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Post-mastectomy cancer recurrence with and without a continuous paravertebral block in the immediate postoperative period: a prospective multi-year follow-up pilot study of a randomized, triple-masked, placebo-controlled investigation

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Abstract

Purpose Retrospective studies have associated perioperative regional anesthesia/analgesia during mastectomy for breast cancer with a decreased incidence of cancer recurrence. However, to date, no prospective data from a randomized controlled trial have been reported. In a previous study we found that extending a single-injection paravertebral block with a multiple-day perineural local anesthetic infusion improves analgesia. This follow-up study investigates the rates of cancer recurrence for the single-injection and multiple-day infusion treatments.

Methods Patients undergoing unilateral ($n = 24$) or bilateral mastectomy ($n = 36$) were included in the study. All patients had been diagnosed with breast cancer or tumor in situ, except for six patients who were receiving prophylactic bilateral mastectomy and were excluded from analyses. Patients received unilateral or bilateral single-injection

thoracic paravertebral block(s) corresponding to their surgical site(s) with ropivacaine and perineural catheter(s). Subsequently, patients were randomized to receive either ropivacaine 0.4% ($n = 30$) or normal saline ($n = 30$) via their catheter(s) until catheter removal on postoperative day 3. Cancer recurrence from the date of surgery until at least 2 years post surgery was investigated via chart review.

Results Five of the 54 (9.2%) patients experienced a cancer recurrence following mastectomy—3 of 26 (11.5%) of the patients with perineural ropivacaine and 2 of 28 (7.1%) of the patients with perineural saline.

Conclusions This pilot study found no evidence that extending a single-injection paravertebral block with a multi-day perineural local anesthetic infusion decreases the risk of post-mastectomy cancer recurrence. However, due to the small sample size of this investigation, further research is needed to draw definitive conclusions.

Keywords Continuous paravertebral block · Mastectomy · Cancer recurrence

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Introduction

Over 3 million women are currently living with a history of breast cancer in the United States alone [1], and approximately 30% diagnosed with localized cancer will eventually develop recurrent advanced or metastatic disease [2]. There is now greater recognition that early micrometastases are common and that, even in skilled hands, mastectomy to remove the primary lesion may disperse malignant cells [3]. While surgical removal of a tumor can reduce a patient's cancer burden significantly, 'minimal residual disease' is often present and the body's own immune system remains a critical line of defense [3].

Regional anesthetic techniques such as peripheral nerve blocks that provide intraoperative anesthesia and postoperative analgesia may mitigate surgical insults to immune defenses. Multiple investigators have theorized that regional anesthesia and analgesia may help preserve host defenses in patients undergoing tumor resection via three mechanisms—attenuating the surgical stress response, decreasing dosages of general anesthetics, and reducing requirements for opioid medications [3, 4]. In particular, surgical stress promotes tumor angiogenesis, inhaled anesthetics impair cell-mediated immunity, and opioid analgesics likely cause both deleterious effects [3, 5, 6]. Retrospective studies have associated the use of perioperative regional anesthesia/analgesia with a decreased incidence of cancer recurrence [7–10]. This has led multiple investigators to hypothesize that providing potent perioperative anesthesia and analgesia may decrease cancer recurrence [3, 4, 7, 11]. However, to date, no prospective data from a randomized controlled trial have been reported [12].

In a previously published, randomized, triple-masked, placebo-controlled study we demonstrated that extending a single-injection paravertebral block with a multiple-day perineural local anesthetic infusion improves analgesia and decreases pain-related dysfunction during the 3-day infusion as well as at 1 year following surgery [13, 14]. We now report the results of a prospectively designed follow-up pilot study of these patients to investigate the cancer recurrence rates of the two different perioperative treatments. To our knowledge, this pilot study is the first prospective, randomized, masked, placebo-controlled study involving continuous peripheral nerve blocks to provide such data.

Methods

Enrollment

The trial was prospectively registered at clinicaltrials.gov (NCT01231204). The protocol was in accordance with the precepts established by the World Medical Association's Helsinki Declaration of 1964 and subsequent amendments [15]. The local Institutional Review Board (University California San Diego, San Diego, CA, USA) approved all study procedures, and all patients provided written informed consent. Details of the original study perioperative intervention have been published previously [13]. In brief, patients offered enrollment included 60 women aged ≥ 18 years undergoing unilateral or bilateral mastectomy with or without axillary lymph node dissection, and desiring a single-injection paravertebral block(s) for postoperative analgesia.

Preoperatively, all patients received an ipsilateral paravertebral perineural catheter inserted with ultrasound guidance between the third and fourth thoracic

vertebrae (StimuCath Plus; Teleflex Medical, Research Triangle Park, NC, USA), followed by a single injection of long-acting local anesthetic (15 mL of ropivacaine 0.5% with epinephrine 5 $\mu\text{g}/\text{mL}$). Catheter placement was considered successful if, within 30 min, the patient experienced any decreased sensation to cold temperature with an alcohol pad over the approximate level of the ipsilateral third thoracic dermatome. Misplaced catheters were replaced successfully, or the patient excluded from further study participation. For patients undergoing bilateral mastectomy, a catheter using the same protocol was subsequently inserted in the contralateral side. Intraoperatively, patients received a general anesthetic with induction using intravenous propofol and maintenance using inhaled volatile anesthetic combined with nitrous oxide. Intravenous opioid (fentanyl, hydromorphone, or morphine) was titrated to heart rate and blood pressure increases, as needed. All patients underwent immediate reconstruction following mastectomy and had two drains inserted per mastectomy.

Study intervention

Prior to leaving the operating room, a perineural infusion was initiated using an elastomeric portable infusion pump with a fixed basal rate of 5 mL/h and 300 mL reservoir (LV5 Infusor; Baxter Healthcare International, Deerfield, IL, USA). Patients were randomized to one of two treatment groups—placebo (normal saline) or ropivacaine (0.4%). Patients having bilateral mastectomies received two separate infusion pumps, each affixed to a separate catheter, and always containing the identical solution. Patients, investigators, observers, statisticians, and all clinical staff were masked to treatment group assignment through data analysis of the first study involving the first 4 postoperative weeks.

For postoperative analgesia, all subjects received the single-injection ropivacaine paravertebral block (initiated via the catheter), as well as oral acetaminophen (975 mg four times daily). Administration of rescue analgesics for breakthrough pain was determined by pain severity using the numeric rating scale (NRS)—oxycodone 5 mg (NRS <4) or 10 mg (NRS ≥ 4). While hospitalized, pain was reassessed 30 min later and intravenous morphine (2–4 mg) was repeated every 30 min until the NRS was <4 .

Patients remained hospitalized for at least one night, and were subsequently discharged home with their perineural catheter(s) in situ that were removed on postoperative day (POD) 3. Patients were contacted by telephone at 1, 4, 8, and 28 days and at 3 and 12 months following surgery and administered the Brief Pain Inventory and other phantom pain- and sleep-related questions.

Cancer recurrence pilot study

Six patients without a history of breast cancer who received prophylactic bilateral mastectomies were excluded from analyses for cancer recurrence. A minimum of two years following surgery, the remaining patients were assessed for cancer recurrences via a chart review of medical and surgical oncology records/notes, pathology reports and positron emission tomography scans. The dates of local or systemic recurrences were recorded, as well the updated staging at that time. Also noted was patient morbidity/mortality, as well as information regarding chemotherapy, radiation, or endocrine/hormonal therapy as adjuvant or neoadjuvant treatment.

Statistical analyses

Chi-squared tests were carried out to examine potential differences in the distribution of the stages of breast cancer at the time of surgery and the likelihood of recurrence between randomized groups. In addition, a Kaplan–Meier plot was constructed to graphically compare the time to recurrence for the ropivacaine and placebo groups. Further statistical analyses were not able to be performed as the risk of Type 1 or Type 2 error was thought to be too high due to the small sample size. Our intention is for others to combine our results into future meta-analyses in order to explore similar questions with a higher degree of power.

Results

From December 2010 through to November 2012, 60 patients had unilateral ($n = 24$) or bilateral ($n = 36$) catheter(s) inserted successfully per protocol.

Acute pain phase

Results for the acute phase of the postoperative period have been published previously [13]. In brief, average pain queried on POD 1 for patients receiving perineural ropivacaine ($n = 30$) was a median (interquartile range) of 2 (0–3) compared with 4 (1–5) for patients receiving saline ($n = 30$; $P = 0.021$). As a result, on POD 1 during the infusion, patients receiving perineural ropivacaine experienced less pain-induced physical and emotional dysfunction, as measured with the Brief Pain Inventory (lower score = less dysfunction)—14 (4–37) vs 57 (8–67) for patients receiving perineural saline ($P = 0.012$). In contrast, following infusion discontinuation there were no statistically significant differences detected between treatment groups on POD 4, 8, and 28.

Patients who were randomized to the ropivacaine group required less morphine in the recovery room compared with those in the placebo group (1.0 vs 2.4 mg morphine equivalents, $P = 0.013$). However, by POD 1 they were using statistically equivalent amounts of morphine (1.5 vs 3.3 mg morphine equivalents, $P = 0.402$).

Chronic pain phase

Results for the chronic pain phase of the postoperative period have been published previously [14]. In brief, there was no statistically significant difference between treatments at 3 months following surgery—the Brief Pain Inventory total for patients receiving ropivacaine was a mean (SD) of 14.1 (28.6) versus 6.2 (11.7) for patients receiving saline ($P = 0.624$). However, nine months later, i.e., 12 months following surgery, the Brief Pain Inventory total for patients who had received ropivacaine had decreased to 1.6 (4.6). In contrast, during this same time period, the total for patients receiving saline changed minimally at 5.9 (11.3) [intergroup comparison, $P = 0.007$]. In addition, by month 12, only 1 patient (3%) in the ropivacaine group experienced any phantom breast pain (described as occurring a single time in the previous 9 months) compared with 9 (30%) in the placebo group ($P = 0.006$).

Cancer recurrence results

Six patients (4 in the ropivacaine group and 2 in the placebo group) without a history of breast cancer but who received prophylactic bilateral mastectomies were excluded from analyses for cancer recurrence. Five of the 54 (9.3%) remaining patients experienced a cancer recurrence following mastectomy—3 of 26 (11.5%) of the patients with perineural ropivacaine and 2 of 28 (7.1%) of the patients with perineural saline (Table 1). In addition, chi-squared tests showed no significant difference in the distribution of the stages or likelihood of recurrence between groups (Table 2). Figure 1 shows a Kaplan–Meier plot graphically comparing the time to recurrence for the ropivacaine and placebo groups.

Four (7.4%) patients died within the follow-up period, all of whom had received ropivacaine; chi-squared analyses showed this was a statistically significant difference at $P = 0.038$. Three patients died due to metastatic disease—the first died 6 years after the original breast cancer diagnosis and 3 years after mastectomy, the second died 1 year after diagnosis and 9 months after mastectomy, and the third died 2 and a half years after diagnosis and 2 years after mastectomy. The final patient died due to heart failure (18 months after diagnosis, 1 year after mastectomy).

Table 1 Population data

Perineural infusion	Ropivacaine (<i>n</i> = 26)	Placebo (<i>n</i> = 28)
Age (years)	48 (41–56)	50 (41–58)
Height (cm)	165 (161–170)	165 (162–170)
Weight (kg)	61 (56–73)	61 (54–69)
Body mass index (kg/m ²)	23 (20–26)	23 (20–25)
Tumor in situ* (per pathology report)	6 (23.1%)	9 (32.1%)
Unilateral mastectomy		
With lymph node dissection	8	10
Without lymph node dissection	3	3
Bilateral mastectomy		
With lymph node dissection	14	12
Without lymph node dissection	1	3
Recurrence since mastectomy	3 (11.5%)	2 (7.1%)
Death	4 (15.4%)	0 (0%)

Values are reported as median (interquartile) or number of patients (percentage of group), as indicated

* Tumor in situ is a pre-cancerous or non-invasive cancerous lesion that has a 1–2% chance of recurrence when treated with mastectomy [21]

Table 2 Distribution of the stages in both groups and analysis of differences in recurrence between groups

	Placebo	Ropivacaine	<i>p</i> value
Stage	<i>n</i> = 28	<i>n</i> = 26	0.098
0	9 (32.1%)	8 (30.8%)	
1	1 (3.6%)	6 (21.4%)	
2	11 (39.3%)	4 (15.4%)	
3	7 (25.0%)	7 (26.9%)	
4	0 (0%)	1 (3.8%)	
Recurrences	2	3	0.92
Stage 0	0/9	1/8	
Stage 1	0/1	0/6	
Stage 2	1/11	0/4	
Stage 3	1/7	1/7	
Stage 4	0/0	1/1	

Discussion

This prospective follow-up pilot study of a randomized, triple-masked, placebo-controlled clinical trial found no evidence that adding a multiple-day continuous ropivacaine infusion to a single-injection paravertebral block in the immediate postoperative period decreases the risk

of post-mastectomy cancer recurrence. Due to the small sample size of this pilot study these results should be interpreted as preliminary in nature; however, they are notable because, to our knowledge, this is the first randomized controlled study to investigate the relationship between perioperative analgesia (in this case continuous paravertebral blocks) and breast cancer recurrence. As noted previously, breast cancer in particular is an excellent target for investigation into the relationship between regional anesthesia and cancer recurrence as it has an ‘intermediate prognosis and reasonably rapid growth’, yet is not frequently disseminated at the time of initial diagnosis [3].

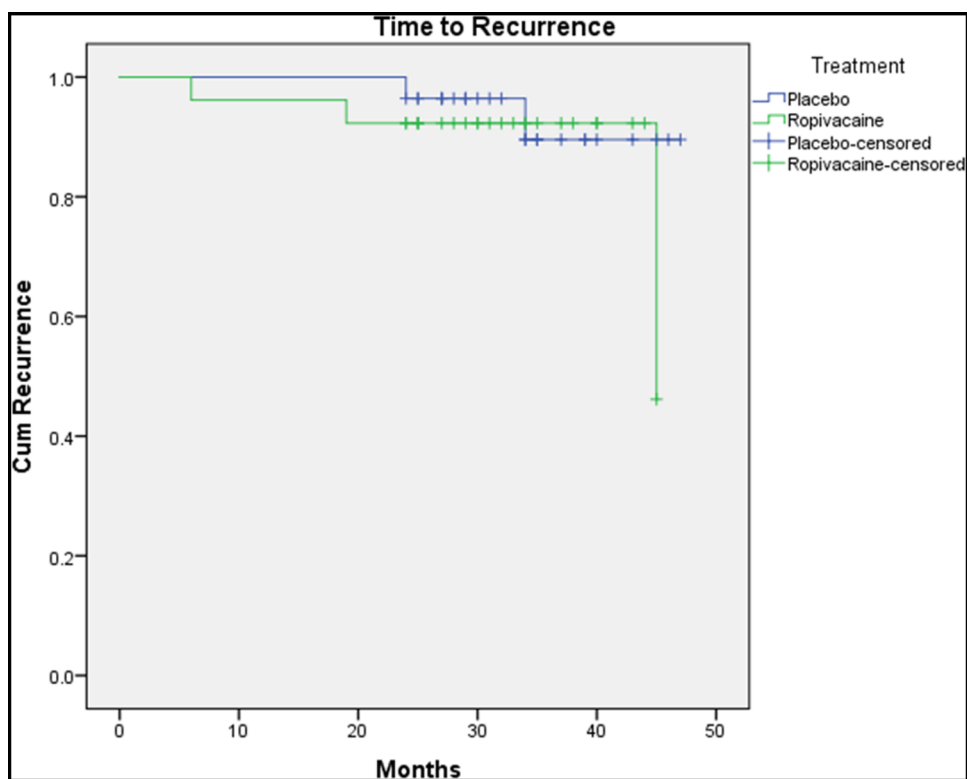
Previous retrospective investigations of anesthetic/analgesia use and cancer recurrence have yielded promising results. One study found that thoracic paravertebral blocks reduced cancer recurrence in patients who underwent mastectomy [7]. However, in addition to its retrospective design, patients in the group who did not receive a nerve block had relatively larger tumors, smaller margins, and higher chemotherapy rates (although these differences did not reach statistical significance). Subsequently, a retrospective study of open prostatectomy under general anesthesia with or without an epidural reported that patients with an epidural had a significantly lower rate of cancer recurrence [8]. Two retrospective investigations of colorectal cancer showed similar positive findings [9, 10]. However, multiple subsequent retrospective studies failed to identify an association between perioperative use of regional anesthesia/analgesia and cancer recurrence [16–18], leading some to question the strength of evidence for a protective effect [12].

It is noteworthy that of the four patients of our study who died, all had received perineural ropivacaine. Three expired from metastatic breast cancer and one from heart failure. There is no suggestion within the literature that perineural ropivacaine infusion for 60 h might increase the risk of death 9–36 months subsequently, and we presume this difference between treatments is due solely to the limited number of patients in our study combined with normal statistical variability.

Limitations

Due to the small sample size of study patients, our hope is that these results can be collated with others into a meta-analysis of similar studies in the future. While the relatively small sample size of our study is the largest limitation of this investigation, other factors should be considered as well. Patients were followed for a minimum of two years, which is less than the 5–10 years that major studies investigating cancer recurrence rates have tracked their patient populations [19]. In addition, previous retrospective studies

Fig. 1 A Kaplan–Meier plot graphically compares the time to recurrence for the ropivacaine and placebo groups



identifying a difference in cancer recurrence rates with the use of continuous peripheral nerve blocks utilized control groups that received no regional anesthesia. In contrast, in our study all patients received a single-injection paravertebral block with ropivacaine that usually provides 8–16 h of anesthesia/analgesia (before being randomized to receive a perineural infusion of either ropivacaine or saline). This may have decreased the differences between treatment groups by decreasing surgical stress and early opioid requirements in both treatment groups. Studies comparing no regional anesthetic/analgesic to a single-injection or continuous paravertebral block might have different results.

In conclusion, this multi-year follow-up of a randomized, triple-masked, placebo-controlled study found no evidence that a perineural paravertebral ropivacaine infusion added to a single-injection ropivacaine block results in a decreased rate of cancer recurrence following mastectomy. However, due to the small number of patients in this pilot study, our results should be viewed exclusively as exploratory in nature. Investigations with a larger sample size are greatly needed in this area of research [20].

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