Paper I

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A bilateral clinical model for the study of acute and chronic pain after breast-reduction surgery

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Background: There is a need for new clinical models to investigate effectively the development of pain after surgery and the effect, if any, of pre-emptive treatment. Bilateral models are of special interest, since the patient serves as his/her own control. The objective of this preliminary study was to test a clinical model for the study of acute and chronic pain after bilateral reduction mammoplasty.
Methods: Eight patients participated in the study where the breasts were randomized to test and control groups. In each patient, one breast was preoperatively infiltrated with lidocaine and adrenaline and the other breast infiltrated with saline and adrenaline. Assessment included visual analogue scale (VAS) pain intensity, thermal thresholds, mapping for punctate hyperalgesia and tactile sensation. Assessments were made preoperatively, postoperatively and at 6 months after surgery.
Results: With regard to acute postoperative pain intensity, the model demonstrated a clear difference between lidocaine and placebo treated breasts. There was no difference between lidocaine and placebo treated breasts with regard to chronic pain, but these results are inconclusive due to small number of patients.
Conclusion: The model is sensitive and may be useful in studies of mechanisms of development and prevention of chronic pain after surgery.

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Key words: Pre-emptive analgesia; bilateral model; postoperative pain; lidocaine infiltration; thermal thresholds.

POSTOPERATIVE PAIN is a common and difficult problem encountered in clinical practice. It is reported that 50–70% of patients experience severe, and 20–40% moderate pain after surgery (1). This makes postoperative pain one of the most common forms of acute pain.

There is an increasing body of literature reporting chronic pain syndromes after surgery. Several reports (2–5) cite development of chronic pain following mastectomies, i.e phantom breast pain, scar pain and postmastectomy pain. In our own clinic, the results of a questionnaire study in 1994 revealed that 47% of patients experience chronic pain and/or dysaesthesia following breast reduction mammoplasty. In 50% of these patients pain was located to the scars. Chronic postoperative pain is typically refractive to treatment. Therefore, effective preventive measures are important. The studies of both Tasmuth et al. (4) and Katz et al. (6) show how important acute pain is for the development of chronic pain after surgery.

Peripheral tissue damage or nerve injury often leads to pathological pain processes such as hyperalgesia, allodynia and spontaneous pain that persist despite tissue healing. These phenomena may be demonstrated using quantitive sensory testing (QST).

Peripheral neural mechanisms such as nociceptor sensitization and neuroma formation have previously been regarded as the most likely explanations for such chronic pain phenomena. In recent years, however, evidence has been accumulating, indicating that changes in central neural functions may also play a significant role in persisting pain (7).

Experimental studies have shown that stimulation of C-fibres leads to changes in spinal dorsal horn neuronal activity (8, 9). Nachemson et al. (10) have demonstrated in rats that spinal dorsal horn neurons may even be damaged following tissue injury such as a surgical procedure. They propose this to be a nociceptor driven excitotoxic insult which may well contribute to persistent postoperative pain since some of the damaged neurons may represent pain inhibiting interneurons.

The recognition that central nervous system changes produced by afferent nociceptive activity can induce longlasting pain syndromes, has led to the concept of pre-emptive analgesia (11). Pre-emptive analgesia aims to reduce or inhibit these central nervous system functional changes by, for example, reducing the afferent barrage of nociceptive signals which arise as a direct result of surgery. Sotgiu et al. (12) demon-

strated in an animal study that lidocaine pretreatment prevents behavioural and thermal manifestations of neuropathy in rats. A recent study (13) in dogs found that preoperative pethidine clearly reduces postoperative hyperalgesia. Whether a similar result is clinically possible in humans remains to be shown, and the concept of pre-emptive analgesia so far has proved disappointing (14, 15). This is in part because of misunderstanding of the neurophysiology behind the sensitization process (16, 17) and too simplistic a study design attempting to document pre-emptive analgesic effect (17). Recently Stubhaug et al. (18) demonstrated that perioperative ketamine plus morphine treatment reduces postoperative hyperalgesia following nephrectomy. More clinical studies are definitely needed but present methodological problems. There is a need for new clinical models in order to investigate effectively the development of pain after surgery and the effect, if any, of various forms of pre-emptive treatment. Bilateral models are of special interest as the patient serves as his/her own control.

The objective of this preliminary study was to test a new clinical model for the study of acute and chronic postoperative pain after bilateral reduction mammaplasty. Local infiltration with lidocaine was chosen as an active treatment to be compared with placebo. The results of a prospective, randomized, controlled, double-blind study are described.

Methods

The study was approved by the regional Ethics Committee and by the Norwegian Medicines Control Authority (SLK). Eight healthy (American Society of Anesthesiologists physical status 1) females scheduled to undergo elective bilateral reduction mammoplasty were included in the study after having given informed consent. The patients' ages ranged from 18 to 34 years (mean 28.5 years). Patients having undergone previous major breast surgery, using regular analgesics or having known alcohol, drug or medication abuse were excluded from the study.

Sensory and pain measurements

Within 4 weeks prior to surgery the patient was assessed to establish baseline values for sensory thresholds. Threshold temperatures for sensations of cold, warmth, and heat pain were determined by a computerized Thermotest (Somedic A/B, Sweden), as described by Warncke et al. (19). Thermal thresholds were determined from a baseline temperature of 32°C with a 1°C/s rate of change. If cut-off temperatures (10°C and 52°C) were reached before the subject pressed the button, the temperature of the thermode automatically returned to baseline. Warmth threshold (WT) was defined as the lowest temperature above 32 °C perceived as warm, and heat pain detection threshold (HPDT) as the lowest temperature above 32°C perceived as painful. Cold threshold (CT) was defined as the highest temperature below 32°C perceived as cold. The warmth and cold threshold values were calculated as the average of five consecutive temperature recordings. The heat pain detection threshold values were determined as the average of five recordings with 15 s intervals.

Measurement of thermal thresholds was performed at all times on the lower medial quadrant of each breast, approximately 1 cm from the vertical and horizontal surgical wounds/scars, in order to be as close as possible to the wound area, without actually testing over the wound. To ensure intrapatient control (20), the measurement of thermal thresholds was always preceded by measurement of thermal thresholds in the thenar area of both hands.

Sensory investigation of the breasts included testing the whole breast, systematically from the areola to the periphery and in a clockwise manner, with hand-held nylon filaments (von Frey hair, in ascending order of force) and with camel hair brush.

The patient was instructed in the use of a visual analogue pain scale (VAS).The VAS scale was from 0 to 100. Three separate VAS measurements for breast pain were performed for each breast: the patient resting supine, on coughing, and on elevation of the ipsilateral arm. All patients were pain-free (VAS 0) prior to surgery.

Anaesthesia and postoperative analgesia

All patients received a standardized general anaesthesia: premedication with oxazepam, induction with pentothal sodium, fentanyl and muscle relaxation with pancuronium. Anaesthesia was maintained with nitrous oxide/oxygen, isoflurane and fentanyl. Glycopyrrolate/neostigmine was used for reversal of muscle relaxation.

Analgesics for postoperative pain relief were administered according to the following protocol:

Day of surgery: rectal paracetamol 1000 mg×3 and Ketogan® (ketobemidon 5 mg+(RS)-3-dimethylamino-1, 1-diphenylbut-1-en (A29) 25 mg) 0.5 ml iv or 1 ml im on request.

Day 1: Paracetamol tablets 1000 mg×3 and Ketogan® 5 mg im on request.

Day 2: Tablets containing paracetamol 400 mg+ codeine 30 mg (Paralgin forte®) 1–2 tablets on request, but not more than 8 tablets daily.

The patients' breasts were randomized to test and control groups. Each patient received preoperative infiltration with 100 ml lidocaine (5 mg/ml) with adrenaline (5 μg/ml) in one breast and 100 ml 0.9% saline with adrenaline (5 μg/ml) in the other breast. The procedure was performed double blind. Infiltration was completed 5 min prior to incision. The dose of lidocaine was the maximum single dose approved by the Norwegian authorities (SLK). Plasma levels of lidocaine were measured 1, 3, 6, 8, 10 and 12 h after start of infiltration and in no patient reached toxic levels. The pharmacokinetic results are planned to be published separately. The surgery was performed by the same surgeon using the superomedial pedicle technique. The incision was closed in layers with 3.0 and 4.0 absorbable sutures and the skin closed with stainless steel staples.

Outcome measures

Pain intensity (VAS) was recorded at 2, 3, 4, 6, 8 and 10 h after wound closure, at the postoperative control between 9 and 16 days after surgery, and at 6 months after surgery.

Sensory testing as described above was performed at the postoperative control 9–16 days after surgery and at 6 months after surgery. Primary outcome measures were sum of VAS 2–10 h after wound closure for acute pain and Δ change of thermal thresholds, threshold for cold, heat pain detection threshold and area of touch allodynia and punctate hyperalgesia. Occurrence of spontaneous pain at 6 months after surgery was taken as an indication of chronic post-reduction mammoplasty pain.

Statistics

For measurements over time (i.e. VAS pain intensity scores) the area under the curve (AUC) was calculated for lidocaine and saline responses. In order to avoid the multiple testing problem, the AUC values, rather than the original values, were used in the statistical analysis. The difference between saline and lidocaine responses was evaluated using the Wilcoxon signed rank test. All *P*-values are two sided and $P<0.05$ was considered to be significant.

Results

The first patient included in the study had to be excluded due to spillage of the study drug. Patients number 2–9 completed the study.

Acute postoperative pain

The sum of VAS scores for pain intensity was significantly lower in the lidocaine group than in the placebo group for the entire registration period of 10 h after wound closure. The median VAS score in the lidocaine treated breast group was 5 compared to 23 in the placebo group. The results are shown in a whisker box plot (Fig. 1). The box (rectangle) indicates the middle 50% of the data, from the 25 percentile to the 75 percentile. The median is marked with a horizontal line inside the box. The whiskers indicate the upper and lower 25% of the data.

VAS pain intensity scores for the immediate postoperative period and at 11 days are shown in Table 1.

Sensory changes after surgery

Thermal thresholds

There was no statistically significant difference between lidocaine and placebo groups regarding thermal thresholds. Thermal threshold values are presented in Table 2. A total of five patients exhibited large changes (±5°C) in temperature thresholds 11 days after surgery. The three patients who reported ongoing breast pain at the 6 month control (patients 2, 7 and 8) showed significant thermal threshold changes at 6 months.

Sensory mapping with brush and von Frey filaments

A total of three patients demonstrated sensory changes at 6 months. All three patients showed areas of reduced sensibility for touch and punctate pressure. One patient exhibited a small area of punctate hyperalgesia in one breast at the 6 month control. No patient reported allodynic response to the camel hair brush. There was no significant difference between

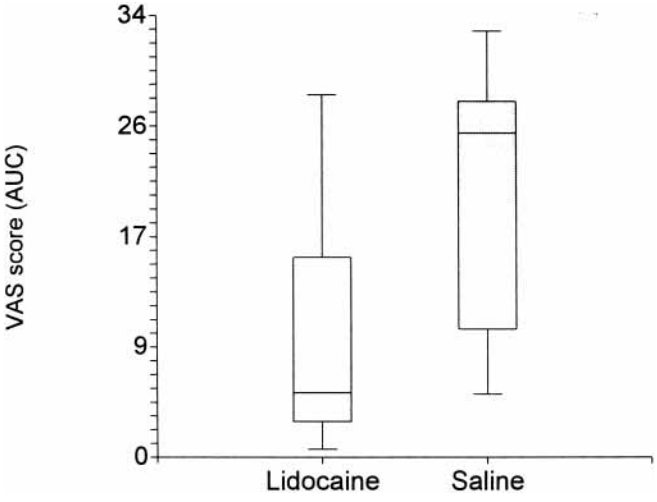

Fig. 1. Sum of pain intensity scores for the 10 h observation period (AUC).

Table 1

Postoperative VAS scores (0–100).

	2 h		3 h		4 h		6 h		8 h		10 h		11 days	
	Lid.	Sal.	Lid.	Sal.	Lid.	Sal.	Lid.	Sal.	Lid.	Sal.	Lid.	Sal.	Lid.	Sal.
Patient 2														
At rest	68	90	0	18	0	0	4	6	0	2	0	16	0	40
Coughing	68	90	0	18	0	0	4	6	0	2	0	20	0	40
Raising arm	68	100	0	55	4	36	7	35	0	38	3	45	0	50
Patient 3														
At rest	60	56	74	50	20	19	40	36	60	59	0	5	3	3
Coughing	72	49	74	50	20	19	40		60	50	0	5	3	3
Rasing arm	18	25	27	22	5	0	11	14	40	11	4	3	6	10
Patient 4														
At rest	25	25	0	0	0	0	0	14	0	0	0	0	0	0
Coughing	25	25	0	0	0	0	0	14	0	0	0	0	6	3
Raising arm	25	25	25	22	16	0	0	14	16	16	11	12	0	0
Patient 5														
At rest	0	21	0	6	0	0	0	0	21	20	0	0	0	0
Coughing	0	21	0	6	0	0	0	0	21	20	0	0	0	0
Raising arm	6	49	5	32	5	40	5	49	21	49	23	45	29	41
Patient 6														
At rest	0	30	0	50	0	60	0	21	0	0	0	0	0	0
Coughing	0	30	0	65	2	60	2	29	0	23	0	2	1	0
Raising arm	0	30	0	65	0	60	2	29	0	23	0	2	1	0
Patient 7														
At rest	0	60	0	50	0	36	0	19	41	59	0	13	0	9
Couging	0	60	0	50	0	50	0	19	41	61	0	13	0	9
Raising arm	50	75	0	75	35	50	36	37	41	62	10	30	31	45
Patient 8														
At rest	22	38	22	50	0	10	0	15	0	15	0	12	0	0
Coughing	18	38	22	50	0	10	0	22	0	22	0	32	0	0
Raising arm	15	50	22	50	16	22	38	50	38	50	25	51	9	9
Patient 9														
At rest	41	45	25	50	23	43	0	0	0	40	26	38	25	0
Coughing	41	45	25	50	23	43	0	0	0	40	26	38	25	0
Raising arm	41	45	25	50	23	43	0	0	0	40	26	38	39	27

lidocaine-adrenaline and saline-adrenaline infiltrated breasts. The results are presented in Fig. 2.

Chronic postoperative pain

At the 6 month control patients were asked whether they had any pain or discomfort following surgery. No patient had pain at the time of testing; however, three patients reported ongoing periodic pain.

Patient 2 reported tenderness in scar areas bilaterally. This patient had shortly before the 6 month control undergone bilateral cosmetic scar correction under local anaesthesia and had bilateral substantially raised warmth thresholds (WT) (Table 2).

Patient 7 reported periodic, stabbing pain localized "deep" in the lidocaine treated breast. This patient exhibited sensory changes with WT value approaching HPDT, indicating reduced sensibility and possibly neuropathic pain.

Patient 8 reported periodic aching in both breasts since surgery and at the postoperative control exhibited obvious sensory changes with reduced sensation of both heat and cold in both breasts, and dysaesthesia in both breasts on thermal stimulation. Dysaesthesia was still present in the left breast on assessment 6 months after surgery.

Discussion

The main objective of this study was to investigate the possibility of using reduction mammoplasty as a bilateral model in clinical pain research. With regard to acute postoperative pain, it demonstrates a clear difference between placebo and lidocaine treated breasts, despite the small number of patients. For chronic postoperative pain no statistically significant differences between lidocaine and saline treated breasts were observed. Due to the small number of patients, the results are inconclusive. Still, the study indicates that the bilateral model is useful for investigations involving peripheral analgesic interventions in chronic as well as acute pain. This is a pilot study, and in a larger study we would suggest modification

Table 2

Thermal thresholds.

		Thresholds lidocaine treated breast (°C)			Thresholds saline treated breast (°C)			
Pt.nr.	Test	Warmth	Cold	Heat pain	Warmth	Cold	Heat pain	Comments
2	Preop.	33.2	30.6	47.8	34.4	28.7	44.7	Postop.: Saline breast: difficulty detecting cold stimulus
	Postop.	35.7	28.1	43.8	36.5	21.5	44.3	
	6 mths.	38.2	27.2	46.5	39.8	27.2	45.4	
3	Preop.	33.8	28.1	45.6	33.8	30.4	46.1	Postop.: Saline breast: trouble detecting warm stimulus.
	Postop.	34.8	30.5	42.5	39.3	29.8	45.0	Dysaesthesia
	6 mths.	35.4	30.9	46.9	37.3	30.2	44.4	
4	Preop.	38.5	30.2	45.1	35.6	29.0	43.8	
	Postop.	38.1	30.0	45.2	35.1	29.6	44.2	
	6 mths.	42.1	26.6	46.8	35.7	30.4	45.9	
5	Preop.	34.4	30.6	44.6	33.7	30.6	45.8	
	Postop.	34.6	31.1	40.7	36.4	30.8	46.2	
	6 mths.	34.2	30.6	46.9	35.1	30.6	46.4	
6	Preop.	35.9	17.6	46.2	37.3	25.2	46.7	
	Postop.	38.0	25.3	47.0	35.8	31.0	46.6	
	6 mths.	39.1	14.8	48.2	40.4	27.6	47.6	
7	Preop.	37.9	30.8	46.2	36.4	28.9	46.1	6 mths.: Lidocaine breast: difficulty detecting warm stimulus. Pricking, stabbling dysesthesia. Saline breast: cold stimulus feels warm
	Postop.	37.2	30.2	46.9	38.2	27.0	47.0	
	6 mths.	46.7	24.8	47.8	40.6	20.9	48.1	
8	Preop.	34.6	29.3	40.9	34.4	29.4	41.8	Postop.: Saline breast: no sensation of warmth (not measurable). No sensation of cold (NM). Warm stimulus perceived as icy sensation. Lidocaine breast: perceives warm stimulus only in small area, latency. No sensation of cold. Dysaesthesia. 6 mths.: Lidocaine breast: dysaesthesia
	Postop.	41.9	NM	NM	NM	NM	NM	
	6 mths.	45.0	NM	46.2	41.4	27.0	46.6	
9	Postop.	36.4	28.3	45.8	43.5	24.2	46.6	6 mths.: Saline breast: no sensation of cold. Heat threshold perceived as stabbing pain. Lidocaine breast: difficulty detecting warm stimulus
	Preop.	34.3	30.0	50.5	35.7	30.1	42.5	
	6 mths.	41.0	28.7	47.1	45.1	NM	47.2	

of the protocol. We performed three VAS pain intensity measurements: ''at rest'', ''coughing'' and ''raising the ipsilateral arm''. Measurement on coughing gave no added information and may be excluded. Sensory testing of the breasts with von Frey filaments is time-consuming and gave little extra information. We would therefore recommend that sensory testing with von Frey filaments be reserved for those patients reporting persistent pain. In general, more focus should be placed on a careful, diagnostic evaluation of the chronic pain. QST should therefore also include testing for cold pain.

We report a high incidence of sensory changes and chronic pain (25%) occurring after reduction mammoplasty, even though the number of patients is very small. This is consistent with previous reports of chronic pain after reduction mammoplasty (22% in 5). The prevalence of chronic pain after mastectomy is reported to be higher and may be due to additional painful procedures such as radiotherapy. The three patients reporting chronic pain in this study were those who also exhibited substantial thermal threshold changes and reduced tactile sensibility at 6 months after surgery. Similar sensory changes are often associated with neuropathic pain. At the 6 month control, patient 7 perceived cold stimulus in the saline treated breast as warm. This paradoxical experience may indicate loss of cold-induced A fibre gating (21). No patient in the study exhibited touch allodynia or significant punctate hyperalgesia. Patient 7 exhibited normal thermal thresholds at the 11 day control, but significantly changed thresholds in both breasts at the 6 month control. This would suggest that something has happened between the 11th day and 6 month testing, for example wound infection. However, patient 7 had normal wound healing, as did all patients in the study. Another possible explanation is that since thermal threshold testing was performed quite close to the wound area, subsequent local tissue changes such as scar or keloid formation could give altered thermal thresholds.

Nachemson and Bennett's (10) animal study demonstrates that surgical procedures, by their very nature, may potentially give rise to tissue injury induced

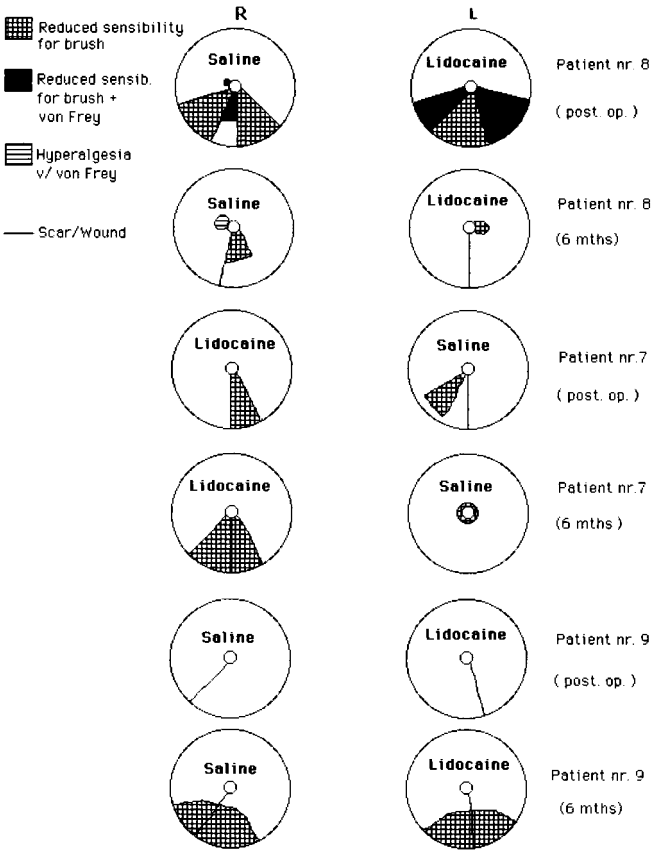

Fig. 2. Sensory changes 11 days and 6 months after surgery.

central neural changes, which in turn can give rise to pathological pain states. However, only some patients who undergo surgery develop persistent pain. It has, for example, been shown that not only the acute pain intensity but also psychological factors such as depression and anxiety during the acute phase of pain can affect the later development of chronic pain (6, 22). The affective component of pain in humans also makes the simple comparison of pain intensity in different patients liable to error. Clinical trials designed to address this problem are therefore fraught with methodological difficulties. The bilateral model in this study effectively eliminates this particular source of error, the patient serving as her own control. The model is, however, limited to the investigation of locally applied drugs that are not absorbed to give systemic effects affecting hypersensitivity phenomena in the central nervous system.

The study has also indicated two interesting findings: a surprisingly longlasting effect of lidocaine with adrenaline on postoperative acute pain. Preoperative infiltration with lidocaine gave significantly lower VAS pain scores compared with placebo, for at least 10 h after infiltration. Infiltrated lidocaine with adrenaline is generally considered to have a much shorter duration of action (2–6 h) (23). Basic scientific findings indicate that it is the amount of incoming pain signals to the central nervous system which determines the development of long-term potentiation (LTP) in dorsal horn cells (24). Local anaesthetic, applied preoperatively, would theoretically reduce this afferent barrage. However, the effect is relatively shortlasting and it would be expected that LTP would develop as soon as the local anaesthetic effect wears off. Methods with longer acting local anaesthetics or continuous application could be investigated using this model.

To prevent unnecessary blood loss, both breasts were infiltrated with adrenaline. Wei et al. (25) have demonstrated that a peripherally administered α2-adrenoceptor agonist effectively attenuates mechanical allodynia induced by an experimental model of chronic neuropathy in the rat. It would therefore be of interest to investigate whether chronic allodynia develops more often after surgery performed without adrenaline infiltration.

There are to date few reports concerning sensory changes and chronic pain after surgery. The subject of pre-emptive analgesia is still controversial. Studies have shown conflicting results, despite the interesting hypothesis developed from basic science models. It would perhaps be more productive to examine preemptive analgesia in the light of chronic postoperative pain, and not just in relation to acute postoperative pain. A still unanswered question is whether pathological pain occurring after surgery is a peripheral, or a mainly central phenomenon. We have presented a clinical model which may be used to investigate the occurrence of and possibly the prevention of chronic postoperative pain.

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