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REVIEW

Acute and chronic pain following breast surgery

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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.

Contents

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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 6 h post-operatively. However, this difference was not significant after 64 h 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.

Technique	Study	Type	Surgery	No. of patients enrolled	Drugs/techniques	Results
IV Ketamine given pre-emptively	Adam et al. [4]	Randomised double-blinded study	Total mastectomy	128, 64 given before surgery 64 given after	0.15 mg/kg ketamine, 0.3 mcg/kg sulfentanil at induction	No hallucinations in both. No sig differences in pain scores. No pre-emptive analgesic effect
Intercostal nerve blocks	Atanassoff et al. [5]	Randomised double-blinded study	Lumpectomy	48	ICNB T3-6 lignocaine 1.5/2% and bupivacaine 0.5% vs. GA	Lower pain scores with ICNB
Paravertebral blocks	Crawford-Sykes et al. [6]	Retrospective	Mastectomy, wide local excision, axillary dissection	21	6 PVB, 2 of 6 converted to GA. 15 PVB with GA	No anaesthetic complications noted, No conclusions on analgesic use deduced
PVB as a sole technique	Weltz et al. [7]	Retrospective	MRM, wide excision ALND	15	C7-T7 4 ml/level 0.5% bupivacaine with 1:400,000 epinephrine	No conversions to GA. 9 required no narcotics post-op. 3 PONV. Average pain relief 23 h
PVB vs. GA	Najarian et al. [8]	Retrospective	Mastectomy, SN bx, ALND, reconstruction	289, 125 = PVB, 100 = GA, PVB to GA = 24 planned PVB with GA = 12	T1-6 5 ml/level 0.5% ropivacaine with 1:400,000 epinephrine	Reasons for conversion to GA:inadequate blk (67%)
PVB vs. GA	Coveney et al. [9]	Retrospective	MRM, wide excision, ALND	145 pts. 85.3% completed without supplementa-tion.9% conversion to GA	C7-T 6.3—4 ml/level 0.5% bupivacaine with 1:400,000 epinephrine	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 ($p < 0.0001$).
PVB	Greengrass et al. [10]	Prospective, observational	Lumpectomy, ALND, MRM	25	C7-T 6.3—4 ml/level 0.5% bupivacaine with 1:400,000 epineprhine	5 incomplete blocks. No complications. Minimal PONV. None unsatisfied

Table 1 (*Continued*)

Technique	Study	Type	Surgery	No. of patients enrolled	Drugs/techniques	Results
PVB vs. GA	Terheggen et al. [11]	Prospective randomised	Minor breast surgery	30	PVB via catheter T3/4 15—20 ml of 2% mepivacaine with adrenaline 1:200,000	Lower VAS scores ($p < 0.001$) Significantly higher pt satisfaction scores, lower analgesic requirements in PVB groups
PVB vs. GA	Pusch et al. [12]	Prospective randomised	Lumpectomy to MRM, ALND	86	Single injection PVB 0.3 ml/kg 0.5% bupivacaine at T4	Lower pain scores, lower analgesic requirements, less PONV ($p < 0.05$). 1 epidural spread
PVB vs. GA	Naja et al. [13]	Prospective randomised	Simple, partial or MRM	60	Multilevel PVB	Reduced VAS scores, analgesics, PONV and hospital stay in PVB gp
PVB vs. placebo	Kairaluoma et al. [14]	Randomised blinded placebo controlled	Breast tumour resection, mastectomy	60	PVB at T3. Bupivacaine 1.5 mg/kg vs. saline. All pts had GA	PVB pts had less post-op pain, less opioid use ($p < 0.05$), less sedated until 90 min ($p < 0.05$)
TEA vs. morphine PCA	Correll et al. [15]	Prospective randomised	Mastectomy with TRAM flap reconstruction	18	All GAs. TEA at T8 0.15% ropivacaine & morphine 0.05 mg/l, bolus of 2 mg morphine; run at 8 ml/h	Lower pain scores with TEA ($p < 0.05$), shorter hospital stay $p = 0.0498$
TEA vs. GA (opioids for analgesia)	Doss et al. [16]	Prospective randomised	MRM	60	TEA T6/7 0.2% ropivacaine	TEA gp: higher number ready for discharge from recovery ($p = 0.0006$), less pain and greater pt satisfaction ($p < 0.001$)
Cervical epidural with GA	Kotake et al. [17]	Prospective observational	MRM	21	C7/T1 1% mepivacaine with 2.5 mcg/ml fentanyl at 7 ml/h	No major side-effects noted

Brachial plexus block (BBB) for pain relief	Fassoulaki [18]	Prospective randomised vs. control	MRM	47 block, 48 control	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 ($p < 0.0005$). Longer time before first analgesic required ($p < 0.001$)
TEA with Ipsilateral Brachial plexus block vs. GA	Sundarathiti et al. [19]	Prospective randomised	MRM	50, 25 each group	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 ($p < 0.001$), fewer needed rescue analgesia ($p = 0.002$)
EMLA topically on supraclavicular area and axilla	Fassoulaki et al. [20]	Prospective randomised	MRM, lumpectomy, ALND	46	5 g EMLA vs. placebo	No difference in acute pain. Total incidence and intensity of chronic pain less in EMLA gp
Botulinum toxin (BT) infiltration for pain control vs. control gp	Rakshanda et al. [21]	Prospective	Mastectomy & expander reconstruction	48	BT injected into pectoralis major	Reduced pain scores and narcotic use ($p < 0.0001$)
Continuous local infiltration via a catheter	Baroody et al. [22]	Prospective with retrospective control group	Autologous breast reconstruction	16	0.25% bupivacaine at 2.08 cc/h for 48 h	Reduced analgesic requirements ($p < 0.001$). No complications noted
Continuous local infiltration via a catheter	Morrison et al. [23]	Retrospective	MRM, ALND	48	4 ml/h 0.25% sensorcaine (bupivacaine + epinephrine)	Reduced analgesic requirements ($p < 0.001$)
Continuous local anaesthetic infiltration	Lu et al. [24]	Prospective	Breast reduction, reconstruction	148	0.25% bupivacaine 5—7 cc/h	Reduced pain scores and analgesics in recovery ($p < 0.01$)
Wound infiltration	Johansson et al. [25]	Prospective randomised	Partial mastectomy +/— axillary dissection	45	Post-op 0.375% ropivacaine, 0.375% ropivacaine + fentanyl 0.5 mcg/kg or no wound infiltration	No difference observed in post-op pain relief or PONV vs. GA
Preoperative ropivacaine infiltration	Johansson et al. [26]	Prospective, randomised double-blinded placebo controlled	Partial mastectomy +/— ALND	60	0.3 ml/kg saline or 0.3 ml/kg of 0.75% ropivacaine injected to breast and axilla	No differences in post-op pain management or PONV

Table 1 (*Continued*)

Technique	Study	Type	Surgery	No. of patients enrolled	Drugs/techniques	Results
Bupivacaine irrigation into axillary wound drains at the end of surgery	Talbot et al. [27]	Prospective, randomised double-blinded placebo controlled	Mastectomy and axillary clearance	42	20 ml 0.5% bupivacaine/saline (max 2 mg/kg) infused into drain every 4 h for 6 doses 24 h post-op	No differences in analgesic requirements or pain scores
Comparison of local vs. systemic effect of ketorolac	Bosek et al. [28]	Prospective, randomised placebo-controlled	Mastectomy, lumpectomy with ALND	60 (20 in each group)	20 ml of normal saline +/− 30 mg ketorolac via drain and i.v. at end and 6 h until discharge	Pain control improved in the immediate post-op period regardless of route of administration of ketorolac
Efficacy of i.v. ketoprofen for pre-emptive analgesia	Priya et al. [29]	Prospective, randomised controlled double-blinded	Simple mastectomy, lumpectomy, MRM	50	Gp 1 = 100 mg ketoprofen i.v. 30 min before surgery; Gp 2 = 100 mg ketoprofen i.v. immediately after surgical incision	Lower pain scores, lower analgesic requirements ($p < 0.0001$) in those given ketoprofen pre-emptively
Evaluation of peripheral morphine analgesia	Yarussi et al. [30]	Prospective, randomised double-blind, placebo-controlled	Lumpectomy and axillary node dissection	45	Irrigation of surgical sites with 6 mg morphine compared to i.m. morphine	No differences in pain scores or analgesic requirements between the groups
Clinical efficacy of controlled—release oxycodone 20 mg for post-op pain relief	Kampe et al. [31]	Prospective, randomised, placebo controlled double-blinded	Mastectomy, quadrantectomy with ALND	40	20 mg controlled release oxycodone1 h before surgery and 12 h after. All had access to PCA with piritramide	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

Analgesic efficacy of diclofenac in combination with morphine and paracetamol	Legeby et al. [32]	Prospective, randomised	Mastectomy and immediate breast reconstruction	50	50 mg × 3 diclofenac rectally or placebo plus oral paracetamol and PCA opioids	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 ($p < 0.01$)
Single dose gabapentin vs. placebo on post-op pain	Dirks et al. [33]	Prospective, randomised, double-blind placebo controlled	Unilateral radical mastectomy with axillary dissection	70, 31 in gabapentin, 34 in placebo	1200 mg oral gabapentin 1 h before surgery. PCA morphine post-op in both groups	Reduced total morphine consumption in gabapentin group ($p < 0.0001$). Reduction in movement related pain ($p < 0.0001$). No major side-effects noted
Analgesic effect of gabapentin and mexiletine on acute and chronic pain	Fassoulaki et al. [34]	Prospective, randomised, double-blind placebo controlled	MRM, lumpectomy, ALND	75	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	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 ($p < 0.05$) and movement ($p < 0.005$) on 2nd, 3rd, 4th post-op day. In mexiletine gp, reduced pain scores at rest ($p < 0.05$) and movement ($p < 0.005$) 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 ($p = 0.033$)

Table 1 (*Continued*)

Technique	Study	Type	Surgery	No. of patients enrolled	Drugs/techniques	Results
Multimodal analgesia with gabapentin and local anaesthetics on acute and chronic pain	Fassaoulaki et al. [35]	Prospective, randomised double-blind	MRM, lumpectomy with axillary dissection	50	Gp A control gp given placebo. Gp B given oral gabapentin, EMLA cream and irrigation of brachial plexus and intercostals nerves with ropivacaine intraoperatively	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.
Preincisional dextromethorphan (DM) and opioid requirements	Wong et al. [36]	Prospective, randomised double-blind	MRM	60	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	Longer time to 1st meperidine injection in DM gp. Higher total meperidine consumption in control gp during 1st 48 h ($p < 0.001$).

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 perioperative 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 as 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

[1] Poleshuck EL, Katz J, Andrus CH, Jung BF, Kalick DI, et al. Risk factors for chronic pain following breast cancer surgery: a prospective study. The Journal of Pain 2006;7(9):626—34.

[2] Perkins F, Kehlet H. Chronic pain as an outcome of surgery: a review of predictive factors. Anesthesiology 2000;93(4): 1123—33.

[3] Macrae WA. Chronic pain after surgery. British Journal of Anaesthesia 2001;87(1):88—98.

[4] Adam F, Libier M, Oszustowicz T, Lefebvre D, Beal J, Meynadier J. Preoperative small-dose ketamine has no preemptive analgesic effect in patients undergoing total mastectomy. Anesthesia & Analgesia 1999;89(2):444—7.

[5] Atanassoff PG, Alon E, Weiss BM. Intercostal nerve block for lumpectomy: superior postoperative pain relief with bupivacaine. Journal of Clinical Anesthesia 1994;6:47—51.

[6] Crawford-Sykes AM, Chine DE, Hambleton IR. Paravertebral anaesthesia for breast surgery, an initial experience at the University Hospital of the West Indies. West Indian Medical Journal 2004;53(3):174—7.

[7] Weltz CR, Greengrass RA, Lyerly HK. Ambulatory surgical management of breast carcinoma using paravertebral block. Annals of Surgery 1995;222(1):19—26.

[8] Najarian MM, Johnson JM, Landercasper J, Havlik P, Lambert P, McCarthy D. Parvertebral block: an alternative to general anesthesia in breast cancer surgery. The American Surgeon 2003;69:213—8.

[9] Coveney E, Weltz CR, Greengrass R, Iglehart JD, Leight GS, Steele SM, et al. Use of paravertebral block anesthesia in the surgical management of breast cancer: experience in 156 cases (review article). Annals of Surgery 1998;227(4):496—501.

[10] Greengrass R, O'Brien F, Lyerly K, Hardman D, Gleason D, D'Ercole F. Paravertebral block for breast cancer surgery. Canadian Journal of Anaesthesia 1996;43(8):858—61.

[11] Terheggen MA, Wille F, Borel Rinkes IH, Ionescu TI, Knape JT. Paravertebral blockade for minor breast surgery. Anesthesia & Analgesia 2002;94(2):355—9.

[12] Pusch F, Freitag H, Weinstabl C, Obwegeser R, Huber E, Wilding E. Single-injection paravertebral block compared to general anaesthesia in breast surgery. Acta Anaesthesiologica Scandinavica 1999;43:770—4.

[13] Naja MZ, Ziade MF, Lonnqvist PA. Nerve-stimulator guided paravertebral blockade vs. general anaesthesia for breast surgery: a prospective randomized trial. European Journal of Anaesthesiology 2003;20(11):897—903.

[14] Kairaluoma PM, Bachmann MS, Korpinen AK, Rosenberg PH, Pere PJ. Single-injection paravertebral block before general anesthesia enhances analgesia after breast cancer surgery with and without associated lymph node biopsy. Anesthesia & Analgesia 2004;99(6):1837—43.

[15] Correll DJ, Viscusi ER, Grunwald Z, Moore JH. Epidural analgesia compared with intravenous morphine patient controlled analgesia: postoperative outcome measures after mastectomy with immediate TRAM flap breast reconstruction. Regional Anesthesia and Pain Medicine 2001;26(5):444—50.

[16] Doss NW, Ipe J, Crimi T, et al. Continuous thoracic epidural anesthesia with 0.2% ropivacaine versus general anesthesia for perioperative management of modified radical mastectomy. Anesthesia & Analgesia 2001;92(6):1552—7.

[17] Kotake Y, Matsumoto M, Morisaki H, Takeda J. The effectiveness of continuous epidural infusion of low-dose fentanyl and mepivacaine in periooperative analgesia and hemodynamic control in mastectomy patients. Journal of Clinical Anesthesia 2004;16:88—91.

[18] Fassoulaki A. Brachial plexus block for pain relief after modified radical mastectomy. Anesthesia & Analgesia 1982; 61(12):986—7.

[19] Sundarathiti P, Pasutharnchat K, Kongdan Y, Suranutkarin P-E. Thoracic Epidural Anesthesia (TEA) with 0.2% ropivacaine in combination with ipsilateral brachial plexus block for modified radical mastectomy. Journal of the Medical Association of Thailand 2005;88(4):513—20.

[20] Fassoulaki A, Sarantopoulos C, Melemini A. EMLA reduces acute and chronic pain after breast surgery for cancer. Regional Anesthesia and Pain Medicine 2000;25(4): 350—5.

[21] Layeeque R, Hochberg J, Siegel E, Kunkel K, Kepple J, Henry-Tillman RS, et al. Botulinum toxin infiltration for pain control after mastectomy and expander reconstruction. Annals of Surgery 2004;240(4):608—14.

[22] Baroody M, Tameo MN, Dabb RW. Efficacy of the pain pump catheter in immediate autologous breast reconstruction. Journal of the American Society of Plastic Surgeons 2004;114(4):895—8.

[23] Morrison JE, Jacobs VR. Reduction or elimination of postoperative pain medication after mastectomy through use of a temporarily placed local anaesthetic pump vs. control group. Zentralblatt fur Gynakologie 2003;123:17—22.

[24] Lu L, Fine NA. The efficacy of continuous local anesthetic infiltration in breast surgery: reduction mammaplasty and reconstruction. Journal of Plastic and Reconstructive Surgery 2005;115(7):1927—34.

[25] Johansson A, Kornfalt J, Nordin L, Svensson L, Ingvar C, Lundberg J. Wound infiltration with ropivacaine and fentanyl: effects on postoperative pain and PONV after breast surgery. Journal of Clinical Anesthesia 2003;15:113—8.

[26] Johansson A, Axelson J, Ingvar C, Luttropp H-H, Lundberg J. Preoperatvie ropivacaine infiltration in breast surgery. Acta Anaesthesiologica Scandinavica 2000;44:1093—8.

[27] Talbot H, Hutchison SP, Edbrooke DL, Wrench I, Kohlhardt SR. Evaluation of a local anaesthesia regimen following mastectomy. Anaesthesia 2004;59(7):664—7.

[28] Bosek V, Cox CE. Comparison of analgesic effect of locally and systemically administered ketorolac in mastectomy patients. Annals of Surgical Oncology 1996;3(1):62—6.

[29] Priya V, Divatia JV, Sareen R, Upadhye S. Efficacy of intravenous ketoprofen for pre-emptive analgesia. Journal of Postgraduate Medicine 2002;48(2):109—12.

[30] Yarussi A, Sands R, Edge S, Lema MJ, de Leon-Casasola OA. Evaluation of peripheral morphine analgesia for lumpectomy and axillary node dissection: a randomized, double-blind, placebo-controlled study. Regional Anesthesia and Pain Medicine 1999;24(2):142—5.

[31] Kampe S, Warm M, Kaufmann J, Hundegger S, Mellinghoff H, Kiencke P. Clinical efficacy of controlled-release oxycodone 20 mg administered on a 12 h dosing schedule on the management of postoperative pain after breast surgery for cancer. Current Medical Research and Opinion 2004;20(2):199—203.

[32] Legeby M, Sandelin K, Wickman M, Olofsson C. Analgesic efficacy of diclofenac in combination with morphine and paracetamol after mastectomy and immediate breast reconstruction. Acta Anaesthesiologica Scandinavica 2005;49:1360—6.

[33] Dirks J, Fredensborg BB, Christensen D, Fomsgaard JS, Flyger H, Dahl JB. A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy. Anesthesiology 2002;97:560—4.
[34] Fassoulaki A, Patris K, Sarantopoulos C, Hogan Q. The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. Anesthesia & Analgesia 2002;95: 985—91.
[35] Fassoulaki A, Triga A, Melemeni A, Sarantopoulos C. Multimodal analgesia with gabapentin and local anesthetics prevents acute and chronic pain after breast surgery for cancer. Anaesthesia & Analgesia 2005;101(5):1427—32.
[36] Wong C-S, Wu C-T, Yu J-C, Yeh C-C, Lee M-S, Tao P-L. Preincisional dextromethorphan decreases postoperative pain and opioid requirement after modified radical mastectomy. Canadian Journal of Anesthesia 1999;46(12):1122—6.
[37] Legeby M, Segerdahl M, Sandelin K, Wickman M, Östman K, Olofsson C. Immediate reconstruction in breast cancer surgery requires intensive post-operative pain treatment but the effects of axillary dissection may be more predictive of chronic pain. The Breast 2002;11:156—62.
[38] Rowbotham D. Gabapentin: a new drug for postoperative pain? British Journal of Anaesthesia 2006;96(2):152—5.
[39] Stevens PE, Dibble SL, Miaskowski C. Prevalence, characteristics and impact of postmastectomy pain syndrome: an investigation of women's experiences. Pain 1995;61: 61—8.
[40] Cairns W, Smith S, DiBourne, Squair J, Phillips DO, Chambers WA. A retrospective cohort study of post-mastectomy pain syndrome. Pain 1999;83:91—5.
[41] Macdonald L, Bruce J, Scott NW, Smith WCS, Chambers WA. Long-term follow-up of breast cancer survivors with post-mastectomy pain syndrome. British Journal of Cancer 2005;92:225—30.
[42] Katz J, Poleshuck EL, Andrus CH, Hogan LA, Jung BF, Kalick DI, et al. Risk factors for acute pain and its persistence following breast cancer surgery. Pain 2005;119:16—25.
[43] Tasmuth T, von Smitten K, Hitanen P, Kataja M, Kalso E. Pain and other symptoms after different treatment modalities of breast cancer. Annals of Oncology 1995;6:453—9.
[44] Özalp G, Sarioglu R, Tuncel G, Aslan K, Kadiogullari N. Preoperative emotional states in patients with breast cancer and postoperative pain. Acta Anaesthesiologica Scandinavica 2003;47:26—9.
[45] Wallace MS, Wallace AM, Lee J, Dobke MK. Pain after breast surgery: a survey of 282 women. Pain 1996;66:195—205.
[46] Salmon RJ, Ansquer Y, Asselain B. Preservation versus section of intercostal-brachial nerve in axillary dissection for breast cancer-a prospective randomized trial. European Journal of Surgical Oncology 1998;24:158—61.
[47] Torresan RZ, Cabello C, Conde DM, Brenelli HB. Impact of the preservation of the intercostobrachial nerve in axillary lymphadenectomy due to breast cancer. The Breast Journal 2003;9(5):389—93.
[48] Tasmuth T, Blomqvist C, Kalso E. Chronic post-treatment symptoms in patients with breast cancer operated in different surgical units. European Journal of Surgical Oncology 1999;25:38—43.
[49] Gerber L, Lampert M, Wood C, Duncan M, D'Angelo T, Schain W, et al. Comparison of pain, motion, and edema after modified radical mastectomy vs. local excision with axillary dissection and radiation. Breast Cancer Research and Treatment 1992;21:139—45.
[50] Deutsch M, Flickinger JC. Shoulder and arm problems after radiotherapy for primary breast cancer. American Journal of Clinical Oncology 2001;24(2):172—6.
[51] European Society of Regional Anaesthesia and Pain Therapy, www.postoppain.org.