Acute and chronic pain following breast surgery

Serene H. Chang*, Vivek Mehta, Richard M. Langford

Barts and The London NHS Trust, United Kingdom

Received 16 July 2008; received in revised form 9 December 2008; accepted 2 January 2009
Available online 10 February 2009

Summary

Background: Successful acute pain management after breast surgery remains challenging, and if not achieved, may increase the likelihood of subsequent chronic pain.

Aims: This article aimed to evaluate the evidence for varied techniques described for peri-operative pain management in breast surgery, and to review the literature on chronic pain after breast surgery and particularly 'post-mastectomy pain syndrome'.

Method: A Pubmed search was performed, with the key words 'mastectomy' and 'pain' for articles in the English language in the adult human population (age > 19 years), looking specifically for different analgesic techniques that have been evaluated.

Results: Thirty-three peer-reviewed publications with pain outcome data were included, ranging from 15 to 289 patients per study (total n = 2104). Twenty-three were randomised controlled trials and the rest were prospective or retrospective audits and case series. Inconsistent trial methodology precluded a meta-analysis. Paravertebral local anaesthetic nerve blockade resulted in lower pain scores and fewer side effects than opioid-based regimens. Three risk factors emerged predicting chronic pain post-mastectomy: higher post-operative pain scores, age < 65 years and inclusion of major reconstructive surgery.

Conclusion: Paravertebral block should be considered for use in major breast surgery. Pain control should be optimised/a priority for both acute care and to potentially reduce chronic pain.

© 2009 Elsevier B.V. All rights reserved.
Introduction

Surgery in the form of either lumpectomy, or modified radical mastectomy with axillary node dissection, in combination with chemotherapy or radiotherapy remains the treatment of choice for breast cancer. A wide variety of analgesic techniques are employed for managing the post-surgical pain, which often proves difficult to treat in the early post-operative period. It is increasingly recognised that complex chronic pain syndromes may develop months to years later [1—3]. Poorly managed pain can slow recovery, create burdens for patients and their families, and increase costs to the healthcare system. Though various risk factors have been suggested, inappropriate acute post-operative pain management has been associated with the development of chronic post-mastectomy pain, a complex post-surgical pain syndrome that may occur following any type of breast surgery [3].

In this article, we aim to summarise the evidence with regards to various techniques which have been used to manage peri-operative pain associated with breast surgery and also highlight the problem of post-mastectomy pain syndrome (PMPS)—an extensively reported but poorly understood complication that could follow any form of breast surgery.

Analgesic techniques

We performed a Pubmed search with the key words “mastectomy” and “pain” for articles in the English language, in the adult (over 19 years of age) population looking specifically for the analgesic techniques that have been evaluated. We included all trials including non-randomised trials, prospective and retrospective studies, looking specifically at analgesic techniques that have been used in breast surgery. Our search tool reported 312 articles, however only 33 were found suitable for inclusion, as the majority were either not related to the post-operative period in breast surgery, or were not associated specifically with analgesic techniques used in surgery. Table 1 summarises the evidence comparing different analgesic techniques for breast surgery. Though traditional opioid-based analgesia remains the mainstay, different techniques including regional local anaesthetic infiltrations, paravertebral and neuraxial analgesia, anticonvulsants, anti-neuropathic analgesics and NMDA antagonists have all been used either in isolation or in combination.

Opioid-based regimens

Most of the studies have compared their technique of choice, against PCA morphine or morphine as the main stay of rescue analgesia, as is widely seen in clinical practice. There is one study by Kampe et al., looking at the clinical efficacy of controlled release oxycodone, which showed that there was a reduction in pain scores and less rescue analgesia needed [31]. The study by Legeby et al. looking at the efficacy of diclofenac in combination with morphine and paracetamol, found an opioid sparing effect in the first 6h post-operatively. However, this difference was not significant after 64h and post-operative bleeding was significantly higher with diclofenac [32]. In a different study by Yarussi et al., an evaluation of morphine, via the intramuscular route, versus placebo found no
## Table 1  
Comparison of various peri-operative analgesic techniques for pain management in breast surgery.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Study</th>
<th>Type</th>
<th>Surgery</th>
<th>No. of patients enrolled</th>
<th>Drugs/techniques</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Ketamine given pre-emptively</td>
<td>Adam et al. [4]</td>
<td>Randomised double-blinded study</td>
<td>Total mastectomy</td>
<td>128, 64 given before surgery 64 given after</td>
<td>0.15 mg/kg ketamine, 0.3 mcg/kg sufentanil at induction</td>
<td>No hallucinations in both. No sig differences in pain scores. No pre-emptive analgesic effect</td>
</tr>
<tr>
<td>Intercostal nerve blocks</td>
<td>Atanassoff et al. [5]</td>
<td>Randomised double-blinded study</td>
<td>Lumpectomy</td>
<td>48</td>
<td>ICNB T3-6 lignocaine 1.5/2% and bupivacaine 0.5% vs. GA</td>
<td>Lower pain scores with ICNB</td>
</tr>
<tr>
<td>Paravertebral blocks</td>
<td>Crawford-Sykes et al. [6]</td>
<td>Retrospective</td>
<td>Mastectomy, wide local excision, axillary dissection</td>
<td>21</td>
<td>6 PVB, 2 of 6 converted to GA. 15 PVB with GA</td>
<td>No anaesthetic complications noted, No conclusions on analgesic use deduced No conversions to GA. 9 required no narcotics post-op. 3 PONV. Average pain relief 23 h Reasons for conversion to GA: inadequate blk (67%)</td>
</tr>
<tr>
<td>PVB as a sole technique</td>
<td>Weltz et al. [7]</td>
<td>Retrospective</td>
<td>MRM, wide excision ALND</td>
<td>15</td>
<td>C7-T7 4 ml/level 0.5% bupivacaine with 1:400,000 epinephrine</td>
<td></td>
</tr>
<tr>
<td>PVB vs. GA</td>
<td>Najarian et al. [8]</td>
<td>Retrospective</td>
<td>Mastectomy, SN bx, ALND, reconstruction</td>
<td>289, 125 = PVB, 100 = GA, PVB to GA = 24 planned PVB with GA = 12</td>
<td>T1-6 5 ml/level 0.5% ropivacaine with 1:400,000 epinephrine</td>
<td></td>
</tr>
<tr>
<td>PVB vs. GA</td>
<td>Coveney et al. [9]</td>
<td>Retrospective</td>
<td>MRM, wide excision, ALND</td>
<td>145 pts. 85.3% completed without supplementation. 9% conversion to GA</td>
<td>C7-T 6.3–4 ml/level 0.5% bupivacaine with 1:400,000 epinephrine</td>
<td>Low complication rate (2.6%). Epidural extension in 2 cases 1 required GA peri-operatively. 1 pneumothorax. Shorter hospital stay, less post-op analgesia, less PONV (p &lt; 0.0001). 5 incomplete blocks. No complications. Minimal PONV. None unsatisfied</td>
</tr>
<tr>
<td>PVB</td>
<td>Greengrass et al. [10]</td>
<td>Prospective, observational</td>
<td>Lumpectomy, ALND, MRM</td>
<td>25</td>
<td>C7-T 6.3–4 ml/level 0.5% bupivacaine with 1:400,000 epinephrine</td>
<td></td>
</tr>
<tr>
<td>Technique</td>
<td>Study</td>
<td>Type</td>
<td>Surgery</td>
<td>No. of patients enrolled</td>
<td>Drugs/techniques</td>
<td>Results</td>
</tr>
<tr>
<td>----------------------------</td>
<td>--------------------------------</td>
<td>-----------------------</td>
<td>------------------------------</td>
<td>--------------------------</td>
<td>------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>PVB vs. GA</td>
<td>Terheggen et al. [11]</td>
<td>Prospective randomised</td>
<td>Minor breast surgery</td>
<td>30</td>
<td>PVB via catheter T3/4 15–20 ml of 2% mepivacaine with adrenaline 1:200,000</td>
<td>Lower VAS scores (p &lt; 0.001) Significantly higher pt satisfaction scores, lower analgesic requirements in PVB groups</td>
</tr>
<tr>
<td>PVB vs. GA</td>
<td>Pusch et al. [12]</td>
<td>Prospective randomised</td>
<td>Lumpectomy to MRM, ALND</td>
<td>86</td>
<td>Single injection PVB 0.3 ml/kg 0.5% bupivacaine at T4</td>
<td>Lower pain scores, lower analgesic requirements, less PONV (p &lt; 0.05). 1 epidural spread</td>
</tr>
<tr>
<td>PVB vs. GA</td>
<td>Naja et al. [13]</td>
<td>Prospective randomised</td>
<td>Simple, partial or MRM</td>
<td>60</td>
<td>Multilevel PVB</td>
<td>Reduced VAS scores, analgesics, PONV and hospital stay in PVB gp PVB pts had less post-op pain, less opioid use (p &lt; 0.05), less sedated until 90 min (p &lt; 0.05)</td>
</tr>
<tr>
<td>PVB vs. placebo</td>
<td>Kairaluoma et al. [14]</td>
<td>Randomised blinded placebo controlled</td>
<td>Breast tumour resection, mastectomy</td>
<td>60</td>
<td>PVB at T3. Bupivacaine 1.5 mg/kg vs. saline. All pts had GA</td>
<td></td>
</tr>
<tr>
<td>TEA vs. morphine PCA</td>
<td>Correll et al. [15]</td>
<td>Prospective randomised</td>
<td>Mastectomy with TRAM flap reconstruction</td>
<td>18</td>
<td>All GAs. TEA at T8 0.15% ropivacaine &amp; morphine 0.05 mg/l, bolus of 2 mg morphine; run at 8 ml/h TEA T6/7 0.2% ropivacaine</td>
<td>Lower pain scores with TEA (p &lt; 0.05), shorter hospital stay p = 0.0498</td>
</tr>
<tr>
<td>TEA vs. GA (opioids for analgesia)</td>
<td>Doss et al. [16]</td>
<td>Prospective randomised</td>
<td>MRM</td>
<td>60</td>
<td>TEA T6/7 0.2% ropivacaine</td>
<td>TEA gp: higher number ready for discharge from recovery (p = 0.0006), less pain and greater pt satisfaction (p &lt; 0.001)</td>
</tr>
<tr>
<td>Cervical epidural with GA</td>
<td>Kotake et al. [17]</td>
<td>Prospective observational</td>
<td>MRM</td>
<td>21</td>
<td>C7/T1 1% mepivacaine with 2.5 mcg/ml fentanyl at 7 ml/h</td>
<td>No major side-effects noted</td>
</tr>
</tbody>
</table>

Note: VAS = Visual Analog Scale, PVB = Paravertebral Block, GA = General Anaesthesia, MRM = Modified Radical Mastectomy, ALND = Axillary Lymph Node Dissection, TEA = Targeted Epidural Anesthesia, PCA = Patient Controlled Analgesia, PONV = Post Operative Nausea and Vomiting, GPA = General Practitioner Anesthesia.
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Study Design</th>
<th>Setting</th>
<th>Sample Size</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fassoulaki [18]</td>
<td>Brachial plexus block (BBB) for pain relief</td>
<td>Prospective randomised vs. control</td>
<td>MRM</td>
<td>47 block, 48 control</td>
<td>Infraclavicular block at the end of surgery. 15 ml 0.5% bupivacaine with 1:200,000 epinephrine. Intercostal spaces underneath the skin incision infiltrated with 5 ml bupivacaine. BBB pts fewer required analgesics in first 24 h post-op ($p &lt; 0.0005$). Longer time before first analgesic required ($p &lt; 0.001$)</td>
</tr>
<tr>
<td>Sundarathiti et al. [19]</td>
<td>TEA with Ipsilateral Brachial plexus block vs. GA</td>
<td>Prospective randomised</td>
<td>MRM</td>
<td>50, 25 each group</td>
<td>TEA T4/5 10–15 ml 0.2% ropivacaine, BRB 8 ml 0.2% ropivacaine. GA–fentanyl/tramadol. None converted to GA. Lower pain scores in TEA gp ($p &lt; 0.001$), fewer needed rescue analgesia ($p = 0.002$)</td>
</tr>
<tr>
<td>Fassoulaki et al. [20]</td>
<td>EMLA topically on supraclavicular area and axilla</td>
<td>Prospective randomised</td>
<td>MRM, lumpectomy, ALND</td>
<td>46</td>
<td>5 g EMLA vs. placebo</td>
</tr>
<tr>
<td>Rakshanda et al. [21]</td>
<td>Botulinum toxin (BT) infiltration for pain control vs. control gp</td>
<td>Prospective</td>
<td>Mastectomy &amp; expander reconstruction</td>
<td>48</td>
<td>BT injected into pectoralis major</td>
</tr>
<tr>
<td>Baroody et al. [22]</td>
<td>Continuous local infiltration via a catheter</td>
<td>Prospective with retrospective control group</td>
<td>Autologous breast reconstruction</td>
<td>16</td>
<td>0.25% bupivacaine at 2.08 cc/h for 48 h</td>
</tr>
<tr>
<td>Morrison et al. [23]</td>
<td>Continuous local infiltration via a catheter</td>
<td>Retrospective</td>
<td>MRM, ALND</td>
<td>48</td>
<td>4 ml/h 0.25% sensorcaine (bupivacaine + epinephrine)</td>
</tr>
<tr>
<td>Lu et al. [24]</td>
<td>Continuous local anaesthetic infiltration</td>
<td>Prospective</td>
<td>Breast reduction, reconstruction</td>
<td>148</td>
<td>0.25% bupivacaine 5–7 cc/h</td>
</tr>
<tr>
<td>Johansson et al. [25]</td>
<td>Wound infiltration</td>
<td>Prospective randomised</td>
<td>Partial mastectomy +/− axillary dissection</td>
<td>45</td>
<td>Post-op 0.375% ropivacaine, 0.375% ropivacaine + fentanyl 0.5 mcg/kg or no wound infiltration</td>
</tr>
<tr>
<td>Johansson et al. [26]</td>
<td>Preoperative ropivacaine infiltration</td>
<td>Prospective, randomised double-blinded placebo controlled</td>
<td>Partial mastectomy +/− ALND</td>
<td>60</td>
<td>0.3 ml/kg saline or 0.3 ml/kg of 0.75% ropivacaine injected to breast and axilla</td>
</tr>
</tbody>
</table>

**Note:** MRM = Modified Radical Mastectomy, ALND = Axillary Lymph Node Dissection, BBB = Brachial Plexus Block, TEA = Thoracic epidural analgesia, EMLA = Eutectic Mixture of Local Anesthetics, BT = Botulinum toxin, GA = General Anaesthesia, PONV = Postoperative nausea and vomiting.
<table>
<thead>
<tr>
<th>Technique</th>
<th>Study</th>
<th>Type</th>
<th>Surgery</th>
<th>No. of patients enrolled</th>
<th>Drugs/techniques</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine irrigation into axillary wound drains at the end of surgery</td>
<td>Talbot et al. [27]</td>
<td>Prospective, randomised double-blinded placebo controlled</td>
<td>Mastectomy and axillary clearance</td>
<td>42</td>
<td>20 ml 0.5% bupivacaine/saline (max 2 mg/kg) infused into drain every 4 h for 6 doses 24 h post-op</td>
<td>No differences in analgesic requirements or pain scores</td>
</tr>
<tr>
<td>Comparison of local vs. systemic effect of ketorolac</td>
<td>Bosek et al. [28]</td>
<td>Mastectomy, lumpectomy with ALND</td>
<td>60 (20 in each group)</td>
<td>Prospective, randomised placebo-controlled</td>
<td>20 ml of normal saline +/- 30 mg ketorolac via drain and i.v. at end and 6 h until discharge</td>
<td>Pain control improved in the immediate post-op period regardless of route of administration of ketorolac Lower pain scores, lower analgesic requirements ($p &lt; 0.0001$) in those given ketoprofen pre-emptively No differences in pain scores or analgesic requirements between the groups</td>
</tr>
<tr>
<td>Efficacy of i.v. ketoprofen for pre-emptive analgesia</td>
<td>Priya et al. [29]</td>
<td>Simple mastectomy, lumpectomy, MRM</td>
<td>50</td>
<td>Prospective, randomised controlled double-blinded</td>
<td>Gp 1 = 100 mg ketoprofen i.v. 30 min before surgery; Gp 2 = 100 mg ketoprofen i.v. immediately after surgical incision Irrigation of surgical sites with 6 mg morphine compared to i.m. morphine</td>
<td>Lower pain scores, lower analgesic requirements ($p &lt; 0.0001$) in those given ketoprofen pre-emptively No differences in pain scores or analgesic requirements between the groups</td>
</tr>
<tr>
<td>Evaluation of peripheral morphine analgesia</td>
<td>Yarussi et al. [30]</td>
<td>Lumpectomy and axillary node dissection</td>
<td>45</td>
<td>Prospective, randomised double-blind, placebo-controlled</td>
<td>No differences in pain scores or analgesic requirements between the groups</td>
<td></td>
</tr>
<tr>
<td>Clinical efficacy of controlled—release oxycodone 20 mg for post-op pain relief</td>
<td>Kampe et al. [31]</td>
<td>Mastectomy, quadrantectomy with ALND</td>
<td>40</td>
<td>Prospective, randomised, placebo controlled double-blinded</td>
<td>20 mg controlled release oxycodone 1 h before surgery and 12 h after. All had access to PCA with piritramide</td>
<td>Lower opioid consumption and lower pain ($p = 0.01$), less rescue analgesia needed ($p = 0.005$) at 24 h. Lower pain scores at rest ($p = 0.05$) but not on movement</td>
</tr>
<tr>
<td>Study Description</td>
<td>Author(s)</td>
<td>Study Design</td>
<td>Procedure</td>
<td>Participants</td>
<td>Intervention</td>
<td>Outcomes</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>---------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>--------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Analgesic efficacy of diclofenac in combination with morphine and paracetamol</td>
<td>Legeby et al. [32]</td>
<td>Prospective, randomised</td>
<td>Mastectomy and immediate breast reconstruction</td>
<td>50</td>
<td>50 mg x 3 diclofenac rectally or placebo plus oral paracetamol and PCA opioids</td>
<td>In 1st 20 h, less pain in diclofenac group at rest but not on movement. 34% less opioids used in 1st 6 h ($p = 0.007$). No significant differences in opioid consumption after 64 h. No differences in PONV. Post-op bleeding significantly higher with diclofenac ($p &lt; 0.01$)</td>
</tr>
<tr>
<td>Single dose gabapentin vs. placebo on post-op pain</td>
<td>Dirks et al. [33]</td>
<td>Prospective, randomised, double-blind placebo controlled</td>
<td>Unilateral radical mastectomy with axillary dissection</td>
<td>70, 31 in gabapentin, 34 in placebo</td>
<td>1200 mg oral gabapentin 1 h before surgery. PCA morphine post-op in both groups</td>
<td>Reduced total morphine consumption in gabapentin group ($p &lt; 0.0001$). Reduction in movement related pain ($p &lt; 0.0001$). No major side-effects noted</td>
</tr>
<tr>
<td>Analgesic effect of gabapentin and mexiletine on acute and chronic pain</td>
<td>Fassoulaki et al. [34]</td>
<td>Prospective, randomised, double-blind placebo controlled</td>
<td>MRM, lumpectomy, ALND</td>
<td>75</td>
<td>Gp 1 = 200 mg mexiletine, Gp 2 = 400 mg gabapentin, Gp = placebo. Three times per day for 1st 10 post-op days starting the evening before surgery</td>
<td>No differences in pain scores at rest/movement in 1st 24 h post-op in all groups. In Gabapentin gp, reduced pain scores at rest ($p &lt; 0.05$) and movement ($p &lt; 0.005$) on 2nd, 3rd, 4th post-op day. In mexiletine gp, reduced pain scores at rest ($p &lt; 0.05$) and movement ($p &lt; 0.005$) on the 3rd post-op day. Three months post-surgery, no differences in incidence of pain at any site. However, burning pain was increased in the control gp ($p = 0.033$)</td>
</tr>
<tr>
<td>Technique</td>
<td>Study</td>
<td>Type</td>
<td>Surgery</td>
<td>No. of patients enrolled</td>
<td>Drugs/techniques</td>
<td>Results</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td>---------------------------------</td>
<td>----------------------------------------------</td>
<td>---------------------------------</td>
<td>--------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Multimodal analgesia with gabapentin and local anaesthetics on acute and chronic pain</td>
<td>Fassaoulaki et al. [35]</td>
<td>Prospective, randomised double-blind</td>
<td>MRM, lumpectomy with axillary dissection</td>
<td>50</td>
<td>Gp A control gp given placebo. Gp B given oral gabapentin, EMLA cream and irrigation of brachial plexus and intercostals nerves with ropivacaine intraoperatively</td>
<td>Reduction in number requiring analgesia in recovery ($p = 0.007$). Reduced paracetamol requirements in recovery ($p = 0.03$). Significantly reduced pain scores at rest in recovery and on post-op days 1, 3 and 5 and on movement on days 2, 4 and 8.</td>
</tr>
<tr>
<td>Preincisional dextromethorphan (DM) and opioid requirements</td>
<td>Wong et al. [36]</td>
<td>Prospective, randomised double-blind</td>
<td>MRM</td>
<td>60</td>
<td>Gp 1 = 40 mg DM and 20 mg chlorpheniramine maleate (CPM) i.m.; Gp 2 = 20 mg CPM i.m. Both given 30 min before incision</td>
<td>Longer time to 1st meperidine injection in DM gp. Higher total meperidine consumption in control gp during 1st 48 h ($p &lt; 0.001$).</td>
</tr>
</tbody>
</table>

**MRM:** modified radical mastectomy; **ICNB:** intercostals nerve block; **ALND:** axillary lymph node dissection.
difference in post-operative opioid requirements. In this study, fentanyl was used as the rescue analgesic. These were only two relatively small studies. It would seem however, that the intravenous route, unsurprisingly, would be the standard of choice.

Regional analgesia

In general, the studies reflect that, regional techniques have a better outcome in terms of less post-operative pain, higher patient satisfaction scores and earlier time to discharge from recovery as well as from the hospital.

Paravertebral blocks

There have been four retrospective and five prospective studies investigating the efficacy of paravertebral analgesia. Four of the prospective studies were randomised, two of them comparing paravertebral analgesia with general anaesthesia and one with placebo [12–14]. Majority of the patients had modified radical mastectomy with or without axillary lymph node dissection. There was a better outcome with shorter hospital stay, less post-operative analgesic requirements and minimal post-operative nausea and vomiting in patients receiving paravertebral analgesia in all the three studies. In one retrospective study (Coveney et al. [9]), one patient was intubated peri-operatively after complaining of arm paresthesia and shortness of breath whilst another patient developed a small pneumothorax which was managed conservatively without the need for chest drain insertion. Overall, there was no major untoward incident reported and the complication rates remained low in all the studies, with those patients having a successful paravertebral block achieving better pain scores in recovery and a higher overall patient satisfaction. Hence use of paravertebral block may be an extremely useful adjunct to provide peri-operative analgesia in patients having major breast surgery.

Transthoracic epidurals (TEAs)

Two small prospective studies (18 and 60 patients, respectively), demonstrated lower pain scores, shorter hospital stay and higher patient satisfaction. In another prospective randomised trial of 50 patients undergoing modified radical mastectomy individuals were randomised to receive either TEA analgesia in combination with ipsilateral brachial plexus blockade or general anaesthesia. None of the patients in the TEA group needed conversion to general anaesthesia and had lower pain scores ($p < 0.001$) with fewer needing rescue medication ($p = 0.002$). They reported this combination as safe and useful technique, especially for patients who are at a higher risk with a general anaesthetic, though clearly a very high-risk strategy. Interestingly there has been one small prospective observational study of 21 patients (Kotake et al. [17]) which has demonstrated the efficacy of cervical epidural analgesia in combination with general anaesthesia without any major side effects. With a significant complication risk, this technique should be reserved for isolated cases to be done by expertise in the area.

Topical creams

Fassoulaki et al. [20] showed that the topical use of EMLA applied on the operation site up to 4 days post-surgery, reduced post-operative analgesic requirements and the incidence and intensity of chronic pain at 3 months post-surgery.

Local anaesthetic regimes

The evidence for the use of local anaesthetic infusion regimes into the wound site or irrigation drains remains equivocal. There have been two retrospective reviews, one prospective study, and three randomised studies looking at the use of different local anaesthetic regimes. Indeed, in the three randomised studies (Johansson et al. [25], Johansson et al. [26] and Talbot et al. [27]) which involved a total of 106 patients all together, their use of local anaesthetic regimes showed no improvement in post-operative pain management.

Non-steroidal anti-inflammatory drugs

The three randomised placebo-controlled studies in the table indicate that the use of NSAIDs had an opioid sparing effect following breast surgery. Patients in the studies were given either intravenous ketoprofen or ketorolac or diclofenac. Patients who had ketoprofen (Priya et al. [29]) or ketorolac (Bosek et al. [28]) had lower pain scores in the immediate post-operative period. In the study using diclofenac (Legeby et al. [37]), its addition showed a reduction in pain scores in the first 20 h post-operatively.
Anticonvulsants

Gabapentin

There is now increasing evidence that gabapentin, and perhaps pregabalin, does have a significant role to play in peri-operative and post-operative pain relief in general and thus perhaps could be appropriate for use in breast cancer surgery [38].

The use of gabapentin has been investigated in three randomised double-blind trials. Gabapentin whether used alone or in combination with other drugs such as mexiletine and local anaesthetics showed a reduction in total opioid use and overall reduced analgesia requirements. In a prospective, randomised, double-blind placebo study, 70 patients were randomised to receive either placebo or gabapentin 1200 mg an hour before unilateral breast surgery with axillary dissection [33]. The results indicated that the patients in the gabapentin group had a morphine sparing effect as well as a reduction in pain scores at 4 h post-radical mastectomy, without significant side effects.

Similarly, Fassoulaki et al. [34] looked at the analgesic efficacy of mexiletine or gabapentin versus placebo on acute and chronic pain post-breast cancer surgery in 75 patients. There was a reduction in codeine and paracetamol consumption in the second to the tenth post-operative day. The pain scores were significantly less in both the mexiletine and gabapentin groups on day 3 post-operatively whilst pain scores on movement in the gabapentin group were also reduced from the second to fifth post-operative days. Interestingly the incidence of chronic pain was not affected by either treatment.

In 2005, Fassoulaki et al. [35] investigated the effect of multimodal analgesia (gabapentin 400 mg, EMLA cream and irrigation of the brachial plexus intraoperatively with 10 ml of 0.75% ropivacaine and the third, fourth and fifth intercostals spaces with 3 ml of the same solution) by the operating surgeon. The treatment group consumed less paracetamol and codeine than the controls and also had lower pain scores at rest on post-operative days 1, 3 and 5. Again there was no significant effect on chronic pain at 3 months after surgery.

Chronic pain after breast surgery

Post-mastectomy pain syndrome is a poorly understood chronic pain phenomenon that may occur following surgical procedures for breast cancer. The pain after breast surgery is quite variable in onset and may persist beyond the acute post-operative period. Though again variable in character the pain is predominantly neuropathic, involving the region innervated by the damaged nerves in the axilla, arm or shoulder of the affected side. The symptoms are also quite variable with the patients describing anything from burning sensation, electric shock like pain or stabbing like pain sensation. Further they may also complain of phantom breast pain which is similar to the phenomenon of phantom limb pain experienced by persons who lose an arm or leg. The effects of the chronic pain are usually debilitating and the overall impact on the function and capacity of the individual extends much beyond the dermatomal distribution of the pain. Chronic pain following surgery in oncology is multi-factorial and ancillary treatments such as radiotherapy and chemotherapy certainly have a significant contribution in its generation. Due to the poor quality of available evidence, it would be impossible to quantify the effect of ancillary treatments in the analysis. The studies looking at analgesic techniques do not indicate whether these treatments had been used in the patient population studied. Described as post-mastectomy pain syndrome, its mechanisms and the risk factors remain unclear, though surgical damage of nerves, age at surgery, post-surgical radiation therapy, and severe acute post-operative pain have all been implicated. With few randomised controlled trials, the evidence predominantly consists of case reports, retrospective studies and from expert opinion in the field.

Prevalence

PMPS is a poorly recognised phenomenon that may be more widespread than previously thought. It has been estimated that over 50% of women suffer from post-mastectomy pain with the onset ranging from 2 weeks to 6 months following surgery (Stevens et al. [39]). An epidemiological study in 1996 conducted in northeast Scotland reported a similar cumulative prevalence of 43% at 3 years post-surgery for women who had undergone mastectomy for breast cancer. This retrospective cohort study of cases of PMPS over a 6-year period, evaluated results from a questionnaire returned by 408 patients (Cairns et al. [40]) who underwent mastectomy for breast cancer. In this study the diagnosis of PMPS was established on three criteria: the character of the pain (neuropathic pain often with unpleasant sensory changes, e.g. numbness, pins and needles, burning, stabbing or formication), the location of the pain and the onset/duration of the pain. Of
those patients who reported these symptoms, 30% described an immediate onset, 25% describing onset at less than 1 month after surgery, and 15% reported it at occurring between 1 and 3 months while 24% reported it after more than 3 months duration.

When these patients were followed up 12 years after the surgery (138 eligible patients out of 175 patients who had reported PMPS in the initial study), 58 patients reported pain suggesting that as much as 17% women may have PMPS even after 12 years post-surgery (Macdonald et al. [41]).

**Risk factors for development of chronic pain**

Various risk factors which might contribute to development of PMPS have been proposed.

**Age**

The evidence exists mainly in the form of retrospective/prospective studies and surveys. In a multivariate analysis in a prospective study investigating the risk factors for chronic pain following breast cancer surgery in 95 women Poleshuck et al. [1] reported that of all the clinical and demographic covariates (including age at surgery, breast cancer history, preoperative breast pain, surgery type, cancer status, radiation therapy, chemotherapy, and clinically meaningful acute pain), only younger age was associated with a significantly increased risk of developing chronic pain at 3 months after surgery. Similar findings were reported in three other retrospective studies suggesting that younger age is an important predisposing factor in development of chronic pain following breast surgery (Macdonald et al., Smith et al., and Katz et al. and Pain 2005 [40–42]).

In their retrospective cohort study of cases of PMPS Cairns et al. there also appears be a correlation between the age and the PMPS with an incidence of PMPS being 65% in the 30–49 age group, 40% in the 50–59 years and then decreasing to 26% in the group aged 70 years or over [40].

**Acute pain management**

The most established risk factor for chronic pain following breast cancer surgery, appears to be severe acute post-operative pain. Poleshuck et al., found that clinically meaningful acute post-operative pain predicted more intense chronic pain at 3 months after surgery [1]. Another questionnaire survey reported an association between increased pain intensity in the immediate post-operative period after breast surgery and the development of chronic pain (Tasmuth et al. [43]). The remembered intensity of early post-operative pain and its relation to development of chronic pain was found by Tasmuth to be the “most important determinant for the development of chronic pain”. There is great variation in post-operative pain requirements in patients undergoing similar procedures and besides the surgery itself; psychological variables such as anxiety and depression also play a big role [44]. It has been suggested that acute pain itself is more severe among women who were younger, unmarried, had more invasive surgery and greater preoperative emotional distress. In further analysis of data, greater preoperative anxiety was the one variable that made an independent contribution predicting clinically meaningful acute pain at 2 days post-surgery while a younger age, being unmarried, and preoperative anxiety each made an independent contribution to predicting clinically meaningful acute pain that persisted from 2 days onwards until 30 days after surgery [42]. Hence it appears that there may be some association and quite complex inter-related relationship with anxiety, younger age and acute pain, with ultimately a poor acute pain management scenario subsequently leading to development of PMPS.

**Type of surgery**

The type of surgery has also been investigated as a risk factor for PMPS. Chronic pain appeared to be more common after breast-conserving surgery than after radical surgery. Two hundred eighty two women were surveyed following one of four breast surgery procedures: mastectomy, mastectomy with reconstruction, cosmetic augmentation, and breast reduction [43]. The incidence of pain occurring at least one year after surgery in the mastectomy and reconstruction group (49%) was significantly higher than the mastectomy alone (31%) and breast reduction (22%) groups. Further the incidence of breast pain was found to be highest in the mastectomy and reconstruction group and augmentation groups which was assumed to be secondary to breast implants. Interestingly, the incidence of pain in women who had reconstruction without implants was identical to those women who had mastectomy without reconstruction. Tissue expansion and radiation therapy resulted in a slight increase in chronic pain. Delayed breast reconstruction after the primary procedure has also been associated with a higher incidence of pain. Further it has been suggested that the use of silicone implants as opposed to saline implants may result in a lower incidence of pain [45].
In terms of pain characteristics this survey reports that arm pain was significantly higher in the mastectomy, and mastectomy and reconstruction groups as compared to the breast reduction group.

This data correlates well with the previous findings of Poleshuck et al. [1], who reported that more invasive surgery predicted more intense chronic pain 3 months after surgery.

Axillary dissection used to accurately stage breast cancer, may itself present with numerous complications including nerve injury. The post-operative symptoms following such injury may include paraesthesia in the arm and the axilla and may then be subsequently related to longer term hypoesthesia, hyperesthesia or pain.

The role of the intercostobrachial nerve which divides into three branches: one upper branch to the nervus cutaneous brachii medialis and two lower branches that innervate the axilla and skin on the arm has also been implicated in the development of PMPS. It has been suggested that although intercostobrachial nerve is most frequently damaged during operative procedures in breast surgery, particularly those involving axillary dissection. Other nerves that innervate the breast and underlying structures may also be injured. Nerves that supply the deep musculature of the chest wall included the long thoracic nerve, thoracodorsal nerve, lateral pectoral nerve, and medial pectoral nerve. Surgical intention is to spare these nerves during mastectomy but it is conjectured that injury due to traction or scarring, may lead to pain syndromes. Randomised studies evaluating the relationship between preservation of the intercostobrachial nerve in axillary dissection remain equivocal as to whether there is a direct relationship between preservation of the intercostobrachial nerve and pain sensitivity of the arm [46,47].

A survey done by Tasmuth et al. on 265 women, reported that procedures performed in hospitals with less experience in breast cancer surgery (low volume units) had more chronic pain symptoms. In high volume units, more experience including expertise in surgical handling techniques, appear to reduce the risk of chronic pain post-surgery [48].

Radiotherapy post-surgery

Radiotherapy used in the treatment of breast carcinoma may itself be implicated in PMPs. This may be a result of radiation-associated neuromodulatory changes at the peripheral neuronal level. Due to lack of specific randomised controlled trials it is very difficult to quantify the exact burden of neuropathic pain that may be attributed to radiotherapy, however there is a strong indication from available case studies that there may be some association. In the study by Poleshuck et al., radiation therapy after surgery predicted more intense chronic pain 3 months after breast surgery [1]. A prospective study by Gerber et al. [49] showed that patients who had axillary dissection and radiotherapy found that chest wall tenderness was a clinically significant problem at 1–2 years post-surgery compared to those who had a modified radical mastectomy alone. It has been suggested that the combination of axillary dissection and radiotherapy may lead to arm oedema and limited shoulder mobility generating higher pain as compared to radiotherapy after lumpectomy [50].

Summary

The relief of pain should be a central component of patient care and it holds true also for patients undergoing breast surgery. There is now increasing evidence that the treatment of acute post-operative pain, may not only aid in recovery from surgery, but may also reduce the risk of persisting, chronic pain syndromes. Though a number of risk factors have been identified, including younger age, type of surgery, presence of implants, radiotherapy, inadequately treated acute pain is a key factor which can be potentially addressed. There does however remain a need for adequately powered large outcome studies that might help us to establish best practice in this difficult area. As recommended in a number of reports and guidelines, dedicated acute pain services, protocols, evidence based selection of treatment and staff education serves to improve acute pain management [50]. This review revealed a very wide variety of analgesic techniques, with no obvious gold standard analgesic technique for breast surgery. Lack of adequately powered trials of consistent design, prevent a direct comparison between the different analgesic techniques, hence the evidence is predominantly dependent on isolated studies with relatively small numbers. However, paravertebral block emerges as a potentially useful strategy with a positive risk benefit analysis, and has been advocated elsewhere [51]. Obviously, the individual techniques need to be appraised with respect to local experience and facilities.

Appropriate acute pain management however remains the common goal in all the studies of pain after breast surgery, with the aim of achieving patient satisfaction and accelerated recovery and rehabilitation, and the potential later benefit of a reduction in chronic post-mastectomy pain.
Conflict of interest

There are no conflicts of interest.

References


