BREAST CANCER RECURRENCE IN PATIENTS RECEIVING
EPIDURAL AND PARA VERTEBRAL ANESTHESIA:
A RETROSPECTIVE, CASE-CONTROL STUDY

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Abstract

Purpose: Studies have suggested an association between the use of regional paravertebral 
or epidural anesthesia and a reduction in tumor recurrence following breast cancer surgery. To 
examine this relationship we performed a retrospective case-control study of patients undergoing 
breast cancer surgery receiving regional, regional and general, or general anesthesia.

Methods: A retrospective chart review was performed of patients undergoing surgery for 
stage 0 to III breast cancer. Patients identified as receiving regional anesthesia were then matched 
for age, stage, estrogen receptor (ER) status, progesterone receptor status, and HER-2 expression 
with patients who received no regional anesthesia. Univariate (Pearson’s χ² test and odds ratio) 
and multivariate logistic analyses with backward stepwise regression were performed to determine 
factors associated with cancer recurrence.

Results: Between 1998 and 2007, 816 women underwent surgery for stage 0-III breast 
cancer at our institution. Forty-five patients developed tumors. Univariate analysis showed the 
use of regional anesthesia trended towards reduced cancer recurrence, but it did not achieve 
statistical significance (p=0.06). Higher recurrence rates were associated with ER positive status 
(p=0.003) and higher tumor stage (p <0.0001). Age and HER-2 status were not associated with 
increased cancer recurrence (both p>0.11). Multivariate analysis confirmed ER status and stage as 
independently influential (p = 0.002 and p<0.0001 respectively).

Conclusion: Although we found a trend towards reduced breast cancer recurrence with the 
use of regional anesthesia, univariate analysis did not reach statistical significance.

Key words: Epidural anesthesia; Paravertebral Block; Regional Anesthesia; Recurrence.

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Introduction

Breast cancer is the most common cancer in women in the United States with an overall incidence of 118.7 per 100,000 females in the year 20101. Surgery remains the primary and most definitive treatment for breast cancer. Despite optimal surgical technique, tumor recurrence occurs in 10 to 20 percent of patients. The mechanism by which recurrence following surgery occurs is multifactorial and likely includes release of tumor cells into the bloodstream during surgery from tumor manipulation, increase of systemic and local growth factors during surgery, and perioperative immunomodulation2,3. Recent studies suggest that paravertebral and epidural anesthesia may reduce breast cancer recurrence following surgery by decreasing surgical stress, minimizing the use of opioids, and avoiding certain inhalational agents4. In order to explore the relationship between regional anesthesia and tumor recurrence we performed a retrospective case-control analysis comparing oncologic outcomes in patients receiving regional, regional and general, and general anesthesia for breast cancer surgery.

Methods

Between 1998 and 2007, 858 patients underwent surgical intervention for breast cancer at our institution. A retrospective chart review was conducted of these patients. Study exclusion criteria were male gender, stage IV disease at presentation, and use of local anesthesia alone. Eight hundred and sixteen (816/858) women underwent surgery for stage 0-III breast cancer. Of these, 213/816 (26.1%) patients received regional anesthesia with or without general anesthesia. Patients receiving any regional anesthesia were then matched at a ratio of 1:2 for age (less than 40, 41-50, 51-70, and 71 and older), cancer TNM stage, estrogen receptor (ER) status, progesterone receptor (PR) status, and HER-2 expression with those patients receiving no regional anesthesia. Twenty regional anesthesia patients could only be matched with one control. A total of 619 patients were, therefore, available for analysis. Univariate (Pearson’s χ² test and odds ratio) and multivariate logistic regression analyses with backward stepwise were performed using SAS (version 9.2, Cary, North Carolina) to determine factors associated with cancer recurrence. Age, cancer stage, ER, PR, HER-2, and anesthesia type were all evaluated. End points for the study were first local, regional, or distant metastatic recurrence.

Results

A total of 619 patients were included in the study. Two hundred and thirteen patients (213/619; 34.4%) received regional anesthesia and were matched with 406/619 (65.6%) controls who received only general anesthesia. Median age was 64.7 (range 25-95 years), and tumor size was 1.5 cm (range 0.1-10 cm). Five hundred (500/619; 80.8%) were ER+ tumors, and 50/619 (8.1%) were HER-2 positive tumors. The majority of patients were Caucasian (569/619). Thirty-seven were African American; the remainders were reported as Hispanic, Native American, or other. Mean follow-up was nine years (range 5-13 years). Two hundred and eighty-eight patients had breast conserving surgery. Three hundred and thirty-one had total mastectomy. Diagnoses included ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), invasive ductal carcinoma, tubular carcinoma, invasive lobular carcinoma, mucinous carcinoma, and other. The majority of cancers were located in the upper outer quadrant (208/619; 33.6%). All patients who underwent breast conservation surgery also received adjuvant radiation therapy. A total of six surgeons performed the operations.

Two hundred and thirteen (34.4%) patients received paravertebral or epidural anesthesia. Of those, 123 (57.7%) received solely regional anesthesia (Figure 1). Overall, 45/619 (7.3%) patients developed local, regional, or distant metastases at a mean follow-up of nine years (range 5-13 years). Recurrence occurred in seven patients who had regional anesthesia (5.7%), three patients who received regional and general anesthesia (3.3%), and 35 general anesthesia patients (8.6%). Univariate analysis (Pearson χ² and simple logistic regression) revealed statistically significant greater recurrence rates in patients who were ER positive and higher TNM stage. PR status, HER-2 status, and age were not found to be statistically significant.
Having a form of regional anesthesia, with or without general anesthesia trended toward lower recurrence rates, but did not reach statistical significance. When the anesthesia type was further divided into regional, regional plus general, and general, there was no significant difference in recurrence rate. See Table 1 for details. Multivariate analysis confirmed ER status and cancer stage as independently influential ($p = 0.002$ and $p < 0.0001$, respectively).

**Discussion**

The role that anesthesia plays in the recurrence of disease following cancer surgery is complex and poorly defined. There are conflicting data at this point as to whether anesthetic technique can influence serological markers of cancer recurrence or the recurrence of clinically relevant metastatic disease\(^{5-11}\).

The results of this retrospective chart review indicate that while there is a trend towards lower chance of metastatic recurrence in breast cancer patients that receive regional anesthesia, it is not a statistically significant benefit. Only estrogen receptor status and cancer stage were independently influential factors on whether or not a recurrence was likely. However, a previously published report on this subject found that metastatic recurrence was significantly reduced in patients receiving regional anesthesia\(^{10}\). Our results are disappointing, as we had hoped to find a definitive benefit. Other previous in vitro data on this subject are mixed in that some cytokines associated with breast cancer are attenuated while others are not\(^{7-9}\).

The benefits of regional anesthesia for breast cancer surgery have been shown to include decreased nausea and vomiting, lower pain scores, and decrease length of stay\(^{12}\). The fact that our data had a trend towards lower recurrence in the regional anesthesia group is
encouraging, but not compelling. Although our data lack statistical significance, complications of regional anesthesia are rare, and because of the aforementioned benefits to using this technique, we advocate regional anesthesia for breast cancer surgery when possible. Whether or not a definitive benefit can be gained through the use of regional anesthesia is a question yet to be answered. The oncology literature has suggested that perhaps utilizing specific chemotherapeutic medications can mimic any benefit gained through anesthetic technique\textsuperscript{13}. Whether or not that would make anesthetic technique irrelevant in regards to breast cancer recurrence is unknown at this time. There is one prospective trial in the literature that addressed the use of epidural anesthesia and cancer recurrence in major abdominal surgery\textsuperscript{14}. Unfortunately this trial failed to demonstrate any difference in cancer free survival. A large randomized multicenter trial comparing regional and standard anesthetic techniques is currently being performed and the results of that study may help answer the question of whether or not anesthetic technique can influence recurrence in breast cancer\textsuperscript{15}. 
References


The key to

Lock-up

Postoperative Pain

Initial bolus
Inject 1 ampoule Tramal® 100 mg I.V. or I.M. slowly over 2-3 minutes

Ways of administration after initial bolus

Infusion
Inject 3 ampoules Tramal®, each 100 mg, in 500 ml of infusion solution. Infusion rate 10-24 mg Tramal®/h (10-20 drops/min or 30-60 ml/h).

Subsequent increments of 25 mg with a lock-out time of 5 minutes.

If needed further doses of Tramal® 50 mg up to a total of 200 mg (excluding the initial bolus) within the first 60 min.

PCA
Usual dose 50 mg or 100 mg 44 hourly up to a total daily dose of 400 mg except in special clinical circumstances which might necessitate daily doses up to 800 mg. Further treatment with Tramal® bolus on demand.

Injection

STEP I

STEP II

Follow-up

Intra-Operative

Intra-operative loading dose of Tramal® will reduce PONV rates

2.5 - 3 mg/kg at wound closure

Loading Dose

2.5 - 3 mg/kg at wound closure

If intra-operative dose not given then:
BOLUS I.V.*
100 mg over 2-3 mins**

STEP III

Post-Anaesthesia Care Unit

1 tablet every 12 h

1 suppository every 4-6 h

20-40 drops every 4-6 h

1-2 capsules every 4-6 h

50 mg

50 mg

100 mg

150 mg, 200 mg

1 tablet

100 mg

100 mg, 150 mg, 200 mg

* if needed further doses of 50 mg up to a total of 200 mg (incl. the initial bolus) may be given within the first 60 min.

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For patients with localized BURNING, SHOOTING, STABBING, Neuropathic pain

versatis
5% lidocaine medicated plaster

WORKS WHERE IT HURTS

GRUNENTHAL
BRIDION—

for **optimal neuromuscular blockade management** and improved recovery

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### Predictable and complete reversal

- **98%** of BRIDION patients recovered to a TOF ratio of 0.9 from reappearance of T₂ within 5 minutes
- **97%** of BRIDION patients recovered to a TOF ratio of 0.9 from 1 to 2 PTCs within 5 minutes

### Rapid reversal

- BRIDION rapidly reversed patients from reappearance of T₂ in 1.4 minutes
- BRIDION rapidly reversed patients from 1 to 2 PTCs in 2.7 minutes

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BRIDION is indicated for the reversal of neuromuscular blockade induced by rocuronium or vecuronium. In children and adolescents (aged 2-17 years), BRIDION is only recommended for routine reversal of moderate rocuronium-induced neuromuscular blockade.

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**Important safety information**

BRIDION is not recommended in patients with severe renal impairment. Studies in patients with hepatic impairment have not been conducted and, therefore, patients with severe hepatic impairment should be treated with great caution. Care should be exercised when administering BRIDION to pregnant women as no clinical data on exposed pregnancies are available.

BRIDION has not been investigated in patients receiving ketorolac or vecuronium in the intensive care unit (ICU) setting. If neuromuscular blockade is required within 24 hours of BRIDION administration, a nonsteroidal anti-inflammatory drug should be used instead of ketorolac or vecuronium. The most commonly reported adverse reactions were dyspnea (mild or moderate) and anaphylactic complications (e.g., bruising, pruritus, or swelling on the endotracheal tube). In patients treated with BRIDION, a few cases of awareness were reported. These reactions are similar to those in other individuals allergic to narcotics (e.g., fentanyl, propofol). Following BRIDION administration, patients should be observed for the possibility of allergic reactions and allergic-like reactions (e.g., flushing, respiratory distress). In a few studies, severe allergic reactions (e.g., laryngeal edema) were reported following BRIDION administration. These reactions were reported in 2 patients and a causal relationship could not be fully excluded.

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BRIDION patients have demonstrated a slight (12-32%) and transient (<30 minutes) prolongation of the proximal isometric twitch of the adductor pollicis (TP1) and TP2 with BRIDION, however, clinical studies have demonstrated no clinically relevant effect on post-operative hemodynamic complications. An ARDB has been observed in vitro with pharmacodynamic interaction with anticholinesterases in vitro. Precautions should be observed in patients on anticholinesterase (e.g., pyridostigmine) or muscle relaxant medications. This pharmacodynamic interaction is not clinically relevant for patients recovering from propofol and brachial plexus blockade. Although formal interaction studies have not been conducted, no drug interactions were observed in clinical trials. Preclinical data suggest that clinically significant drug interactions are likely with the possible exceptions of cimetidine, furosemide, and hormonal contraceptives.

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**REF: BRIDION Summary of Product Characteristics (SPC)**

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**REFERENCES**

1. BRIDION Summary of Product Characteristics (SPC)

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Please see summary of product characteristics for full prescribing information.
Pioneering Medical Technology

TAP Block And InfiltraLong
For Effective Treatment Of Long And Deep Incisions

Sono Cannulas
For Single Shot UltraSound Guided Nerve Blocks

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For UltraSound Guided Nerve Blocks

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The New Generation Dura Puncture In Minimum Time

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