Pain Physician 2015; 18: E757-80.

5. Karmakar MK. Thoracic paravertebral block. Anesthesiology 2001; 95: 771-80.

6. Pace MM, Sharma B, Anderson-Dam J, Fleischmann K, Warren L, Stefanovich P. Ultrasound-guided thoracic paravertebral blockade: a retrospective study of the incidence of complications. AnesthAnalg 2016; 122: 1186-91.

7. Kahramanlar AA, Aksoy M, Ince I, Dostbıl A, Karadenız E. The Comparison of Postoperative Analgesic Efficacy of Ultrasound-Guided Paravertebral Block and Mid-Point Transverse Process Pleura Block in Mastectomy Surgeries: A Randomized Study. J Invest Surg. 2022 Sep;35(9):1694-1699. doi: 10.1080/08941939.2022.2098544. Epub 2022 Jul 17. PMID: 35848451.

8. Costache I, de Neumann L, Ramnanan CJ, Goodwin SL, Pawa A, Abdallah FW, McCartney CJL. The mid-point transverse process to pleura (MTP) block: a new end-point for thoracic paravertebral block. Anaesthesia. 2017 Oct;72(10):1230-1236. doi: 10.1111/anae.14004. Epub 2017 Aug 1. PMID: 28762464.

9. Costache I. Mid-point transverse process to pleura block for surgical anaesthesia. Anaesth Rep. 2019 Mar 11;7(1):1-3. doi: 10.1002/anr3.12003. PMID: 32051934; PMCID: PMC6931287.

10.Mohammed HA, Belal AM, Elkalla RS, Soliman SM. Analgesic efficacy of pre-emptive ultrasound-guided mid-point transverse process to pleura block for patients undergoing

posterolateral thoracotomy incisions: Randomized controlled trial. Egyptian Journal of Anaesthesia. 2023 Dec 31;39(1):538-45.

11. Singh S, Kumar G. Ultrasound-guided erector spinae plane block for postoperative analgesia in modified radical mastectomy: a randomised control study. Indian journal of anaesthesia. 2019 Mar 1;63(3):200-4.

12. Faul, F., Erdfelder, E., Lang, A.-G. & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods, 39, 175-191