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The Use of Regional Anesthesia with a Paravertebral Nerve Block and its Effects on Breast Cancer Recurrence and Metastasis

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THE USE OF REGIONAL ANESTHESIA WITH A PARAVERTEBRAL NERVE BLOCK AND ITS EFFECTS ON BREAST CANCER RECURRENCE AND METASTASIS

by

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Abstract

Title: The Use of Regional Anesthesia with Paravertebral Nerve Block and its Effects on Cancer Recurrence and Metastasis

Background: Surgical removal of breast cancer remains a mainstay treatment. The use of regional anesthesia may be associated with improved long-term outcomes and lower rates of recurrence and metastasis. Regional anesthesia attenuates the body's surgical stress response, reduces immunosuppression and need for opioid and general anesthetic consumption.

Purpose: The purpose of this independent project is to review the current literature regarding the effect regional anesthesia has on recurrence or metastasis of breast cancer after tumor removal surgery.

Process: A comprehensive review of the literature was performed utilizing CINAHL and PubMed databases from the University of North Dakota's Health Sciences Library. Each reference was carefully selected, reviewed, and applied.

Results: It was determined inconclusive as to whether regional anesthesia improves rates of breast cancer recurrence or metastasis. The use of regional anesthesia has been associated with lower levels of inflammation and better immune response when compared to general anesthesia and opioid use.

Implications: A majority of the research to date has been small retrospective studies. A large randomized control trial is currently underway, which may strengthen evidence and practice recommendations.

Keywords: Regional anesthesia, breast cancer, metastasis, neoplasm, neoplasm metastasis, and anesthesia conduction.

The Use of Regional Anesthesia with a Paravertebral Nerve Block and its Effects on Cancer Recurrence and Metastasis

The American Cancer Society (2018) reports that breast cancer remains the most common cancer, (besides skin cancer) and the second leading cause of cancer death among American women. One in eight women will develop breast cancer during her lifetime. In 2018, over 330,000 new cases of breast cancer will be diagnosed. Typical treatment for breast cancer is surgical tumor removal. Depending on how advanced the cancer is, treatment may also include chemotherapy, radiation and hormone therapy (American Cancer Society, 2018). An estimated 30-40% of patients who develop metastatic recurrence of breast cancer will die despite treatment (Pérez-González, Cuéllar-Guzmán, Soliz, & Cata, 2017). Despite the attempts to remove the cancer cells along with adjuvant therapies, metastatic disease remains a significant cause of death (Xuan, Hankin, Zhao, Yao, & Ma, 2014). Anesthesia providers are caring for and providing anesthesia for cancer patients daily. Since 2006 the question has been posed as to whether the anesthetic technique used during tumor removal surgical procedures influence the metastasis of cancer (Barela & Welliver, 2017).

The perioperative period is a critical time in the prognosis of long-term outcomes in breast cancer. The use of regional anesthesia has been hypothesized to improve breast cancer recurrence and metastasis (Sessler, Shamgar, Mascha, Parat, & Buggy, 2017). During surgical intervention of tumor resection, cancer cells can be inadvertently disseminated into the circulation, increasing the risk for metastasis (Sessler et al., 2017). The surgical stress response is also activated, which contributes to postoperative immunosuppression (Xuan et al., 2014). According to Barela and Welliver (2017), “the stress of surgery results in a neuroendocrine response, depressing the immune system, causing a decrease in cell-mediated immunity” (p. 75).

The use of opioids and volatile anesthetics can worsen immunosuppression, putting the patient at a higher risk for cancer growth (Barela & Welliver, 2017). Local anesthetics and regional anesthesia have been shown to reduce local inflammation at the surgical site, attenuating the immunosuppression (Barela & Welliver, 2017). Regional anesthesia significantly reduces the amount of general anesthetic required and provides excellent pain relief during the intraoperative and postoperative periods requiring little to no use of opioids and avoiding their adverse effects on the immune function (Karmakar et al., 2017).

Breast cancer affects a sizable portion of the population. New advances and research are continually being conducted to improve outcomes. Anesthesia is part of the care these patients require. The following pages include a case report of a patient undergoing a mastectomy due to diagnosed breast cancer, review of the literature including pathophysiology, pharmacology and results from recent studies conducted on the outcome of patients with breast cancer.

Purpose

The purpose of this independent project is to review a case report and provide anesthesia professionals with evidence-based research regarding long-term outcomes of anesthetic technique used for breast cancer tumor removal surgeries. The effects of surgery, general anesthetics, and medications at a cellular level, has been hypothesized to affect the recurrence and metastasis of cancer. Being aware of the alternate choices to general anesthesia may affect the long-term prognosis of the patients' cancer diagnosis.

Case Report

A 64-year-old, 71 kilograms (kg), 160 centimeters (cm), Caucasian female presented for a right modified radical mastectomy with axillary sentinel lymph node dissection for the treatment of invasive ductal carcinoma of the right breast. She had allergies to prednisone and

exposure to environmental factors. Her medical history included asthma, fibromyalgia, hiatal hernia, hypokalemia, urinary tract infection, hypomagnesemia, invasive ductal carcinoma of the right breast, antineoplastic chemotherapy, chemotherapy-induced diarrhea, neutropenia, drug-induced pancytopenia, sepsis and neutropenic fever. Surgical history included sinus surgery, knee arthroscopy, colon polyp biopsy, venous access insertion, hysterectomy, carpal tunnel release and upper endoscopy. There was no history of anesthetic complications. Her medications included fluticasone, dronabinol, prochlorperazine, tramadol, ondansetron, dexamethasone, pantoprazole, azelastine, multi-vitamin, calcium, magnesium, zinc, ipratropium bromide/albuterol nebulizer, acetaminophen, vitamin D3 – cholecalciferol and nasal moisturizer.

The patient was considered an American Society of Anesthesiologists physical status level three with a Mallampati class II. Bilateral breath sounds were clear to auscultation, and preoperative electrocardiogram (EKG) revealed sinus tachycardia at 102 beats per minute (BPM). Preoperative vital signs were: heart rate 98 BPM, blood pressure 139/92 mmHg, respirations 18/minute, pulse oximetry 98% on room air, and temperature 97.7° Fahrenheit (F). A peripheral intravenous line was started by the nurse in the holding room, and 2 milligrams midazolam (mg) intravenously (IV) was administered. The patient was then transported to the operating room where she was assisted onto the operating table. Non-invasive monitors were applied which included: a finger pulse oximeter, a 5-lead electrocardiogram (EKG), and a blood pressure cuff.

The patient was given two puffs of an albuterol inhaler and then pre-oxygenated via facemask at 8 liters per minute. Vital signs were: heart rate 105 BPM, blood pressure 147/96 mmHg, and pulse oximetry of 100%. One hundred micrograms (mcg) of fentanyl, 50 mg of lidocaine, and 150 mg of propofol were all given IV for induction. The ability to ventilate was

confirmed with chest rise, end-tidal carbon dioxide (ETCO2) and mask fogging. Subsequently, 30 mg rocuronium IV was administered for relaxation. A 7.0 cuffed endotracheal tube (ETT) was placed by direct laryngoscopy utilizing a Macintosh three blade with a grade one Cormack and Lehane view. After intubation, bilateral breath sounds were auscultated, ETCO2 monitoring was present, and the ETT was secured at 21 centimeters (cm) at the lip. The patient was placed on volume control mode with a rate of 12/min, and a tidal volume of 500 mL as well as initiating sevoflurane to achieve a half MAC at 1%. Inspired oxygen was titrated to 50%, and the air was administered to keep total flows at 2 liters (L) per minute. The patient's blood pressure increased to 162/101 mmHg during induction, an additional 50 mcg of fentanyl IV was administered, and a propofol infusion was started at 80 mcg/kg/min. A nasopharyngeal probe was inserted for temperature monitoring with a temperature of 97.5°F throughout the procedure. The patient’s blood pressure decreased to 87/39 mmHg. Therefore, 100 mcg of phenylephrine IV was administered, followed by another 100 mcg of phenylephrine IV three minutes later for a blood pressure of 92/40 mmHg. Two grams (g) of cefazolin IV was administered for a preoperative antibiotic. Ten milligrams of dexamethasone and 4 mg of ondansetron were given IV for nausea prophylaxis.

The patient was positioned supine with arms secured on padded arm boards, prepped, and draped. A lower body Bair hugger was placed. Ten minutes after the incision was made the patient's blood pressure was 142/79 mmHg, subsequently 1 mg of hydromorphone IV was administered. Twenty-six minutes later her blood pressure was 152/83 mmHg, and heart rate was 105 BPM. Therefore, an additional 1 mg of hydromorphone IV was administered. Ten milligrams of labetalol IV was administered for a blood pressure of 156/84 mmHg and a consistent sinus tachycardia with a heart rate of 110 BPM. Upon emergence the patient had 4/4

train of four with sustained tetany, the propofol infusion was turned off, and the patient was breathing spontaneously at 12-14 respirations per minute with tidal volumes of 400-500 mL, following commands and able to sustain a head lift greater than 5 seconds. Neuromuscular blockade reversal was not administered as patient met adequate extubation criteria and had received one dose of rocuronium that was 2 hours and 7 minutes earlier.

During the two-hour twenty-one-minute surgical case, the patient received a total of 1,400 mL of lactated ringers. Estimated blood loss was 100 mL. The patient was admitted to a medical-surgical unit overnight; her pain was treated with morphine IV and acetaminophen/hydrocodone orally. She was discharged home the following day.

Literature Search

Relevant articles were obtained through searches completed via the University of North Dakota's Health Sciences Library utilizing the CINAHL and PubMed databases. A MeSH Pubmed search for scholarly medical articles and research was conducted, where several useful articles were found. Keywords searched were: regional anesthesia, which prompted the use of "anesthesia, conduction"; other keywords were cancer and metastasis. The MeSH Pubmed search was *anesthesia, conduction* AND *neoplasms* AND *neoplasm metastasis*. This search resulted in 92 relevant articles and was then filtered for the past ten years and narrowed down to 37 related articles. Nine articles will be used from the Pubmed database search. A search was also conducted on the CINAHL database for scholarly medical articles and research journals. Keywords used were: *anesthesia, cancer,* and *metastasis,* which resulted in 53 related articles from 2006-2017, and four articles will be used.

Factors within the literature review included categories of anesthetic drugs such as volatile anesthetic gases, opioids and local anesthetics and their effect on cancerous cells and

studies relating to the effect of regional anesthesia on the metastasis of cancer. Reference lists of pertinent articles were also reviewed, which resulted in the use of 3 articles. Articles lacking adequate references and those not in the English language were excluded.

Review of Literature

Thoracic Paravertebral Block

Thoracic paravertebral block (TPVB) is a regional anesthetic technique used for thoracic and breast surgeries by injecting local anesthetic in the paravertebral space, near the point where the thoracic spinal nerves emerge from the intervertebral foramina (Cali, Biffoli, Francesconi, Patrella, & Buonomo, 2017). Use of TPVB has been shown to significantly reduce pain and opioid use, lower chronic pain occurrence by greater than 30%, as well as decrease post-operative nausea and vomiting, and shortening hospital stays (Wardhan, 2015; Cali et al., 2017). The use of regional anesthesia-analgesia appears to attenuate perioperative immunosuppression and may minimize metastases (Cali et al., 2017).

The use of ultrasound imaging while performing thoracic paravertebral block has been associated with fewer complications compared to using landmarks alone (Pace et al., 2016). An ultrasound-guided technique provides direct visualization of the paravertebral space during the procedure, thereby reducing the risk of complications (Pace et al., 2016). Potential complications of TPVB include accidental pleural puncture, symptomatic pneumothorax, hypotension, bradycardia, and local anesthetic toxicity (Pace et al., 2016). A study conducted on the incidence of complications with ultrasound-guided TPVB revealed very few complications, where only six complications were noted in 856 patients (0.70%), none of which were a pneumothorax (Pace et al., 2016).

When examining the financial aspect of using TPVB for mastectomies, Offodile et al. (2017) report a cost-effective analysis:

> Preoperative paravertebral blocks are a cost-effective strategy in reducing acute postoperative pain following mastectomy. Given that breast cancer is the most common malignancy afflicting women with 37-40% receiving mastectomy, preoperative paravertebral block should be considered where and when available. In a time where the American people and US health system are battling an opioid epidemic, cost-effective strategies that reduce postoperative pain are needed to improve public health. (p. 483)

This study indicates a realistic perspective and supports the use of paravertebral blocks from a cost-effective point of view.

Cancer Biology

Common among all articles reviewed, was a discussion on the biology of cancer itself and what promotes growth and metastasis of cancer cells. Tedore (2015) states on a cellular level, the microenvironment of a tumor is made up of cancer cells and different types of inflammatory cells and mediators. Inflammatory cells and mediators promote cancer formation and its progression (Tedore, 2015). The “initiation” and first step in cancer is when there is damage to the DNA (Tedore, 2015). The second injury is called “promotion,” and can be triggered by several things including inflammation, injury or irritants (Tedore, 2015). During the promotion stage, there is an increase in inflammatory cells, release of chemical mediators and oxidative damage which makes it hard for the body to destroy the cancerous cells resulting in cellular proliferation (Tedore, 2015). Angiogenesis (formation of new vessels from existing endothelial cells) is critical for the survival and growth of tumor cells (Tedore, 2015).

Cancer Promotion

Surgical stress affects the neuroendocrine response, suppresses the immune system, and lowers cell-mediated immunity (CMI) (Barela & Welliver, 2017). The degree of surgical stress can vary depending on how invasive the surgical procedure is (Barela & Welliver, 2017). Suppression of the immune system results in overproduction of stress hormones and increased inflammatory response (Tedore, 2015). Pain has also been shown to activate the body's stress response and suppress CMI (Tedore, 2015). According to Tedore (2015):

> Pro-inflammatory cytokine concentrations and the duration of their elevation have been shown to be correlated with surgical insult, lasting as long as 3–5 days after surgery. Both experimental and clinical studies have shown that surgery inhibits T-cell, B-cell, and natural killer (NK) -cell function for days after a surgical insult. (p. 36)

Natural killer cells are the bodies' primary defense against cancer cells (Snyder & Greenburg, 2010). During surgery there is also a large release of inflammatory mediators (IL-6 and TNF-α), this inflammatory storm suppresses CMI (NK, cytotoxic T, and dendritic cell activity), which is one of the body's vital defense mechanisms against cancer (Xuan et al., 2015). Cell-mediated immunity does not eradicate the primary tumor, but if it is not suppressed, it may eliminate minimal residual disease, preventing metastasis and recurrence (Snyder & Greenburg, 2010).

Pharmacology

Volatile anesthetics such as inhalational agents and IV anesthetic agents including ketamine and thiopental used in general anesthesia have been shown to increase the destruction of immune cells such as natural killer cells and T-lymphocytes, which leads to tumor progression (Barela & Welliver, 2017). Beneficial properties of propofol, an IV anesthetic, have been shown to inhibit the enzyme matrix metalloproteinase (MMP), which reduces cancer cell proliferation (Barela & Welliver, 2017). Propofol also reduces inflammatory cytokines, preserving NK-cell

activity, and inhibiting cancer spread (Xuan et al., 2015). Propofol conjugates have been shown to inhibit cellular adhesion, migration, and apoptosis in breast cancer cells and have been looked at as a treatment for breast cancers (Snyder & Greenburg, 2010).

Local anesthetics (LA) have shown to be beneficial in reducing the spread and growth of cancer cells (Barela & Welliver, 2017). At high concentrations, LA are known to be cytotoxic to the cancer cells, via necrosis or apoptosis (Xuan et al., 2015). Inhibition of cancer cell proliferation, migration, and invasion along with anti-inflammatory properties are among other benefits (Xuan et al., 2015).

Perioperative and chronic administration of opioids has been shown to promote angiogenesis and immunosuppression resulting in tumor cell proliferation (Snyder & Greenburg, 2010; Barela & Welliver, 2017). Fentanyl has been shown to inhibit natural killer cells (Barela & Welliver, 2017). Other evidence has suggested that at higher, more adequate pain-relieving doses opioids may show tumor-suppressive effects due to blocking pain and the stress response to surgery (Tedore, 2015).

Research Trial Review

An initial retrospective study was conducted on a group of patients by Exadaktylos, Buggy, Moriarty, Mascha, and Sessler (2006), who hypothesized the use of regional anesthesia combined with general anesthesia (GA) would have lower cancer recurrence and metastasis rates than GA with opioid administration. The first group of patients had surgery with a paravertebral nerve block combined with general anesthesia. The second group received general anesthesia and postoperative morphine analgesia. The percentage of recurrence and metastasis-free survival of the paravertebral nerve block group was 94% at 24 months and 94% at 36 months. Whereas

the group that received GA with morphine was 82% and 77% respectively. The magnitude of benefit seen in the results from this study prompted further research.

Several similar retrospective studies have been conducted over recent years. Starnes-Ott, Goravanchi, and Meininger (2015) conducted a retrospective study comparing paravertebral combined with general anesthesia to general anesthesia alone and showed no statistical difference between the two groups. Tsigonis et al. (2016) conducted a retrospective study comparing patients who received only local or regional anesthesia and those who received general anesthesia. Follow up was performed five years after the initial surgery and patients from each anesthesia group were categorized into one of three groups: overall survival, disease-free survival, or local/regional recurrence. Results showed no significant differences between the two types of anesthesia. Cata et al. (2016) conducted a retrospective study comparing patients who received paravertebral block anesthesia to patients who were treated with opioid-based analgesia and found no statistical difference between recurrence of breast cancer at 5.8 and six years following the initial surgery. Among all retrospective studies in this review, pain control was better in those who received regional anesthesia with less opioid administration.

A study conducted by Chen et al. (2015) used perioperative propofol-paravertebral anesthesia (PPA) technique, which combines a paravertebral nerve block (PVB) with a propofol infusion. It is hypothesized that PPA demonstrates a lower incidence of chronic postsurgical pain with avoiding opioids and inhibits surgical suppression of cellular immunity. PPA elevates the number of NK cells and T cells to increase NK toxicity and augment cancer cell apoptosis. The use of propofol also reduces the expression of MMP. Chen et al. (2015) states:

> PPA participates in several bioprocesses in the development of breast cancer including inhibiting hypoxia-inducible factor activity, elevating serum

> concentration of nitric oxide index, depression of neuroepithelial cell transforming gene 1 signal pathway, blocking the nuclear factor kappa B pathway following a decreased expression of MMP, increasing NK cytotoxicity, and affecting transforming growth factor-β-targeted ras and HER2/neu gene pathways. (p.8259)

Therefore, supporting the hypothesis of beneficial use of PPA. Although results from this study did not show a difference in rates of recurrence or metastasis of breast cancer between the two groups, Chen et al. (2015), points out that the reviews of the bioprocesses relating PPA to alterations in the cell matrix which should not be ignored. Similar studies regarding the use of PPA have shown an improvement in the prognosis of breast cancer (Chen et al., 2015).

A randomized controlled trial was conducted by Karmakar et al. (2017) which divided patients up into 3 study groups: GA only with total intravenous anesthesia (TIVA); TIVA with a single-injection thoracic paravertebral block (TPVB) and placebo infusion for 72 hours postoperatively; and TIVA with continuous TPVB for 72 hours postoperatively. Neither local recurrence nor metastasis or mortality differed statistically with or without regional block compared to general anesthesia.

Buckley, McQuaid, Johnson, and Buggy (2014) conducted a study in which blood samples were examined from patients in the propofol-paravertebral block group and sevoflurane-opioid anesthesia group. Serum samples were then analyzed for NK cells, NK cell activating receptors and cytokine production. Serum from the women who were randomly assigned to the PPA group maintained healthy donor NK anti-tumor cell activity compared to the women from the sevoflurane-opioid anesthetic group.

Discussion

The level of evidence is rather low considering most of the studies are retrospective studies and only one randomized control trial was included. One study noted a reportable difference in favor of regional anesthesia and a lower recurrence rate or metastasis of breast cancer compared to general anesthesia and use of opioids. Other studies reported no statistically significant difference between anesthetic techniques used. Other limitations include selection bias, different statistical analysis, heterogenicity in the type of anesthetic technique, and lack of information regarding tumor size, staging, the presence of mutations, and additional treatments such as chemotherapy or radiation (Perez-Gonzalez et al., 2017). In Starnes-Ott et al. (2015) study it was determined that patients who received paravertebral blocks had more advanced stages of cancer, more invasive treatments, longer surgery times and a lower BMI compared to the general anesthesia alone group. Many of the studies were underpowered and required a larger group of over 1000 participants to detect a difference (Karmakar et al., 2015). Patients who received regional anesthesia reported less severe chronic pain and experienced a better physical and mental state (Karmakar et al., 2015). Patients receiving regional anesthesia required a considerably less amount of opioids and experienced less postoperative nausea, vomiting, and unplanned overnight admissions (Tsigonis et al., 2016).

Findings from the studies completed to date are helpful for planning future studies and including important limitations and requirements. A prospective, randomized clinical trial (RCT) is currently being conducted of patients with breast cancer who are undergoing mastectomies or isolated lumpectomy with axillary node dissection. These patients will be randomly assigned to a thoracic epidural or paravertebral anesthesia/analgesia group or a general anesthesia and morphine group. The trial will follow-up with patients over a ten-year period to determine cancer

recurrence or metastasis (Starnes-Ott et al., 2015). The RCT (NCT00418457) is expected to finish recruiting in 2019 (Perez-Gonzalez et al., 2017).

Conclusion

After reviewing the literature, the data neither supports or refutes the use of regional anesthesia for reduction of cancer recurrence or metastasis. However, it has been shown that regional anesthesia may decrease inflammation by reducing surgical stress and preventing immune suppression. The use of regional anesthesia is associated with better pain control, and patients require fewer opioids in the perioperative and postoperative periods, thereby reducing the risk of nausea and vomiting.

Paravertebral nerve blocks have been shown to cause no harm and have been associated with a very low risk of complications. There is a minor difference between the cost of regional and general anesthetic. Some anesthesia providers may need further training on specific techniques of regional blocks if they do not frequently perform them. Surgeons performing the procedures should also be aware of the anesthetic techniques being used. Patients also need education on their anesthetic options as well as the risks and benefits before making their decision and giving consent.

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Appendix A

Regional Anesthesia and its Effects on Breast Cancer Recurrence and Metastasis

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Introduction

- The use of regional anesthesia with paravertebral nerve blocks in mastectomies for breast cancer treatment has been thought to reduce the recurrence and metastasis of breast cancer by:
  - Reducing surgical stress response
  - Reducing immunosuppression
  - Reducing need for opioid and general anesthetics consumption
- I will discuss:
  - Case Report
  - Thoracic paravertebral nerve block
  - Cancer biology and promotion
  - Pharmacology
  - Review of Literature

Case Information

- Right modified radical mastectomy with axillary sentinel lymph node dissection for treatment of invasive ductal breast cancer
- 64 year-old
- 71 kg
- Female
- ASA 3
- Allergies: Prednisone, environmental factors

Pre-operative Evaluation

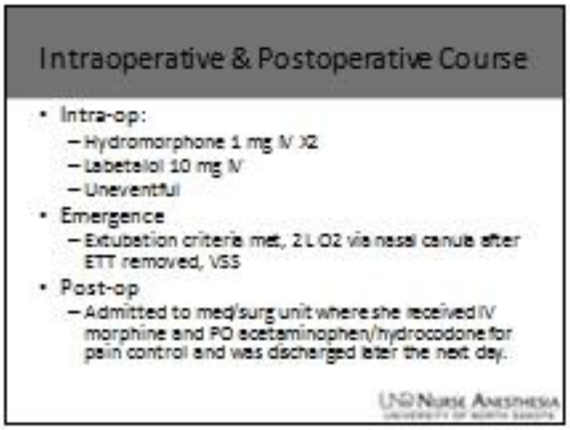
- Past Medical History:
  - Asthma, fibromyalgia, hiatal hernia, hypokalemia, urinary tract infection, hypomagnesemia, invasive ductal carcinoma of the right breast, antineoplastic chemotherapy, chemotherapy-induced diarrhea, neutropenia, drug-induced pancytopenia, sepsis and neutropenic fever
- Surgical History:
  - Sinus surgery, knee arthroscopy, colon polyp biopsy, venous access insertion, hysterectomy, carpal tunnel release and upper endoscopy
- Anesthetic History:
  - No complications

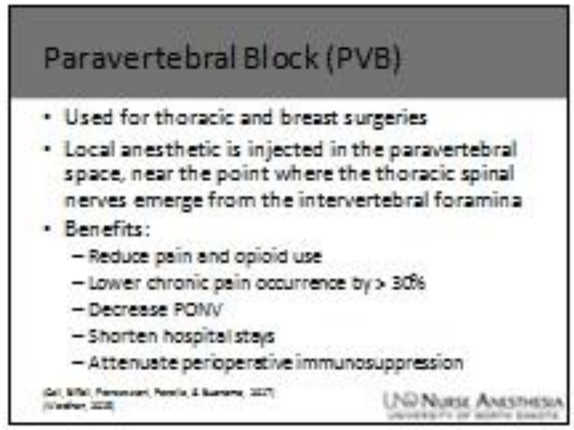
Pre-operative evaluation continued

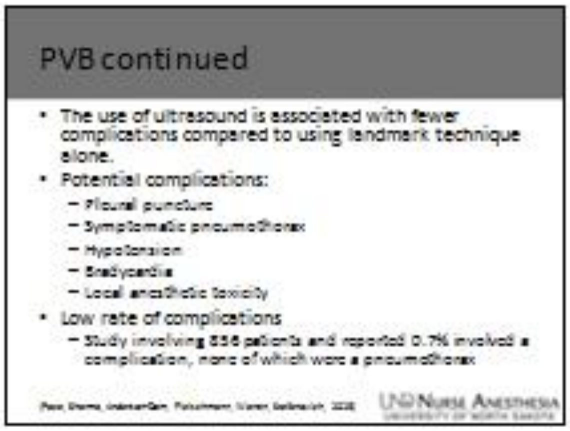
- Pre-op VS:
  - Blood pressure: 139/92 mmHg
  - Heart rate: 98/min
  - Respiratory rate: 18/min
  - Room air oxygen saturation (SpO2): 98%
  - Temperature: 97.7° Fahrenheit
- Mallampati class: 2

Anesthetic Course

- Pre-induction:
  - Midazolam 2 mg IV
- Induction:
  - 2 puffs of albuterol inhaler, oxygen at 8L/min, IV induction with fentanyl 100 mcg, lidocaine 50 mg, propofol 150 mg, rocuronium 30 mg
- Airway:
  - 7.0 ETT, volume control ventilation: rate 12/min, TV 500 ml
- Sevoflurane ½ MAC, propofol infusion 50 mcg/kg/min
- After induction:
  - Fentanyl 50 mcg IV, phenylephrine 100 mcg X2 IV, cefazolin 2 gm IV, dexamethasone 10 mg IV
- Supine position


Intraoperative & Postoperative Course
• Intra-op:
– Hydromorphone 1 mg IV X2
– Labetalol 10 mg IV
– Uneventful
• Emergence
– Extubation criteria met, 2 L O2 via nasal canula after ETT removed, VSS
• Post-op
– Admitted to med/surg unit where she received IV morphine and PO acetaminophen/hydrocodone for pain control and was discharged later the next day.
UND Nurse Anesthesia


Paravertebral Block (PVB)
• Used for thoracic and breast surgeries
• Local anesthetic is injected in the paravertebral space, near the point where the thoracic spinal nerves emerge from the intervertebral foramina
• Benefits:
– Reduce pain and opioid use
– Lower chronic pain occurrence by > 30%
– Decrease PONV
– Shorten hospital stays
– Attenuate perioperative immunosuppression
UND Nurse Anesthesia


PVB continued
• The use of ultrasound is associated with fewer complications compared to using landmark technique alone.
• Potential complications:
– Pleural puncture
– Symptomatic pneumothorax
– Hypotension
– Bradycardia
– Local anesthetic toxicity
• Low rate of complications
– Study involving 856 patients and reported 0.7% involved a complication, none of which were a pneumothorax
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Cancer Biology
• The microenvironment of a tumor is made up of cancer cells, inflammatory cells and mediators
• Inflammatory cells and mediators promote cancer formation and progression
• First step – "initiation" where DNA is damaged
• Second injury – "promotion"
– Triggered by inflammation, injury or irritants
– Increase of inflammatory cells, release of chemical mediators and oxidative damage make it hard for the body to destroy the cancerous cells resulting in cellular proliferation
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Cancer Promotion
• Surgical stress affects the neuroendocrine response, suppresses the immune system, and lowers cell-mediated immunity (CMI) leading to overproduction of stress hormones and increased inflammatory response.
• Pain activates the stress response and suppresses CMI
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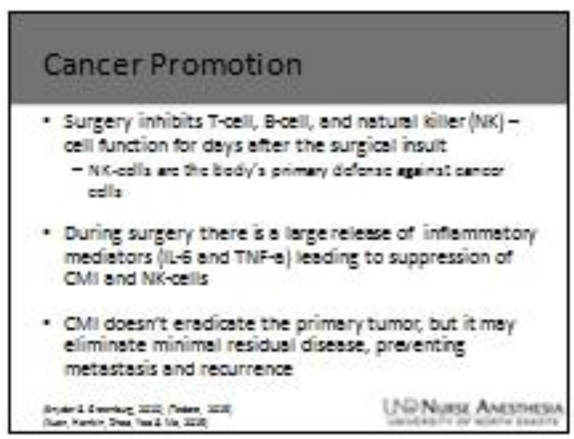
Cancer Promotion
• Surgery inhibits T-cell, B-cell, and natural killer (NK) – cell function for days after the surgical insult
– NK-cells are the body's primary defense against cancer cells
• During surgery there is a large release of inflammatory mediators (IL-6 and TNF-a) leading to suppression of CMI and NK-cells
• CMI doesn't eradicate the primary tumor, but it may eliminate minimal residual disease, preventing metastasis and recurrence
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Pharmacology

- Volatile anesthetics such as inhalational agents and IV anesthetics including ketamine and thiopental
  - Increase destruction of immune cells such as NK-cells and T-lymphocytes, leading to tumor progression

Pharmacology continued

- Propofol
  - Beneficial properties regarding spread of cancer
  - Inhibits enzyme matrix metalloproteinase (MMP)
    - Reduces cancer cell proliferation
  - Reduces inflammatory cytokines
    - Preserves NK-cell activity, inhibiting cancer spread
  - Inhibit cellular adhesion and migration, and has been looked at as a treatment for breast cancer

Pharmacology continued

- Local Anesthetics (LA)
  - At high concentrations, LA are cytotoxic to cancer cells via necrosis or apoptosis
  - Inhibit cancer cell proliferation, migration, and invasion along with anti-inflammatory properties
  - Beneficial in reducing spread and growth of cancer cells

Pharmacology continued

- Opioids
  - Chronic administration promotes angiogenesis and immunosuppression resulting in tumor cell proliferation
  - Fentanyl inhibits NK-cells
  - Other evidence suggests that at higher doses they may have tumor-suppressive effects due to blocking pain and surgical stress response

Research Trial Review

- Exadaktylos et al. conducted an initial retrospective trial in 2006
  - Hypothesized the use of regional anesthesia combined with general anesthesia (GA) would have lower rates of cancer recurrence and metastasis compared to GA with opioid use.
    - Group #1: PVB and GA
    - Group #2: GA and opioid use, postoperative morphine analgesia
  - Metastasis-free survival at 24 and 36 months
    - Group #1: 94%, 94%
    - Group #2: 82%, 77%
  - Results prompted further research

Research Trial Review continued

- Retrospective Trials
  - Starnes-Ott, Goravanchi, and Meininger (2015)
  - Tsigonis et al. (2016)
  - Cata et al. (2016)
    - All studies compared regional anesthesia and use of PVB combined with GA to GA alone and post-operative opioid use, and its effects on breast cancer recurrence and/or metastasis
    - All studies showed no difference between the 2 groups
    - All studies showed those who received PVB had better pain control and less opioid use

Research Trial Review continued

- Chen et al. (2015)
  - Used propofol-paravertebral anesthesia (PPA)
  - Hypothesized beneficial use of PPA to have lower chronic postsurgical pain, avoiding opioids and inhibiting surgical stress suppression of cellular immunity
  - PPA elevates NK-cells and T-cells to increase NK toxicity and augment cancer cell apoptosis
  - Propofol reduces expression of MMP
  - Results showed no difference between the 2 groups

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Research Trial Review continued

- Karmakar et al. (2017) RCT
  - 3 anesthetic groups:
    - GA with total intravenous anesthesia (TIVA)
    - TIVA with a single injection TPVB and placebo infusion for 72 hours
    - TIVA with continuous TPVB for 72 hours
  - Showed no statistical difference

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Research Trial Review continued

- Buckley, McQuaid, Johnson, and Buggy (2014)
  - Compared blood samples from PPA to sevoflurane and opioid anesthesia group.
  - Serum samples were analyzed for NK-cells, NK activating receptors and cytokine production
  - PPA group maintained healthy donor NK anti-tumor cell activity
  - GA group showed a reduced expression of NK-cells

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Recommendations

- The literature does not support or refute the use of regional anesthesia for reduction of breast cancer recurrence or metastasis.
  - Low level of evidence, most studies are retrospective.
  - Many limitations within current research including: selection bias, different statistical analysis, heterogenicity in type of anesthetic technique, lack of information regarding tumor size, staging, presence of mutations, and additional treatments such as chemotherapy or radiation.

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Recommendations continued

- Benefits of PVB
  - Less severe chronic pain
  - Require less opioids
  - Experience less PONV
  - Fewer unplanned overnight admissions
  - Experience better physical and mental state

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Recommendations continued

- Further research required
  - Currently enrolling patients in a large, prospective randomized clinical trial
  - Patients assigned to a thoracic epidural or PVB group or a GA and morphine group.
  - Follow-up conducted over a 10 year period

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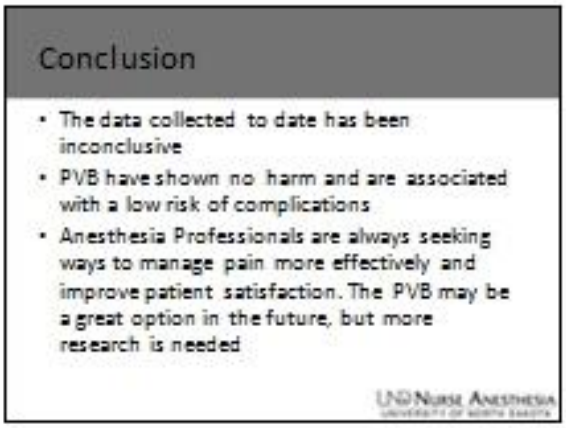
Conclusion
• The data collected to date has been inconclusive
• PVB have shown no harm and are associated with a low risk of complications
• Anesthesia Professionals are always seeking ways to manage pain more effectively and improve patient satisfaction. The PVB may be a great option in the future, but more research is needed
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References
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Thank You
Are There Any Questions?
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