ULTRASOUND GUIDED ERECTOR SPINAE PLANE BLOCK IN BREAST CANCER SURGERY: ANALGESIA, SPREAD AND IMMUNOMODULATION

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INTRODUCTION

Breast cancer is the commonest cancer among Egyptian females (38.8%) and modified radical mastectomy (MRM) is the most common surgical intervention. [1]

Breast cancer surgery induces marked acute nociceptive and neuropathic pain in the chest wall, axilla and ipsilateral arm.[2] Effective postoperative balanced analgesia including regional anaesthesia suppresses the surgical stress response and diminishes opioids needs.[3]

The commonest reasons for overnight stay after breast cancer surgeries are postoperative pain, nausea and vomiting and anxiety.[4] Postoperative hospital stay for breast cancer patients has shortened owing to not only the less invasive surgical technique, but also the efficient pain relief protocols including regional anaesthesia.[5]

Ultrasound-guided fascial plane blocks are novel techniques which showed effectiveness in managing post-mastectomy pain.[6-8]

Erector spinae plane (ESP) block is one of the fascial plane blocks; its efficacy depends on the compartmental spread and the local anaesthetic (LA) distribution to nearby target nerves. The absorption and diffusion of the LA has a role in determining the quality of ESP block. LA may diffuse anteriorly to the ventral and dorsal rami of the spinal nerves and through the intertransverse connective tissue to enter the thoracic paravertebral space.[9]

Local anaesthetic volume and concentration are important factors for unilateral ESPB with volumes ranging from 10 to 40 mL have been used.[10] However, the optimum volume and concentration, distribution and dermatomal coverage is still undetermined.[11]

As the erector spinae fascia extends from the nuchal fascia cranially to the sacrum caudally, local anaesthetic agents extend through several levels, and the block can be effective over a large area.[12]

Cadaveric studies had been performed to assess the spread of dye in this novel block. However, not all of them have had such extensive spread of dye. In one study, only minimal spread had been observed into the paravertebral space and in another it has been failed to demonstrate any spread at all into the paravertebral space or the ventral rami but there was extensive lateral and craniocaudal spread around the Erector Spinae (ES) complex. Till now many questions about the extent of sensory coverage and if there is difference in the spread between cadavers and the living humans, as intrathoracic pressure changes may direct LA spread differently.[13, 14]

Post-mastectomy minimal residual may be unavoidable and the possibility for this to result in metastases and cancer recurrence relies on many factors, including anti-tumor cell mediated immunity and angiogenic and growth signals in sites of the residual.[15] The perioperative neuroendocrine surgical stress response, volatile anaesthetics and opioids have deleterious effects on this process. In another words; the anaesthetic technique could influence perioperative immunosuppression and determine whether the immune response would be capable of eradicating the displaced tumour cells.[16-18]

Natural killer (NK) cells are $CD3^{--}$ $CD56^{+}$ lymphocytes playing a pivotal role in the innate immune response against cancer. Their main purpose is identification and eradication of virus infected cells and metastatic cells. Diminished activity of NK cells is a predisposing factor for cancer recurrence.[19] Preservation of innate immune function and the direct anti-inflammatory effects may be the cause of the protective effects of local anaesthetics and regional techniques.[20-22] Different concentrations of local anaesthetics appear to have different effects on natural killer cells (NKC) cytotoxicity. High concentrations of lidocaine suppress NK cell cytotoxicity,[23] yet clinically relevant concentrations enhance the in vitro function of NK cells via the release of lytic granules.[24]

AIM OF THE WORK

The aim of the present study is to evaluate the effect of US guided unilateral ESPB using different volumes of local anaesthetic on analgesic efficacy, dermatomal spread and immunomodulation in breast cancer surgery.

The primary outcome is the analgesic efficacy of the different local anaesthetic volumes of ESPB.

The secondary outcomes are the dermatomal dye spread and sensory coverage, immunomodulation and complications in breast cancer surgery.

PATIENTS

This study will be carried out on 60 female patients aged between 20-50 years, admitted to Medical Research Institute Hospital for breast cancer surgery.

All patients will be of American Society of Anesthesiology (ASA) physical status I or II, scheduled for mastectomy under the effect of general anaesthesia after taking approval of the Ethical Committee of the Faculty of Medicine, and a written consent from every patient included in the study.

The sample size is determined according to the recommendations of the department of biomedical informatics and medical statistics, Medical Research Institute using NCSS 2004 & PASS 2000 program. A minimal sample size of 15 in each group is required to estimate an average difference of 2 in the median visual analogue scale (VAS) between groups assuming common standard deviation of 2.5, using F test, at level of significance 0.05.

Patients will be randomly allocated using a computer generated random table (Graphpad Software, Inc, La Jolla, CA) and an allocation ratio of 1:1:1. Blinding of the research personnel will be maintained throughout the whole observation period including all postoperative follow-ups.

Group (I): 20 patients will receive US-guided deep ESPB block before induction of general anaesthesia using 20 ml bupivacaine 0.25 % and 5 ml of radiocontrast dye (Omnipaque) at the level of T4.

Group (II): 20 patients will receive US-guided deep ESPB block before induction of general anaesthesia using 40 ml bupivacaine 0.125 % and 5 ml of radiocontrast dye (Omnipaque) at the level of T4.

Group (III): 20 patients will undergo standard general anaesthesia as a control group and postoperative analgesia with intravenous morphine patient controlled analgesia (PCA) and rescue analgesia if required.

Exclusion criteria

1. Age below 18 or more than 70.
2. Scoliosis or any vertebral anomalies or previous spinal surgeries.
3. Morbid obesity (BMI $\geq$ 40 kg/m^2).
4. Allergy or contraindication to any of the studied medications or anaesthetic agents.
5. Chronic opioid analgesic use.
6. Pregnancy.
7. Infection at the site of injection or any other contraindication for regional anaesthesia.
8. Duration of surgery more than 90 minutes.
9. Renal impairment.

METHODS

Preoperative evaluation of the patients:

Evaluation of the patients will be carried out on the day before surgery through proper history taking, clinical examination, complete blood count (CBC) and needed laboratory investigations according to the patient status. Plain X ray chest and ECG will be done for patients above 40 years. All patients will be informed with the procedure of US guided deep ESPB block and they will be trained to use the visual analogue scale (VAS) which consists of 10 cm line, 0 equivalent to no pain and 10 denoting the worst imaginable pain.[25]

Preanaesthetic preparation and premedication:

On arrival to the operative theatre a peripheral venous catheter will be inserted to all patients, multichannel monitor (Vamos- Dragar-Germany) will be attached to the patient to display ECG (lead II), heart rate (beats/min), non-invasive mean arterial blood pressure (mmHg) and peripheral oxygen saturation (SpO_2%). All patients will receive midazolam (0.05mg/kg) and fentanyl (0.5µg/kg) intravenously 3 minutes before performance of the block.

Technique of ultrasound guided deep ESPB block:

Ultrasound guided deep ESPB block will be performed in the block room at Medical Research Institute hospital. Patients will be placed in the prone position and a high-frequency linear probe (L 6-12MHz) of SonoSite, S nerve, 2 D machine, USA will be sterilized. After skin sterilization, the ultrasound probe will be placed 2.5–3 cm laterally to the spinous process in a parasagittal oblique plane, at the seventh cervical vertebra and moved caudally till T4.

After anatomical scanning and identification of the transverse process of T4 and the three muscles (Trapezius, Rhomboid major and Erector spinae), 2 ml of lidocaine 2% will be used to numb the skin then 18-gauge Tuohy needle will be advanced cranio-caudally towards the lateral border of transverse process of T4 using the in-plane technique.

The needle tip will be located in the fascial plane between the transverse process and erector spinae muscle. The correct needle position will be tested by injecting 2 ml of saline resulting in hydrodissection of the plane followed by the injection of:

- 20 ml bupivacaine 0.25% and 5 ml of radiocontrast dye (Omnipaque) in group 1.
- 40 ml bupivacaine 0.125% and 5 ml of radiocontrast dye (Omnipaque) in group 2.

Then, insertion of epidural catheter 2 to 3 cm over the tip of the Tuohy needle under real-time US guidance will be done.

Assessment of deep ESP sensory block:

Field of sensory block from T1 to T6 will be assessed bilaterally every 3 minutes for 15 minutes after deep ESPB using a piece of cotton soaked in iced water. The adequacy of sensory block T1-T6 will be determined before induction of general anaesthesia.

Assessment of ES dye spread:

After deep ESPB, patients will be transferred to the radiology suite where a CT scan of the thoracic region will be performed. The spread of the injected solution in the deep ESP will be evaluated using DICOM image processing for Mac (OsirixX, PixmeoSARL; Bern, Switzerland) and a three-dimensional digital reconstruction of the distribution of the injected contrast will be obtained.

Anaesthesia

All patients will receive standardized anaesthetic technique. General anaesthesia will be induced in each group by intravenous fentanyl 1μg/kg, propofol (2.5 mg/kg) and cisatracurium (0.15 mg/kg) to facilitate endotracheal intubation. Anaesthesia will be maintained with isoflurane (1.2 – 1.5%) and

oxygen/air mixture (50 %, 50 %). Incremental doses of cisatracurium 0.03 mg/kg will be given to maintain anaesthesia guided by train of four (TOF) count using the nerve stimulator module of (TOF watch –Organon-Ireland). Ventilation will be maintained at a tidal volume of 6 ml/kg and a rate to adjust the end-tidal carbon dioxide at (35-40 mmHg) using the ventilator (Fabius GS-Drager-Germany).

At the end of surgery, anaesthesia will be discontinued, residual neuromuscular block will be antagonised by atropine 0.01 mg/kg and neostigmine 0.04 mg/kg, the trachea will be extubated and patients will be transferred to the postoperative anaesthesia care unit (PACU) for the next 24 hours.

Postoperative analgesia:

Bolus of bupivacaine, with the same volume and concentration assigned to each group, will be given in the epidural catheter at the end of surgery in groups I & II.

In the PACU, pain score (as with other measurements) will be assessed by a physician not involved in the study design.

Intravenous morphine patient controlled analgesia (PCA) will be prepared by 50 mg morphine +45 ml normal saline with a concentration of 1 mg morphine /1 ml.

1. Bolus dose of 0.05 mg/kg.
2. Lockout Interval: 10 minutes.
3. Four hourly limiting doses will be 10 mg.

If VAS still ≥ 4, patients will be administered Ketorolac 30 mg IV as rescue analgesia.

Natural killer cells isolation and cytotoxicity assay:[16, 18]

Samples of 1 ml of patients' peripheral blood will be collected on EDTA for flow cytometry to enumerate for both cytotoxic lymphocyte populations (NK cells

and cytotoxic t lymphocytes (Ctls)). CD 56 will be used as a marker for NK cells, while CD 8 will be used as a marker for Ctls.

Cytotoxicity assay will be done by measuring the release of lactate dehydrogenase (LDH) from non-viable cells (Cytotoxicity Detection Kit, 630117; Clontech Laboratories, Mountain View, California) according to the manufacturer's instructions. Then ratio of LDH released specifically from NK cells will be correlated according to the results of flow cytometry.[16, 18]

Measurements

The following measurements will be carried out:

1. Patient demographics including age, sex and weight.

2. Vital signs:

1. Heart rate (beats/min) and ECG will be continuously monitored and will be recorded before induction of anaesthesia, every 15 minutes intraoperatively and at arrival to the PACU, then every 4 hours for the first 24 postoperative hours with recording of any abnormalities.
2. Peripheral oxygen saturation (SpO_2%) will be continuously monitored and will be recorded before induction of anaesthesia, every 15 minutes intraoperatively and at arrival to the PACU, then every 4 hours for the first 24 postoperative hours.
3. Mean arterial blood pressure (MABP) in mmHg will be monitored and recorded before induction of general anaesthesia, every 15 minutes intraoperatively and at arrival to the PACU, then every 4 hours for the first 24 postoperative hours.
4. Postoperative respiratory rate will be recorded every hour for the first 4 hours and then every 4 hours for the rest of the 24 hours.

3. Patient sedation scale:[28]

Patient sedation will be assessed by Richmond Agitation-Sedation scale in PACU every 4 hours for 24 hours.

Table (1): Richmond agitation sedation scale[28]

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behaviour toward staff
+2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	Spontaneously pays attention to caregiver
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

4. Pain assessment:

1. Acute postoperative nociceptive pain will be measured by:
   a. Visual analogue scale (0-10) where 0=no pain, 10=worst imagineable pain every hour for the first 4 hours and then every 4 hours for the rest of the 24 postoperative hours. This will be done during rest and movement.
   b. Total amount of IV morphine will be calculated at the end of the 24 postoperative hours.
   c. Total amount of rescue analgesia will be calculated and first time of its need will be recorded.
2. Acute postoperative neuropathic pain will be detected 10 days after surgery by DN4 (Douleur Neuropathique 4) questionnaire (10 Questions with cut-off value 4/10)[26].

DN4 – QUESTIONNAIRE

To estimate the probability of neuropathic pain, please answer yes or no for each item of the following four questions.

INTERVIEW OF THE PATIENT

QUESTION 1:

Does the pain have one or more of the following characteristics?	YES	NO
Burning	❑	❑
Painful cold	❑	❑
Electric shocks	❑	❑

QUESTION 2:

Is the pain associated with one or more of the following symptoms in the same area?	YES	NO
Tingling	❑	❑
Pins and needles	❑	❑
Numbness	❑	❑
Itching	❑	❑

EXAMINATION OF THE PATIENT

QUESTION 3:

Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?	YES	NO
Hypoesthesia to touch	❑	❑
Hypoesthesia to pinprick	❑	❑

QUESTION 4:

In the painful area, can the pain be caused or increased by:	YES	NO
Brushing?	❑	❑

YES = 1 point
NO = 0 points

Patient's Score: /10

Before patients would be discharged home, DN4 questionnaire will be explained to every patient. Postmastectomy neuropathic pain will be detected in breast, axilla or arm. Its onset (days) and interference with work, sleep or mood will be recorded.

5. Post-block complications:

Any complications after the block will be spotted and recorded:

1. Symptoms or signs of local anaesthetic toxicity (tinnitus, perioral numbness, seizure).
2. Postoperative nausea and or vomiting (PONV) score:
    1. None.
    2. Yes, and relieved by treatment.
    3. Yes, but not relieved by treatment.

Intravenous metoclopramide (10 mg) and ondansetron (4 mg) will be given as the first and second line of treatment of vomiting, respectively.

3. Arrhythmias.
4. Haematoma at the site of injection.
5. Respiratory depression (when respiratory rate < 8 breath / min).

6. CT scan for the spread:

Patients will be imaged 15 minutes after the block and before induction of general anaesthesia and surgery. 3 D reconstruction of the image will be done then Craniocaudal spread of the contrast and spread to Paravertebral space, epidural space or rami of the spinal nerves will be assessed and recorded.

7. Immunomodulatory outcome: [16, 18]

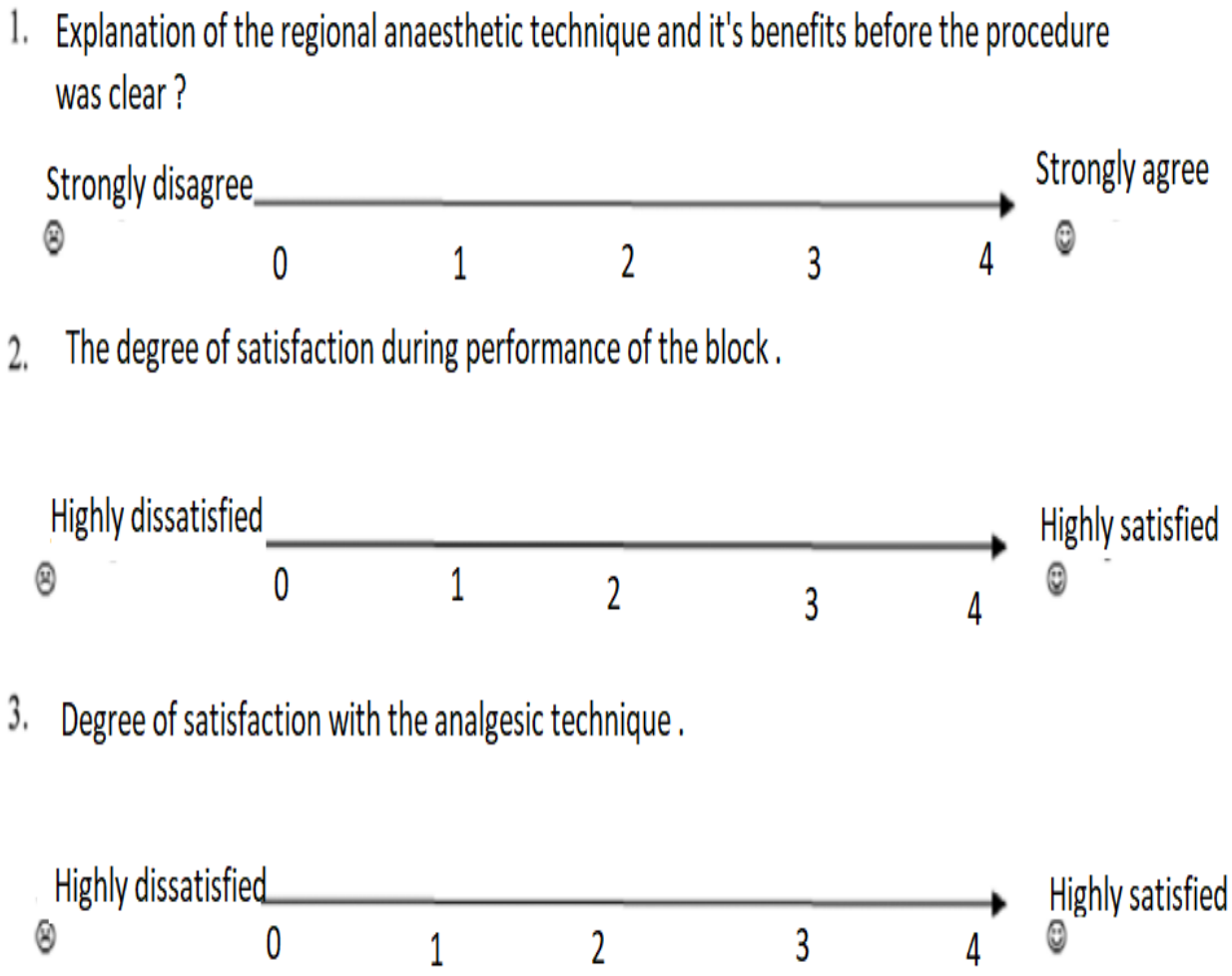
Cytotoxicity of both lymphocyte populations will be assessed by the measuring LDH by enzyme-linked immunosorbent assay or Western blot before deep ESPB and 24 hours after the block.

Then ratio of LDH released specifically from NK cells will be correlated according to the results of flow cytometry for both cytotoxic lymphocyte populations (NK cells and cytotoxic t lymphocytes (Ctls)).

8. Patient satisfaction scale:[27]

Before the patients would be discharged in the second postoperative day, their satisfaction with medical care and the method of postoperative pain relief will be measured by Likert scale, which is a self-report scale where 0 = strong dissatisfaction, 1 = dissatisfaction, 2 = neutral, 3 = satisfaction and 4 = strong satisfaction (for each item of the scale).

Figure (1): Patient satisfaction scale:[27]



ETHICS OF RESEARCH

Research on human or human products:

- ☐ Prospective study: informed consent will be taken from patients. In case of incompetent patients the informed consent will be taken from the guardians.
- ☐ Retrospective study: confidentiality of records will be considered.
- ☐ DNA/genomic material: informed consent for DNA / genomic test and for research will be taken from patients. No further test will be carried out except with further approval of committee and patients. If the samples will travel outside Egypt the researcher will be responsible for transportation and security approval.
- ☐ All drugs used in the research are approved by the Egyptian Ministry of Health.

Research on animal:

- ☐ The animal species are appropriate for the test.
- ☐ After test, if animal will suffer, it will be euthanized and properly disposed.
- ☐ After operation, it will have a proper postoperative care.

RESULTS

Results obtained from this study will be tabulated and statistically analysed using standard statistical methods.

DISCUSSION

The results obtained from this study will be discussed in view of achievement of the aim and compared with available published data in the same field of research.

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