Abstract. Aim: Retrospective and basic science data suggest that perioperative regional anaesthesia (PRA) may reduce tumour recurrence after cancer surgery. This retrospective archive study tested the anti-metastatic effect of PRA. Patients and Methods: We screened the database of the Helsinki University Hospital for patients with breast cancer who had either perioperative paravertebral block (PVB) or sham block (SHAM) in 2000-2003. The exclusion criteria were previous cancer, no cancer, and loss to follow-up. The end-points were disease-free (DFS), distant recurrence-free (DRFS), breast cancer-specific (BCSS) and overall (OS) survival. Results: The median follow-up time of the 45 PVB and 41 SHAM patients analysed was 12 years. DFS was 79% and 83%, DRFS 84% and 92%, BCSS 81% and 95%, OS 74% and 93% in the PVB and SHAM groups, respectively (p-value for OS = 0.035). Conclusion: The results do not demonstrate any anti-metastatic effect of PRA.

Retrospective data in breast cancer and prostate cancer suggest that perioperative regional anaesthesia (PRA) may reduce recurrence (1). Basic science suggests that amide local anaesthetics may have dose-dependent antimetastatic property (2, 3). However, such an antimetastatic property has not been confirmed in any randomized controlled trial (4, 5).

We planned a retrospective archive study to assess the survival of patients who had participated in our pain prevention trials comparing preincisional paravertebral block (PVB) and a sham block (SHAM) during breast cancer surgery in 2000-2003 (6, 7). The current relative survival for patients with breast cancer considering all stages combined is 89%, 83% and 78% at 5, 10 and 15 years, respectively (8). The current 5-year relative survival is 99% for patients with stage 1, 88% for those with stage 2 and 55% for those with stage 3 breast cancer (9).

Patients and Methods

Ethical approval. This study was approved by the Institutional Review Board, approval numbers 94/13042012, 155/04102012 and 45/13.11.2012. Ethics Committee evaluation or clinical trial registration was not considered necessary as this was a retrospective archive study and no identifying data were disclosed.

Hypothesis. Our hypothesis was that PVB improves survival and reduces breast cancer events. The influence of tumour stage was assessed for comparison.

Patients. Patients with breast cancer who had had either thoracic PVB using 1.5 mg/kg bupivacaine or a sham block using saline during breast cancer surgery performed under general anaesthesia between October 2000 and April 2003 were screened for eligibility. Exclusion criteria were prior cancer, prior cancer therapy, preoperative cancer therapy, no breast cancer and loss to follow-up. The patients had been scheduled for breast-conserving surgery or mastectomy with sentinel lymph node biopsy (SNB), axillary lymph node dissection (ALND) or both. The PVB or SHAM intervention had been performed only once. General anaesthesia had been induced with propofol, fentanyl and rocuronium and maintained with sevoflurane in oxygen/air and fentanyl boluses. Oral ibuprofen and intramuscular oxycodone had been offered for postoperative analgesia. Scheduled venous blood samples had been drawn from all study patients and total venous bupivacaine concentrations had been measured. Patients were treated with adjuvant therapies according to national and international guidelines. The relevant data were collected from archives and databases of Helsinki University Hospital and the Hospital District of Helsinki and Uusimaa from October 2000 to December 2013. Bupivacaine concentrations were extrapolated from results of the initial trial using an elimination half-life of 2.6 h (160 min) for bupivacaine (10). The endpoints were disease-free survival (DFS), distant recurrence-free...
survival (DRFS), breast cancer-specific survival (BCSS) and overall survival (OS) (11). Secondary end-points were the number of first breast cancer events and the mean total concentrations of bupivacaine in venous plasma at the beginning and end of surgery.

Statistical analysis. Frequency tables were analysed using Chi-Square test, presenting results as number of cases. Mann-Whitney U-test was used for analysing time distributions, presenting results as the median (range). Student’s t-test was used for analysing age, diameter and concentrations, presenting results as mean±SD. All p-values are two-sided and a value of 0.05 was considered statistically significant. Kaplan–Meier method (12) was used for constructing life tables and log-rank test for comparing survival between groups. Survival was calculated as the time from the date of surgery to the date of first recurrence of cancer, or death, presenting the results as a percentage. Patients alive without recurrence of cancer were censored on the last date of follow-up.

Results

After exclusions, data regarding 45 patients in the PVB group and 41 in the SHAM group were analysed (Figure 1). The groups were statistically well balanced regarding patient and tumour characteristics and cancer treatment (Table I). The survival results are reported for 1, 5, 10 and 12 years (Figure 2). There was no statistically significant difference between

Table I. Patient, tumour and treatment characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group</th>
<th>PVB</th>
<th>SHAM</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>54.5±10.6</td>
<td>54.2±10.2</td>
<td>0.898</td>
</tr>
<tr>
<td>ASA 1/2/3 (n)</td>
<td></td>
<td>15/21/9</td>
<td>21/13/7</td>
<td>0.228</td>
</tr>
<tr>
<td>Tumour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td></td>
<td>22±12</td>
<td>21±13</td>
<td>0.843</td>
</tr>
<tr>
<td>Multifocal (n)</td>
<td></td>
<td>14</td>
<td>7</td>
<td>0.130</td>
</tr>
<tr>
<td>Stage 0/1/2/3</td>
<td></td>
<td>0/14/21/10</td>
<td>1/10/17/13</td>
<td>0.513</td>
</tr>
<tr>
<td>DCIS/ductal/lobular/IBC(n)</td>
<td>0/25/12/8</td>
<td>1/27/11/2</td>
<td>0.331</td>
<td></td>
</tr>
<tr>
<td>ER-positive (n)</td>
<td></td>
<td>35</td>
<td>35</td>
<td>0.202</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WLE/M/WLE+M (n)</td>
<td></td>
<td>15/26/4</td>
<td>19/21/1</td>
<td>0.270</td>
</tr>
<tr>
<td>SNB/SNB+ALND/ALND (n)</td>
<td>7/13/24</td>
<td>10/12/18</td>
<td>0.743</td>
<td></td>
</tr>
<tr>
<td>E/CT+E+CT (n)</td>
<td></td>
<td>10/9/18</td>
<td>6/4/25</td>
<td>0.244</td>
</tr>
<tr>
<td>B/B+LN/CW/CW+LN (n)</td>
<td>8/6/1/19</td>
<td>9/9/2/16</td>
<td>0.506</td>
<td></td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>12 (1-13)</td>
<td>12 (3-14)</td>
<td>0.285</td>
<td></td>
</tr>
</tbody>
</table>


Table II. Breast cancer events. Black circles indicate breast cancer events in the paravertebral group and white circles in the sham group. The number within the circle indicates the tumour stage, an underline indicates multifocal breast cancer, and grey zone indicates death during the follow-up.

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>Time to first breast cancer event (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>2 4 6 8 10 12</td>
</tr>
<tr>
<td>Nodal</td>
<td>②③</td>
</tr>
<tr>
<td>Contralateral</td>
<td>③</td>
</tr>
<tr>
<td>Distant</td>
<td>③③</td>
</tr>
</tbody>
</table>

*Non-breast-cancer death.

Table III. 12-Year breast cancer survival by stage, all patients combined.

<table>
<thead>
<tr>
<th>Survival measure</th>
<th>Stage</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Distant recurrence-free</td>
<td>100%</td>
<td>92%</td>
<td>68%</td>
</tr>
<tr>
<td>Breast cancer-specific</td>
<td>100%</td>
<td>90%</td>
<td>73%</td>
</tr>
<tr>
<td>Overall</td>
<td>100%</td>
<td>91%</td>
<td>69%</td>
</tr>
</tbody>
</table>
PVB and SHAM groups in DFS, DRFS or BCSS but OS was better for the SHAM group. There were nine and seven recurrences (p=0.170), seven and two deaths due to breast cancer (p=0.049) and the time to first recurrence was 50 (9-92) and 64 (13-99) months (p=0.368) in the PVB and SHAM groups, respectively. The estimated mean total venous concentrations of bupivacaine were 1.7±0.7 μM at the beginning and 1.0±0.4 μM at the end of surgery in the PVB group.

Patients who had early recurrence within 2 years or distant recurrence at any time died during follow-up (Table II). There were too few events in both study groups to permit a survival analysis by stage. Stage (13) had a significant influence on survival considering all patients combined (Table III).

Postoperatively, 70 patients (81%) had radiotherapy and 72 (84%) had systemic therapy (Table I). The most common chemotherapeutic combinations were cyclophosphamide plus epirubicin with 5-fluorouracil alone in 18.6%, or in combination with docetaxel in 18.6% or vinorelbine in 17.4%. Endocrine therapy was based on tamoxifen alone in 26.7%, or in combination with aromatase inhibitor letrozole in 19.8% or anastrozole in 8.1%. One patient in the PVB group and three patients in the SHAM group were given trastuzumab.

**Discussion**

Contrary to our hypothesis, PVB did not seem to reduce recurrence, enhance survival or show any anti-metastatic property in this 12-year retrospective follow-up after breast cancer surgery. DFS, DRFS and BCSS were not improved by PVB. In fact, OS was better in the SHAM group. Non-breast cancer mortality may modify the proportion of long-term survivors (14). The number of first breast cancer events was similar for both groups. Recurrences were more common in
patients with higher-stage disease and the prognosis was poor if recurrence appeared earlier than 24 months after surgery or in distant locations, similar to previously published series (15, 16). Our results agree with other retrospective follow-up studies based on previous randomized controlled trials that found no effect on recurrence or survival after cancer surgery using regional anaesthesia (4, 5).

The in vitro anti-inflammatory, anti-proliferative and antimetastatic properties of amide local anaesthetics depend on tissue concentration (2, 3). In spite of finding perioperative venous concentrations of bupivacaine (1.0-1.7 μM) to be in the effective range (1-100 μM), we found no signs of any antimetastatic property.

The survival rates agree with American and UK statistics (8, 9). Most new breast cancer cases (61%) are discovered in the early stage (8). Since the early 1970s, new adjuvant treatments and better use of older drugs have constantly improved the survival for female patients with breast cancer (9).

The observed poorer survival in the PVB group may be coincidental, due to the small number of study patients and observed events. Although the differences in patient and tumour features, such as American Society of Anaesthesiologist physical status classification, tumour grade and multifocality, were not statistically significant, they may have played a role. For example, there were twice as many multifocal carcinomas in the PVB group but the difference was not statistically significant between groups. However, five breast cancer recurrences, three deaths due to breast cancer and two contralateral recurrences occurred among the patients who had multifocal cancer in the PVB group only.

Conclusion

Paravertebral block during breast cancer surgery did not improve the prognosis of patients with breast cancer in our retrospective 12-year follow-up. Large-scale studies are warranted to assess the effect of amide local anaesthetics on cancer recurrence after cancer surgery in the presence of strong confounding factors such as patient, tumour and therapeutic characteristics.

Conflicts of Interest

None of the Authors has a financial conflict of interest to disclose in relation to the content of this article.

References


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