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A double blind, randomised, placebo-controlled trial of continuous sub-pectoral local anaesthetic infusion for pain and shoulder function following mastectomy:

SUB-pectoral Local anaesthetic Infusion following MastEctomy (SUBLIME) study

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Abstract

Introduction

Over 16,000 mastectomies are performed in England and Wales annually. Acute postoperative pain and nausea are common. The most frequently occurring long term complications are chronic pain (up to 50%) and reduced shoulder function (reported at 35%). Regional techniques that improve acute postoperative pain relief may reduce the incidence of these complications. This study assesses the effectiveness of a 24 hour continuous local anaesthetic in the sub-pectoral plane in improving post-operative pain and quality of life in patients undergoing mastectomy.

Methods and analysis

This is a randomised, double blind, placebo-controlled, multi-centre, parallel group trial in females undergoing mastectomy with or without axillary involvement. One hundred and sixty participants will be randomised in a 1:1 ratio to receive either 0.25% levobupivacaine or 0.9% saline by sub-pectoral infusion post-operatively for 24 hours. All participants will be provided with an intravenous morphine patient-controlled analgesia (PCA) system. Participants will be followed-up for 24 hours in hospital and at approximately 14 days and six months post-operatively. Joint primary outcome measures are total morphine consumption and total pain score (captured via patient-recorded visual analogue scale (VAS) 4 hourly) during the first 24 hours post-operatively. Primary statistical analysis of total pain is based on the area under the curve of pain versus time graph. Secondary outcomes include PCA attempts in first 24 hours; VAS pain scores and shoulder function by goniometry at 24 hours, 14 days (approximately) and six months; VRS pain scores in first 24 hours; Brief Pain Inventory and Oxford Shoulder Score at six months; duration of hospital stay; incidence of post-operative nausea and vomiting; cost-effectiveness.

Ethics and dissemination

The study is approved by the South West England Research Ethics Committee (12/SW/0149). Results will be published in a peer-reviewed journal and presented at local, national and international scientific meetings.

Trial registration

ISRCTN46621916. EudraCT 2011-005775-16.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

- This is a double-blind, randomised, placebo-controlled trial.
- This is the first study to assess the use of a continuous local anaesthetic infusion in the sub-pectoral plane.
- This is the first study to assess the effects of continuous local anaesthetic infusion on post-operative shoulder function.
- The study includes an assessment of longer-term pain.

Limitations

- All instruments for measuring post-operative pain, including those used in this study, have limitations. We have attempted to address this by using two measures, morphine consumption and VAS scores, as joint primary outcomes.
- Changing surgical practice means that fewer simple mastectomies are being performed in comparison with breast conservation (wide excision) surgery and skin-sparing mastectomy with

immediate reconstruction. This study does not address whether any benefits demonstrated can be extrapolated to these procedures.

- The study does not assess the effects of surgeon variation or duration of surgery on pain and recovery outcomes for patients.
- The study does not assess the level of sedation in the post-operative period. Reduced sedation is a potential benefit of reduced morphine consumption

INTRODUCTION

In 2010, the lifetime risk in women of developing breast cancer was estimated as 1 in 8, with the disease now the most commonly occurring cancer in the UK [1]. Surgery remains the treatment of choice, with around 43% of women with breast cancer opting for mastectomy [2]. A total of 16,595 mastectomies were performed in England and Wales in 2012-2013 [3]. The most common complications of mastectomy are post-operative acute and chronic pain and slow recovery of shoulder function. Acute pain in mastectomy patients is currently managed with systemic opiates, either by intramuscular injection or using an intravenous patient-controlled analgesia (PCA) device. Chronic post-operative pain is frequent (20–45%) [4-7] and requires significant use of NHS resources. Poor recovery of shoulder function, associated with initial poor analgesia, impacts on quality of life long after the initial recovery period [8,9]. These effects are all the more significant considering the young age at which many patients present.

Post-operative analgesia therefore remains a challenge for these patients despite a range of treatment options [10]. Most post-operative pain in mastectomy occurs within the first 24 hours of surgery. Inadequately managed pain in the acute post-operative phase is a major risk factor of chronic pain syndromes [11], which are present in up to 50% of patients six months after operation [12]. Impaired shoulder function also causes significant problems post-mastectomy [13-15] and it has been suggested that better post-operative analgesia may enhance the effects of early physiotherapy. There is no gold standard for pain relief following mastectomy surgery [10]. Morphine, the mainstay of therapy, is associated with vomiting and excessive drowsiness. Thoracic epidural and paravertebral blocks have been shown to provide adequate analgesia [10], but associated complications (e.g. pneumothorax), although rare, are severe and potentially life threatening. Local anaesthesia wound infiltration has not been adequately studied using randomised controlled trials [10]. An informal survey of current practice in the South West Peninsula of England suggested that its use is patchy and erratic, with a third of surgeons not using any at all and others reporting a range of different methods of administration and doses.

The use of wound catheters to deliver continuous local anaesthetic has been shown to reduce post-operative pain and analgesic requirements in cardiothoracic, orthopaedic and general surgery [6,16,17]. The nerve supply to the breast is predominantly from the lateral and anterior branches of the 2nd to 6th intercostal nerves and the supraclavicular nerves [18]. Nerves pass beneath the pectoral fascia before reaching the breast and it is here that local anaesthetic may be deposited via a catheter, as a bolus or sub-pectoral infusion. The ‘Pecs block’ was described in 2011 [19] as a technique for placing local anaesthesia in the sub-pectoral plane at the time of surgery. There have since been a number of similar descriptions of ultrasound-guided chest wall local anaesthetic techniques for use in breast surgery [20-22]. Case reports and small studies indicate that these techniques are efficacious in reducing post-operative pain, however there are, as yet, no large randomised controlled trials. So far these techniques have not been described with the use of continuous local anaesthetic infusion.

Current published research relating to post-mastectomy local anaesthesia infusion is scant. A meta-analysis of surgically placed wound catheters concluded that there was a trend towards improved analgesia in the immediate post-operative period, however studies were underpowered and often poorly designed [23]. One randomised study [24] of 42 patients found no significant difference in post-operative analgesia (as measured by PCA use and pain scores) between administration of 4-hourly 20ml bolus doses of 0.5% bupivacaine and placebo. However, the technique tested involved infiltration via wound drains which deposited local anaesthetic in a more superficial tissue plane than the sub-pectoral plane and did not use a continuous infusion. Non-randomised, non-blinded, retrospective and observational studies of local anaesthetic infusion [25-27] suggest more favourable results. Baroody et al. [26] demonstrated a five-fold reduction in analgesic requirement following local anaesthetic infusion after reconstructive breast surgery. Morrison et al. [25] compared post-operative opioid use with placebo in mastectomy patients receiving local anaesthetic infusions and found a significant reduction in opiate use and hospital length of stay in the local anaesthetic arm. However, this was an unblinded retrospective analysis and made no attempt to investigate chronic pain or arm mobility. Lu et al. [27] compared local anaesthetic infusion to placebo in patients undergoing reduction mammoplasty and reconstruction. Results showed reductions in opiate use and pain scores in the local anaesthetic group but controls were historical and the study was unblinded and not randomised. Given the limitations of the study designs, it is currently difficult to make firm conclusions or recommendations for clinical practice. There are no published studies assessing the impact of local anaesthetic infiltration on post-operative shoulder function. There has recently been increased interest in post-operative local anaesthesia for the reduction of chronic pain. A 2012 Cochrane analysis pooled the results of two trials and concluded that paravertebral block may favour the reduction of chronic pain following mastectomy in one in five patients [28].

Levobupivacaine is the S(-)-isomer of bupivacaine. In common with other local anaesthetic agents, it is widely accepted that Levobupivacaine blocks nerve conduction in sensory and motor nerves by blocking voltage sensitive sodium channels in the cell membrane. Levobupivacaine exhibits fewer cardiovascular toxicity effects [29,30] than bupivacaine and, as such, is safer for use as an infusion. There appears to be no measurable difference in clinical effectiveness between the two agents [31].

The aim of this study is to establish whether the use of continuous local anaesthetic infusion in the sub-pectoral tissue plane can improve post-operative analgesia and quality of life for patients undergoing mastectomy with or without axillary surgery. If the use of this local anaesthetic infusion technique is shown to be more effective than current practice, the reduction of pain and opiate use in the immediate post-operative period would be a significant benefit to patients. The technique also holds the potential to improve patients' quality of life by reducing the longer term risks of chronic pain and impaired shoulder function.

METHODS AND ANALYSIS

Study design

The study is a double blind, randomised, placebo-controlled, multi-centre, parallel group trial in 160 female patients undergoing mastectomy with or without axillary involvement. Participants will be randomly allocated to receive either 0.25% levobupivacaine or 0.9% sodium chloride by sub-pectoral infusion post-operatively for 24 hours. All participants will be provided with an intravenous (IV) morphine PCA system. Participants will be followed up for 24 hours in hospital and at approximately 14 days and six months post-operatively as out-patients.

Setting and participants

The study is being conducted in breast surgery departments within NHS Trusts in England. Eligible patients comprise all women presenting for unilateral mastectomy, with or without planned axillary clearance, at one of the participating hospitals. Main exclusion criteria are: primary reconstructive surgery; hypotension or hypovolaemia; allergy or sensitivity to local anaesthetic agents, morphine, paracetamol, ondansetron or cyclizine; daily opioid analgesic use; pregnancy. Study participants are patients who meet the screening criteria and are willing and able to give informed consent.

Study recruitment

The recruitment process is designed to fit in with routine clinical practice. Potential participants are identified from those attending out-patient breast clinics for discussion of breast cancer diagnosis and treatment options. Surgery is usually scheduled within a month of the initial clinic appointment, following attendance at a pre-assessment clinic. Women attending clinic for discussion of prophylactic mastectomy may also be eligible to participate in the study.

Patients for whom mastectomy is a potential treatment option and who appear eligible for the study are given a brief verbal introduction to the study by a clinician or nurse at the initial breast clinic consultation and provided with either a brief written study summary or a full participant information sheet, as deemed appropriate. Patients are subsequently telephoned within a few days by the breast care nurse (or research nurse, depending upon local arrangements) and further information about the study is provided verbally and/or by post to patients who express further interest. Patients who are interested in participating in the study are invited to meet the research nurse at the routine pre-operative assessment clinic so that any further questions can be answered and eligibility for the study confirmed. Arrangements are made for the patient to discuss aspects of the study with the surgeon or anaesthetist if required. Written informed consent is obtained from patients willing and eligible to participate, by an appropriately trained member of the research team. Patients who decline to take part in the study are not obliged to give a reason for declining but the reason(s) are recorded by the research nurse if provided.

Study procedures

Figure 1 shows the participant pathway through the study. Following informed consent, each participant is assigned a unique study number. Baseline data are normally collected at the pre-operative assessment clinic, following consent. At this point the research nurse briefly explains use of the morphine PCA system and familiarises the participant with the visual analogue scale (VAS) pain scoring system. Each VAS score is recorded on a separate page of a mini flipchart. The participant turns the page of the flipchart after an entry is made, so that the previous score is not visible for comparison when the next score is recorded.

Interventions

The active investigational medicinal product is 0.25% levobupivacaine (Chirocaine), an established local anaesthetic infusion agent, prepared as a 2.5mg/ml solution and packaged by the manufacturer (Abbott) in ampoules for injection. The comparator solution, 0.9% sodium chloride, is sourced from standard NHS supplies at the participating sites. Active and comparator trial treatments are presented identically in infusion bags prepared by the local hospital pharmacy prior to the operation date and supplied on an individual patient basis according to treatment allocation. Bags are presented in heat-sealed outer packaging and labelled in accordance with current EU regulatory requirements for clinical trials. Each bag is assigned a unique code number and a seven day expiry date.

Anaesthesia and surgery

Study participants receive a standardised anaesthetic protocol with respect to analgesic and antiemetic medication (Appendix 1). Mastectomy is performed with/without sentinel lymph node sampling or clearance, as clinically indicated.

Delivery of trial treatment

Trial treatment is delivered by means of an infusion catheter and device, supplied as a sterile pre-packed kit and licensed for the delivery of local anaesthetic. At the end of the surgical procedure the surgeon inserts the infusion catheter percutaneously into the sub-pectoral plane under direct vision within the surgical field. After skin closure, a 20ml bolus of active or comparator treatment is given via the catheter, which is then connected to the infusion device to provide an infusion of trial treatment at a continuous rate of 5ml/hr for 24 hours. In the active treatment arm this equates to a 50mg bolus of levobupivacaine followed by an infusion of 12.5mg/hr.

Post-operative management and outcome assessment

In the Recovery Unit, post-operative pain is routinely managed with 2-3mg aliquots of IV morphine to achieve a Verbal Rating Scale (VRS) pain score of none-mild pain. All participants are provided with a PCA system set up to deliver IV morphine boluses of 1mg with a 5 minute lock-out and no background infusion. Once all other routine recovery discharge criteria have been met, the patient is transferred to the ward. A baseline VAS pain score is recorded prior to transfer to the ward.

Participants are asked to complete VAS pain scores at rest every four hours, with reminders from ward staff. The sub-pectoral infusion is discontinued after 24 hours and the catheter removed, together with the PCA system. Outcome measures are assessed at 24 hours and at routine follow-up visits, approximately 10-14 days and six months after the day of surgery (Table 1).

Table 1: Trial schedule

	Pre-operative		*Post-operative*		
	Baseline	OPERATION AND SET-UP OF TRIAL INFUSION	24hrs	14 days*	6 months
Screen/eligibility	x				
Consent	x				
BMI	x				
Concomitant medication	x			x	x
Oxford Shoulder Score (OSS)	x				x
Shoulder questions (from OSS)				x	
Shoulder goniometry	x		x	x	x
EQ-5D 5L	x			x	x
Randomisation	x				
VAS pain score			x	x	x
VRS pain score			x		
PCA attempts			x		
Total morphine consumption (oral/IV)			x		
Analgesia use			x	x	x
Adverse events			x	x	x
Brief Pain Inventory					x
Service use					x

*Approximately 10-14 days post-operatively according to local practice

Primary outcome measures

The joint primary outcomes are (i) total morphine consumption (mg) in the first 24 hours (defined as the 24 hours following commencement of the sub-pectoral infusion), including all morphine given in the Recovery Unit and cumulative PCA use as recorded by the PCA device and (ii) total pain over the first 24 hours, as defined by measurement of the area-under-the-curve of each participant's self-reported pain scores at rest, measured using a visual analogue scale (VAS). VAS pain scores are recorded in the Recovery Unit and then at four hourly intervals for the first 24 hours. The VAS is presented as a 100mm horizontal line with verbal anchors at each end of "no pain" and "worst pain possible". The study participant selects and marks with a pen the point along the line that reflects their current pain perception. Periods of sleep are recorded retrospectively by the participant.

Secondary outcome measures

Secondary outcome measures include the number of PCA attempts in the first 24 hours following commencement of infusion; VAS pain scores at rest at 24 hours, 14 days and six months after surgery; incidence of post-operative nausea and/or vomiting (PONV) and use of supplemental analgesics and post-operative anti-emetics in the first 24 hours; self-reported analgesia use at 14 days and six months; duration of hospital stay; shoulder movement assessed by goniometry at 24 hours, 14 days and six months following surgery; Brief Pain Inventory at six months; shoulder function (as measured by the validated Oxford Shoulder Score [32]) at six months. Items from the Oxford Shoulder Score are also assessed at the first follow-up visit in relation to the previous seven days. Following the participant's discharge, the length of stay in hospital is recorded by the research nurse.

Randomisation

Patients who consent to participate and fulfil the eligibility criteria are randomly allocated to receive either levobupivacaine or saline in a 1:1 ratio via a secure web-based randomisation system. The allocation sequence is computer-generated by the UKCRC-registered Peninsula Clinical Trials Unit (CTU) in conjunction with an independent statistician, using a random permuted block design, with blocks of varying sizes. The block sizes will not be disclosed, to ensure concealment. As post-operative pain is expected to differ between patients who are having simple mastectomy, mastectomy with sentinel lymph node sampling or mastectomy with axillary node clearance, randomisation is stratified by planned surgical procedure, and by recruiting centre. To ensure that the study team, including the study statistician, remain blind to participants' allocated study groups, randomisation is undertaken by the relevant hospital pharmacy department.

Blinding and emergency unblinding

This is a double blind study and therefore participants, the surgical/anaesthetic team and the research team are unaware of each participant's allocated treatment group. To help assess the success of blinding, participants and the research nurse completing the follow-up assessments are asked to guess the participant's treatment assignment, at both the 14 day and 6 month follow-up visits.

In the event of a potential suspected unexpected serious adverse reaction (SUSAR), unblinding will be undertaken by the Sponsor in accordance with the regulatory requirements for safety reporting in Clinical Trials of Investigational Medicinal Products (CTIMPs). Unblinding may also be performed at the request of a senior clinician responsible for the care of a trial participant but such requests are likely to occur only in the case of an adverse clinical event and are expected to be rare. Any request to unblind treatment allocation for clinical reasons will be made directly to the relevant hospital pharmacy and the treatment allocation will be reported to the relevant clinician

according to an agreed procedure. The Chief Investigator and CTU trial manager will be kept informed of all instances of unblinding but remain blind to treatment allocations themselves wherever possible. The pharmacy and CTU will maintain a record of all requests for unblinding.

Sample size

The study sample size was calculated to assess the joint aims of the effectiveness of a 24 hour continuous sub-pectoral local anaesthetic infusion on total morphine consumption and total pain over the 24 hour post-surgery period. Few studies have addressed the question of what reduction in total morphine use after breast surgery might be clinically important. A small number of studies have reported total morphine use after breast surgery, at varying end points [33-40]. Four have reported total morphine use at 24 hours post-surgery; three of these were comparative studies. Two of these three studies based their sample size calculations on the same prior belief that the minimum clinically important difference was 10mg (estimated standard deviation of 10mg, estimated mean 24 hour total morphine consumption of 40mg) [39,40]. Therefore the minimum clinically important difference in 24-hour total morphine consumption was set as 10mg. These studies also showed actual standard deviations in 24 hour post-operative total morphine consumption of 10 to 22mg. To allow for the variability in the total morphine consumption being at the upper end of this range, the sample size calculation for total morphine consumption assumed a standard deviation of 20mg. To detect a difference of 10mg between groups, with 80% power and at the 5% significance level, requires 65 participants per group.

Similarly, there is a lack of information on which to base a formal sample size calculation for pain as the (joint) primary outcome measure. With the sample size of 65 participants per group, there will be approximately 80% power to detect an effect size of around 0.5 standard deviations on the measure of pain. Such an effect size would be considered as being of “moderate” size [41]. From studies using a single VAS pain measure, it has been suggested that clinically meaningful differences are of the magnitude of 20mm to 30mm on a 100mm VAS [42], whilst a recent review reported that at the group level the difference in pain levels varied from 4mm to 40mm for acute pain [43]. Assuming the standard deviation of the VAS is between 13mm [44,45] and 26mm [38,46], this suggests that clinically meaningful effect sizes are of the order of at least 0.8 standard deviations. To detect a difference of around 0.8 standard deviations would need 26 patients per group, assuming a two-sided significance level of 5%, with 80% power. Therefore, the sample size of 65 participants per group will be large enough to detect clinically relevant differences between groups, in terms of pain.

The primary outcome measures are at 24 hours with a minimal probability of drop out. However, enough participants will be recruited to attempt to ensure 65 participants per group are followed up at six months. As patients remain engaged with the breast service for clinical reasons, loss to follow-up is also expected to be low but there may be losses to the study because, for example, of the need for further surgery. Therefore, in order to achieve a study sample of 65 women per group at the six month follow-up, the aim is to recruit a total of 160 participants over a two year period, which allows for a loss to follow-up rate of just under 20%.

Statistical analyses

The primary analyses are all pre-specified and a detailed statistical analysis plan will be completed and agreed by the Data Monitoring Committee (DMC) prior to commencement of analyses. Data will be reported and presented according to the CONSORT statement [47]. Ninety five percent confidence intervals will be calculated and presented where possible. The trial statistician will be presented with a database by the CTU containing a group code for each participant but not identifying which group is which; only after final analysis will the individual groups be identified.

The primary statistical analysis will follow an intention-to-treat approach, with the intent-to-treat population defined as all trial participants who completed the baseline assessment and underwent surgery. A per protocol analysis may be undertaken as a sensitivity analysis. The analysis of adverse events will be presented on a per protocol basis.

The primary analysis will compare (i) total morphine consumption and (ii) 24 hour pain AUC at 24 hours post-surgery between the two groups using an analysis of covariance, including the stratification factors as covariates, with suitable transformation of total morphine consumption and pain AUC considered as necessary. The estimates of the differences in mean total morphine consumption and mean pain AUC will be presented, together with a 95% confidence interval for the difference. Secondary outcomes will be compared between groups in a similar way using analysis of covariance for continuous outcomes and logistic regression for binary outcomes such as incidence of post-operative nausea and/or vomiting and use of post-operative anti-emetics in the 24 hours following surgery. Comparisons of interest will be presented with 95% confidence intervals.

Interim analysis

An interim analysis will be undertaken after the 14 day follow-up data have been collected for the first 80 participants recruited. Given the nature of the study a stringent criterion has been set for early termination of the trial on grounds of efficacy, namely $p<0.001$ for both the primary outcomes, else continuation of the trial being recommended. Other outcomes to be included in the interim analysis will be agreed with the DMC but are likely to include pain and vomiting, as well as six month outcomes data available at the time of the interim analysis. The interim analysis will not influence the final statistical analyses; given the single interim analysis and the stringent stopping criteria, any further adjustment is not considered to be necessary. Serious Adverse Events (SAEs) will be routinely reported to the DMC and discussed (by email/telephone) as considered necessary; they will be formally reviewed at the interim analysis within the context of any emerging evidence on efficacy.

Missing data

The nature of missing data will be examined to consider appropriate approaches such as multiple imputation. Where assumptions are necessarily made, alternative assumptions will also be used to conduct additional analyses examining how sensitive the results are to the baseline assumptions. For the joint primary outcome of pain VAS, the AUC can be calculated from available VAS scores even if some are missing, by using linear interpolation; but if one or more observations are missing at the end of the 24-hour period, the last observation recorded will be carried forward in the primary analysis.

Economic evaluation

The study will include an economic evaluation from an NHS perspective. Following the NICE reference case, the primary outcome for the economic evaluation will be the incremental cost per QALY gained. The study will collect resource use data for the main drivers of the marginal cost. Unit costs will be assessed using standard NHS reference costs and prices. Health related quality of life will be measured using the EQ5D-5L data collected at baseline, 14 days and six months and valued using the interim “crosswalk” value set [48]. QALYs will be estimated within trial by assuming a constant tariff value for days 0-14 and a straight line extrapolation between tariff scores at 14 days and six months.

The outcome of the economic evaluation will be the incremental cost effectiveness ratio (ICER) (the additional cost per QALY gained). Sampling variation for the ICER will be reported as the standard deviation, estimated by bootstrapping and illustrated on the cost-effectiveness plane. Sensitivity analysis will be undertaken as appropriate (depending on sampling variation and an analysis of relationships between QALY estimates and the other outcome measures) but it will include an analysis of the sensitivity of the estimated ICER to the functional form of the extrapolation between tariff scores at 14 days and six months.

Ethics and dissemination

Ethical and safety considerations

Post-operatively, all participants are provided with a morphine PCA system in addition to the sub-pectoral infusion of trial treatment and therefore it is not considered that there are any ethical issues in using a placebo control. The recommended maximum single dose of levobupivacaine is 150mg. The dose for post-operative pain management should not exceed 18.75mg/hour and the maximum recommended dose during a 24 hour period is 400mg. The maximum 24 hour dose in this study is 350mg which is therefore well within recognised safe limits.

Research governance

The protocol has been approved by the South West - Central Bristol Research Ethics Committee (REC reference 12/SW/0149) and follows the recent SPIRIT guidelines [49]. The Sponsor is responsible for judging the substantiality of any amendments to the study protocol. Important protocol modifications will be communicated to relevant parties by the Peninsula Clinical Trials Unit.

The study is conducted subject to the terms of a Clinical Trial Authorisation issued by the Medicines and Healthcare products Regulatory Agency (MHRA) and in compliance with the principles of the Declaration of Helsinki, ICH GCP, the Data Protection Act 1988 and the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. The study has been adopted by the NIHR Clinical Research Network and has relevant local NHS Research & Development approvals. The study is sponsored by Royal Cornwall Hospitals NHS Trust and managed by the UKCRC-registered Peninsula Clinical Trials Unit at Plymouth University (Registration No.31).

A Trial Management Team meets regularly to monitor and discuss the progress of the trial and to address any issues that arise. A Trial Steering Committee (TSC), with an independent chair, meets approximately every six to nine months to oversee the overall conduct of the trial. A Data Monitoring Committee (DMC), comprising two independent clinicians and one independent statistician, meets approximately every nine to twelve months to monitor safety and ethics, including issues relating to attrition, overall data completeness and patient safety. The agreed role and responsibilities of both committees are set out in written charters and the DMC provides written recommendations to the TSC following each meeting.

Timelines and dissemination plans

Research Ethics Committee approval was obtained in June 2012. Recruitment and training of staff involved in the study commenced in autumn 2012, and participant recruitment started at the first study site in December 2012. Participant recruitment is due to be completed by the end of 2014, with the final six month follow-up visits in early summer 2015. Statistical analyses will commence once final data collection, monitoring and data cleaning is complete and it is anticipated that the first publications will be ready for submission by early 2016. As well as the submission of research articles to appropriate peer-reviewed journals, research findings will be submitted for presentation

at local, national and international scientific meetings including the European Society of Regional Anaesthesia annual scientific meeting.

The study team will prepare a plain English summary of the study results which will be sent to the study participants as soon as possible after the end of the trial. In addition, the final results of the study will be presented at meetings of the local breast cancer support groups.

Conclusions

The lack of good quality evidence regarding the effectiveness of a continuous local anaesthetic infusion on post-operative pain following mastectomy indicates the need for well-designed clinical trials to investigate this subject. This study has been designed to investigate whether the use of a continuous local anaesthetic infusion in the sub-pectoral tissue plane can improve post-operative analgesia and quality of life for patients undergoing mastectomy, with or without axillary surgery.

This is the first study to assess the use of such a continuous infusion in the sub-pectoral plane, as well as the first study to assess the effects on post-operative shoulder function or the development of chronic pain, and will therefore give a pragmatic answer to the question of whether continuous local anaesthetic infusion in the sub-pectoral tissue plane should be used in these patients.

Author's contributions

IB adapted the sub-pectoral catheter technique and originally conceived the study. RL and IB developed the trial with methodological advice from SC and CP, specialist pain advice from KM and trial management advice from JV. SC is the trial statistician. JV is the trial manager. All authors helped to develop the study protocol to its final version.

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Competing interests

None

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APPENDIX 1

Standardised anaesthesia protocol for SUBLIME trial participants

Pre-op:
No specific premedication

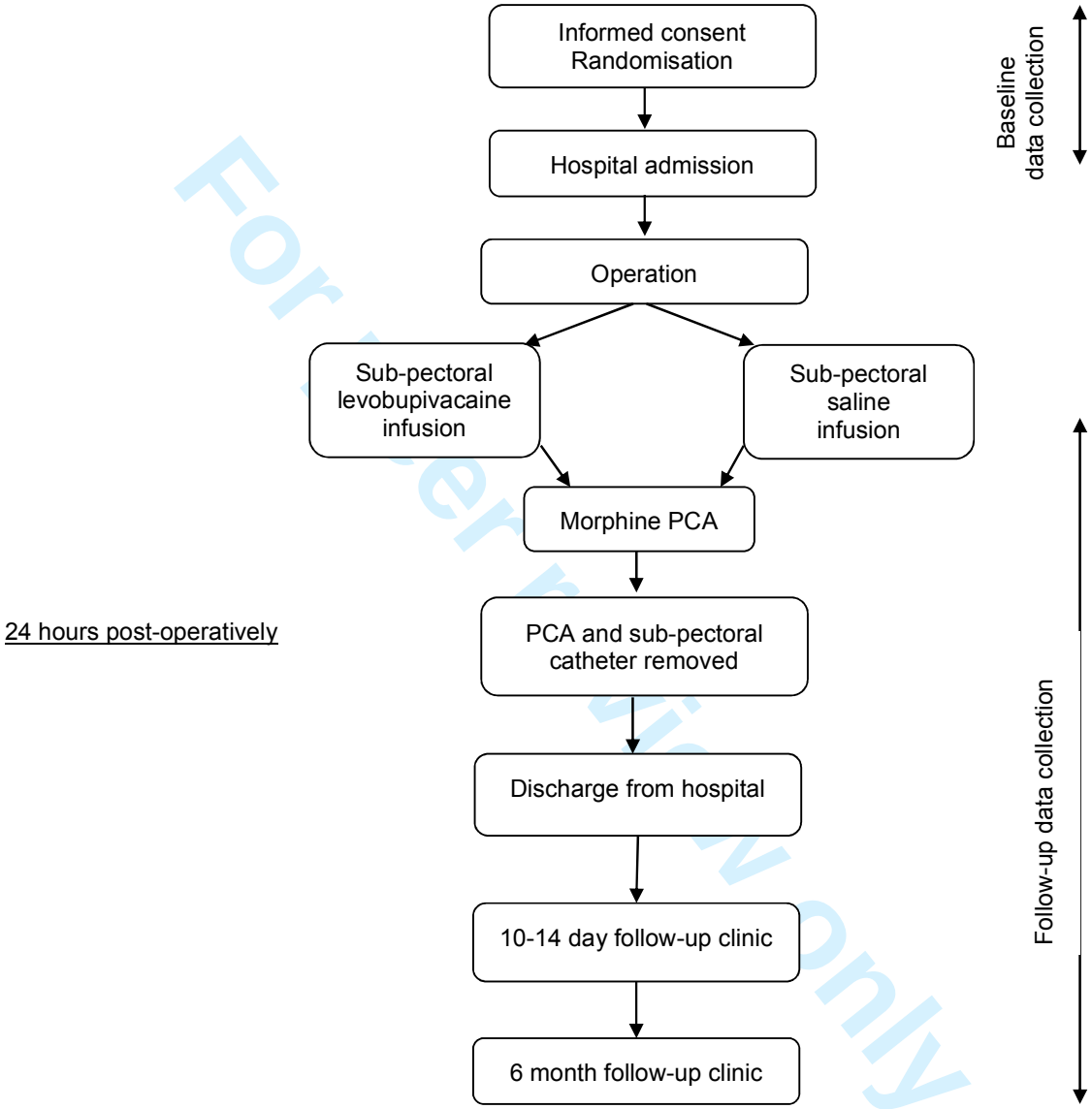
Peri-op:
Paracetamol 1g IV
Ondansetron 4mg IV
Dexamethasone 3.3mg (+/- 0.1mg)* IV unless clinically contraindicated
Intubation and ventilation at anaesthetist's discretion - with muscle relaxant of anaesthetist's choice
Sevoflurane in air: depth of anaesthesia at anaesthetist's discretion
Fentanyl: 3-6 mcg/kg IV during surgery
Fluids: at anaesthetist's discretion
All other non-opiate and non-anti-emetic drugs: at anaesthetist's discretion

Post-op:
IV rescue morphine in recovery unit, 2mg increments
IV morphine PCA, 1mg bolus, 5 minute lockout
Paracetamol 1g 6-hourly orally
Ibuprofen 400mg 8-hourly orally unless contraindicated
PRN: ondansetron 4mg (IV) 8-hrly and cyclizine 50mg (IV) 8-hrly

**Dexamethasone concentration differs between manufacturers and is typically available as 8mg dexamethasone in 2mls (4mg/ml dexamethasone) or as dexamethasome phosphate 4mg/ml (equivalent to 3.3mg/ml dexamethasone). Either preparation is acceptable i.e. 1ml of 4mg/ml dexamethasone phosphate (3.3mg dexamethasone) or 0.8ml of 4mg/ml dexamethasone (3.2mg dexamethasone).*

Figure legend

Figure 1: Trial schematic



SUBLIME protocol paper_31 July 2014_Figure 1

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2-3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4-5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	8
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4,6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	N/A
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	N/A
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	N/A
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	N/A
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Study protocol for a double blind, randomised, placebo-controlled trial of continuous sub-pectoral local anaesthetic infusion for pain and shoulder function following mastectomy:

SUB-pectoral Local anaesthetic Infusion following MastEctomy (SUBLIME) study

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Keywords:	Mastectomy, Local Anaesthetic, Anaesthetic infusion, Pain, Shoulder function

Study protocol for a double blind, randomised, placebo-controlled trial of continuous sub-pectoral local anaesthetic infusion for pain and shoulder function following mastectomy:

SUB-pectoral Local anaesthetic Infusion following MastEctomy (SUBLIME) study

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Abstract

Introduction

Over 16,000 mastectomies are performed in England and Wales annually. Acute postoperative pain and nausea are common. The most frequently occurring long term complications are chronic pain (up to 50%) and reduced shoulder function (reported at 35%). Regional techniques that improve acute postoperative pain relief may reduce the incidence of these complications. This study assesses the effectiveness of a 24 hour continuous local anaesthetic in the sub-pectoral plane in improving post-operative pain and quality of life in patients undergoing mastectomy.

Methods and analysis

This is a randomised, double blind, placebo-controlled, two-centre, parallel group trial in females undergoing mastectomy with or without axillary involvement. One hundred and sixty participants will be randomised in a 1:1 ratio to receive either 0.25% levobupivacaine or 0.9% saline by sub-pectoral infusion post-operatively for 24 hours. All participants will be provided with an intravenous morphine patient-controlled analgesia (PCA) system. Participants will be followed-up for 24 hours in hospital and at approximately 14 days and six months post-operatively. Joint primary outcome measures are total morphine consumption and total pain score (captured via patient-recorded visual analogue scale (VAS) 4 hourly) during the first 24 hours post-operatively. Primary statistical analysis of total pain is based on the area under the curve of pain versus time graph. Secondary outcomes include PCA attempts in first 24 hours; VAS pain scores and shoulder function by goniometry at 24 hours, 14 days (approximately) and six months; VRS pain scores in first 24 hours; Brief Pain Inventory and Oxford Shoulder Score at six months; duration of hospital stay; incidence of post-operative nausea and vomiting; cost-effectiveness.

Ethics and dissemination

The study is approved by the South West England Research Ethics Committee (12/SW/0149). Results will be published in a peer-reviewed journal and presented at local, national and international scientific meetings.

Trial registration

ISRCTN46621916. EudraCT 2011-005775-16.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

- This is a double-blind, randomised, placebo-controlled trial.
- This is the first study to assess the use of a continuous local anaesthetic infusion in the sub-pectoral plane.
- This is the first study to assess the effects of continuous local anaesthetic infusion on post-operative shoulder function.
- The study includes an assessment of longer-term pain.

Limitations

- All instruments for measuring post-operative pain, including those used in this study, have limitations. We have attempted to address this by using two measures, morphine consumption and VAS scores, as joint primary outcomes.
- Changing surgical practice means that fewer simple mastectomies are being performed in comparison with breast conservation (wide excision) surgery and skin-sparing mastectomy with

immediate reconstruction. This study does not address whether any benefits demonstrated can be extrapolated to these procedures.

- The study does not assess the effects of surgeon variation or duration of surgery on pain and recovery outcomes for patients.
- The study does not assess the level of sedation in the post-operative period. Reduced sedation is a potential benefit of reduced morphine consumption.

INTRODUCTION

In 2010, the lifetime risk in women of developing breast cancer was estimated as 1 in 8, with the disease now the most commonly occurring cancer in the UK [1]. Surgery remains the treatment of choice, with around 43% of women with breast cancer opting for mastectomy [2]. A total of 16,595 mastectomies were performed in England and Wales in 2012-2013 [3]. The most common complications of mastectomy are post-operative acute and chronic pain and slow recovery of shoulder function. Acute pain in mastectomy patients is currently managed with systemic opiates, either by intramuscular injection or using an intravenous patient-controlled analgesia (PCA) device. Chronic post-operative pain is frequent (20–45%) [4-7] and requires significant use of NHS resources. Poor recovery of shoulder function, associated with initial poor analgesia, impacts on quality of life long after the initial recovery period [8,9]. These effects are all the more significant considering the young age at which many patients present.

Post-operative analgesia therefore remains a challenge for these patients despite a range of treatment options [10]. Most post-operative pain in mastectomy occurs within the first 24 hours of surgery. Inadequately managed pain in the acute post-operative phase is a major risk factor of chronic pain syndromes [11], which are present in up to 50% of patients six months after operation [12]. Impaired shoulder function also causes significant problems post-mastectomy [13-15] and it has been suggested that better post-operative analgesia may enhance the effects of early physiotherapy. There is no gold standard for pain relief following mastectomy surgery [10]. Morphine, the mainstay of therapy, is associated with vomiting and excessive drowsiness. Thoracic epidural and paravertebral blocks have been shown to provide adequate analgesia [10], but associated complications (e.g. pneumothorax), although rare, are severe and potentially life threatening. Local anaesthesia wound infiltration has not been adequately studied using randomised controlled trials [10]. An informal survey of current practice in the South West Peninsula of England suggested that its use is patchy and erratic, with a third of surgeons not using any at all and others reporting a range of different methods of administration and doses.

The use of wound catheters to deliver continuous local anaesthetic has been shown to reduce post-operative pain and analgesic requirements in cardiothoracic, orthopaedic and general surgery [6,16,17]. The nerve supply to the breast is predominantly from the lateral and anterior branches of the 2nd to 6th intercostal nerves and the supraclavicular nerves [18]. Nerves pass beneath the pectoral fascia before reaching the breast and it is here that local anaesthetic may be deposited via a catheter, as a bolus or sub-pectoral infusion. The ‘Pecs block’ was described in 2011 [19] as a technique for placing local anaesthesia in the sub-pectoral plane at the time of surgery. There have since been a number of similar descriptions of ultrasound-guided chest wall local anaesthetic techniques for use in breast surgery [20-22]. Case reports and small studies indicate that these techniques are efficacious in reducing post-operative pain, however there are, as yet, no large randomised controlled trials. So far these techniques have not been described with the use of continuous local anaesthetic infusion.

Current published research relating to post-mastectomy local anaesthesia infusion is scant. A meta-analysis of surgically placed wound catheters concluded that there was a trend towards improved analgesia in the immediate post-operative period, however studies were underpowered and often poorly designed [23]. One randomised study [24] of 42 patients found no significant difference in post-operative analgesia (as measured by PCA use and pain scores) between administration of 4-hourly 20ml bolus doses of 0.5% bupivacaine and placebo. However, the technique tested involved infiltration via wound drains which deposited local anaesthetic in a more superficial tissue plane than the sub-pectoral plane and did not use a continuous infusion. Non-randomised, non-blinded, retrospective and observational studies of local anaesthetic infusion [25-27] suggest more favourable results. Baroody et al. [26] demonstrated a five-fold reduction in analgesic requirement following local anaesthetic infusion after reconstructive breast surgery. Morrison et al. [25] compared post-operative opioid use in mastectomy patients receiving local anaesthetic infusion or no infusion and found a significant reduction in opiate use and hospital length of stay in the local anaesthetic arm. However, this was an unblinded retrospective analysis and made no attempt to investigate chronic pain or arm mobility. Lu et al. [27] compared local anaesthetic infusion to placebo in patients undergoing reduction mammoplasty and reconstruction. Results showed reductions in opiate use and pain scores in the local anaesthetic group but controls were historical and the study was unblinded and not randomised. Given the limitations of the study designs, it is currently difficult to make firm conclusions or recommendations for clinical practice. There are no published studies assessing the impact of local anaesthetic infiltration on post-operative shoulder function. There has recently been increased interest in post-operative local anaesthesia for the reduction of chronic pain. A 2012 Cochrane analysis pooled the results of two trials and concluded that paravertebral block may favour the reduction of chronic pain following mastectomy in one in five patients [28].

Levobupivacaine is the S(-)-isomer of bupivacaine. In common with other local anaesthetic agents, it is widely accepted that Levobupivacaine blocks nerve conduction in sensory and motor nerves by blocking voltage sensitive sodium channels in the cell membrane. Levobupivacaine exhibits fewer cardiovascular toxicity effects [29,30] than bupivacaine and, as such, is safer for use as an infusion. There appears to be no measurable difference in clinical effectiveness between the two agents [31].

The aim of this study is to establish whether the use of continuous local anaesthetic infusion in the sub-pectoral tissue plane can improve post-operative analgesia and quality of life for patients undergoing mastectomy with or without axillary surgery. If the use of this local anaesthetic infusion technique is shown to be more effective than current practice, the reduction of pain and opiate use in the immediate post-operative period would be a significant benefit to patients. The technique also holds the potential to improve patients' quality of life by reducing the longer term risks of chronic pain and impaired shoulder function.

METHODS AND ANALYSIS

Study design

The study is a double blind, randomised, placebo-controlled, two-centre, parallel group trial in 160 female patients undergoing mastectomy with or without axillary involvement. The study was originally designed as a single centre study in Cornwall, but audit data prior to the study start confirmed a significant reduction in the number of mastectomies being conducted locally, following changes in the surgical team and surgical practice. In order to achieve the required sample size, the study design was therefore amended to include two study sites. At the same time, an emerging trend for early discharge of patients post-mastectomy prompted a change in the timing of primary

outcome data collection from 48 hours to 24 hours post-operatively. These changes to the original study design eventually delayed the study start by approximately ten months.

Participants will be randomly allocated to receive either 0.25% levobupivacaine or 0.9% sodium chloride by sub-pectoral infusion post-operatively for 24 hours. All participants will be provided with an intravenous (IV) morphine PCA system. Participants will be followed up for 24 hours in hospital and at approximately 14 days and six months post-operatively as out-patients.

Setting and participants

The study is being conducted in breast surgery departments within two NHS Trusts in Cornwall and York, England. The second site was selected after expressing interest in the study and because of its similar mastectomy pathway compared with the lead site. Eligible patients comprise all women presenting for unilateral mastectomy, with or without planned axillary clearance, at one of the participating hospitals. Main exclusion criteria are: primary reconstructive surgery; hypotension or hypovolaemia; allergy or sensitivity to local anaesthetic agents, morphine, paracetamol, ondansetron or cyclizine; daily opioid analgesic use; pregnancy. Study participants are patients who meet the screening criteria and are willing and able to give informed consent.

Study recruitment

The recruitment process is designed to fit in with routine clinical practice. Potential participants are identified from those attending out-patient breast clinics for discussion of breast cancer diagnosis and treatment options. Surgery is usually scheduled within a month of the initial clinic appointment, following attendance at a pre-assessment clinic. Women attending clinic for discussion of prophylactic mastectomy may also be eligible to participate in the study.

Patients for whom mastectomy is a potential treatment option and who appear eligible for the study are given a brief verbal introduction to the study by a clinician or nurse at the initial breast clinic consultation and provided with either a brief written study summary or a full participant information sheet, as deemed appropriate. Patients are subsequently telephoned within a few days by the breast care nurse (or research nurse, depending upon local arrangements) and further information about the study is provided verbally and/or by post to patients who express further interest. Patients who are interested in participating in the study are invited to meet the research nurse at the routine pre-operative assessment clinic so that any further questions can be answered and eligibility for the study confirmed. Arrangements are made for the patient to discuss aspects of the study with the surgeon or anaesthetist if required. Written informed consent is obtained from patients willing and eligible to participate, by an appropriately trained member of the research team. Patients who decline to take part in the study are not obliged to give a reason for declining but the reason(s) are recorded by the research nurse if provided.

Study procedures

Figure 1 shows the participant pathway through the study. Following informed consent, each participant is assigned a unique study number. Baseline data are normally collected at the pre-operative assessment clinic, following consent. At this point the research nurse briefly explains use of the morphine PCA system and familiarises the participant with the visual analogue scale (VAS) pain scoring system. Each VAS score is recorded on a separate page of a mini flipchart. The participant turns the page of the flipchart after an entry is made, so that the previous score is not visible for comparison when the next score is recorded.

Interventions

The active investigational medicinal product is 0.25% levobupivacaine (Chirocaine), an established local anaesthetic infusion agent, prepared as a 2.5mg/ml solution and packaged by the manufacturer (Abbott) in ampoules for injection. The comparator solution, 0.9% sodium chloride, is sourced from standard NHS supplies at the participating sites. Active and comparator trial treatments are presented identically in infusion bags prepared by the local hospital pharmacy prior to the operation date and supplied on an individual patient basis according to treatment allocation. Bags are presented in heat-sealed outer packaging and labelled in accordance with current EU regulatory requirements for clinical trials. Each bag is assigned a unique code number and a seven day expiry date.

Anaesthesia and surgery

Study participants receive a standardised anaesthetic protocol with respect to analgesic and antiemetic medication (Appendix 1). Mastectomy is performed with/without sentinel lymph node sampling or clearance, as clinically indicated.

Delivery of trial treatment

Trial treatment is delivered by means of an infusion catheter and device, supplied as a sterile pre-packed kit and licensed for the delivery of local anaesthetic. At the end of the surgical procedure the surgeon inserts the infusion catheter percutaneously into the sub-pectoral plane under direct vision within the surgical field. After skin closure, a 20ml bolus of active or comparator treatment is given via the catheter, which is then connected to the infusion device to provide an infusion of trial treatment at a continuous rate of 5ml/hr for 24 hours. In the active treatment arm this equates to a 50mg bolus of levobupivacaine followed by an infusion of 12.5mg/hr.

Post-operative management and outcome assessment

In the Recovery Unit, post-operative pain is routinely managed with 2-3mg aliquots of IV morphine to achieve a Verbal Rating Scale (VRS) pain score of none-mild pain. All participants are provided with a PCA system set up to deliver IV morphine boluses of 1mg with a 5 minute lock-out and no background infusion. Once all other routine recovery discharge criteria have been met, the patient is transferred to the ward. A baseline VAS pain score is recorded prior to transfer to the ward.

Participants are asked to complete VAS pain scores at rest every four hours, with reminders from ward staff. The sub-pectoral infusion is discontinued after 24 hours and the catheter removed, together with the PCA system. Outcome measures are assessed at 24 hours and at routine follow-up visits, approximately 10-14 days and six months after the day of surgery (Table 1).

Table 1: Trial schedule

	Pre-operative		*Post-operative*		
	Baseline	OPERATION AND SET-UP OF TRIAL INFUSION	24hrs	14 days*	6 months
Screen/eligibility	x				
Consent	x				
BMI	x				
Concomitant medication	x			x	x
Oxford Shoulder Score (OSS)	x				x
Shoulder questions (from OSS)				x	
Shoulder goniometry	x		x	x	x
EQ-5D 5L	x			x	x

Randomisation	x				
VAS pain score			x	x	x
VRS pain score			x		
PCA attempts			x		
Total morphine consumption (oral/IV)			x		
Analgesia use			x	x	x
Adverse events			x	x	x
Brief Pain Inventory					x
Service use					x

*Approximately 10-14 days post-operatively according to local practice

Primary outcome measures

The joint primary outcomes are (i) total morphine consumption (mg) in the first 24 hours (defined as the 24 hours following commencement of the sub-pectoral infusion), including all morphine given in the Recovery Unit and cumulative PCA use as recorded by the PCA device and (ii) total pain over the first 24 hours, as defined by measurement of the area-under-the-curve of each participant's self-reported pain scores at rest, measured using a visual analogue scale (VAS). VAS pain scores are recorded in the Recovery Unit and then at four hourly intervals for the first 24 hours. The VAS is presented as a 100mm horizontal line with verbal anchors at each end of "no pain" and "worst pain possible". The study participant selects and marks with a pen the point along the line that reflects their current pain perception. Periods of sleep are recorded retrospectively by the participant.

Secondary outcome measures

Secondary outcome measures include the number of PCA attempts in the first 24 hours following commencement of infusion; VAS pain scores at rest at 24 hours, 14 days and six months after surgery; incidence of post-operative nausea and/or vomiting (PONV) and use of supplemental analgesics and post-operative anti-emetics in the first 24 hours; self-reported analgesia use at 14 days and six months; duration of hospital stay; shoulder movement assessed by goniometry at 24 hours, 14 days and six months following surgery; Brief Pain Inventory at six months; shoulder function (as measured by the validated Oxford Shoulder Score [32]) at six months. Items from the Oxford Shoulder Score are also assessed at the first follow-up visit in relation to the previous seven days. Following the participant's discharge, the length of stay in hospital is recorded by the research nurse.

Randomisation

Patients who consent to participate and fulfil the eligibility criteria are randomly allocated to receive either levobupivacaine or saline in a 1:1 ratio via a secure web-based randomisation system. The allocation sequence is computer-generated by the UKCRC-registered Peninsula Clinical Trials Unit (CTU) in conjunction with an independent statistician, using a random permuted block design, with blocks of varying sizes. The block sizes will not be disclosed, to ensure concealment. As post-operative pain is expected to differ between patients who are having simple mastectomy, mastectomy with sentinel lymph node sampling or mastectomy with axillary node clearance, randomisation is stratified by planned surgical procedure, and by recruiting centre. To ensure that the study team, including the study statistician, remain blind to participants' allocated study groups, randomisation is undertaken by the relevant hospital pharmacy department.

Blinding and emergency unblinding

This is a double blind study and therefore participants, the surgical/anaesthetic team and the research team are unaware of each participant's allocated treatment group. To help assess the success of blinding, participants and the research nurse completing the follow-up assessments are asked to guess the participant's treatment assignment, at both the 14 day and 6 month follow-up visits.

In the event of a potential suspected unexpected serious adverse reaction (SUSAR), unblinding will be undertaken by the Sponsor in accordance with the regulatory requirements for safety reporting in Clinical Trials of Investigational Medicinal Products (CTIMPs). Unblinding may also be performed at the request of a senior clinician responsible for the care of a trial participant but such requests are likely to occur only in the case of an adverse clinical event and are expected to be rare. Any request to unblind treatment allocation for clinical reasons will be made directly to the relevant hospital pharmacy and the treatment allocation will be reported to the relevant clinician according to an agreed procedure. The Chief Investigator and CTU trial manager will be kept informed of all instances of unblinding but remain blind to treatment allocations themselves wherever possible. The pharmacy and CTU will maintain a record of all requests for unblinding.

Data management

Data will be collected and stored in accordance with the Data Protection Act, 1998. Data will be recorded on study specific data collection forms and transferred to the CTU for double-data entry on to a password-protected database stored on a restricted access, secure server. Participants' anonymity will be maintained on all documents. Direct access to the trial data will be restricted to members of the research team and the CTU, with access granted to the Sponsor on request.

All participants will be encouraged to continue with follow-up as per protocol although they may withdraw from the study at any time without it affecting their care. Data collected prior to withdrawal will be included in the study analysis unless a participant specifically requests that their data are removed from the database.

Sample size

The study sample size was calculated to assess the joint aims of the effectiveness of a 24 hour continuous sub-pectoral local anaesthetic infusion on total morphine consumption and total pain over the 24 hour post-surgery period. Few studies have addressed the question of what reduction in total morphine use after breast surgery might be clinically important. A small number of studies have reported total morphine use after breast surgery, at varying end points [33-40]. Four have reported total morphine use at 24 hours post-surgery; three of these were comparative studies. Two of these three studies based their sample size calculations on the same prior belief that the minimum clinically important difference was 10mg (estimated standard deviation of 10mg, estimated mean 24 hour total morphine consumption of 40mg) [39,40]. Therefore the minimum clinically important difference in 24-hour total morphine consumption was set as 10mg. These studies also showed actual standard deviations in 24 hour post-operative total morphine consumption of 10 to 22mg. To allow for the variability in the total morphine consumption being at the upper end of this range, the sample size calculation for total morphine consumption assumed a standard deviation of 20mg. To detect a difference of 10mg between groups, with 80% power and at the 5% significance level, requires 65 participants per group.

Similarly, there is a lack of information on which to base a formal sample size calculation for pain as the (joint) primary outcome measure. With the sample size of 65 participants per group, there will be approximately 80% power to detect an effect size of around 0.5 standard deviations on the measure of pain. Such an effect size would be considered as being of "moderate" size [41]. From

studies using a single VAS pain measure, it has been suggested that clinically meaningful differences are of the magnitude of 20mm to 30mm on a 100mm VAS [42], whilst a recent review reported that at the group level the difference in pain levels varied from 4mm to 40mm for acute pain [43]. Assuming the standard deviation of the VAS is between 13mm [44,45] and 26mm [38,46], this suggests that clinically meaningful effect sizes are of the order of at least 0.8 standard deviations. To detect a difference of around 0.8 standard deviations would need 26 patients per group, assuming a two-sided significance level of 5%, with 80% power. Therefore, the sample size of 65 participants per group will be large enough to detect clinically relevant differences between groups, in terms of pain.

The primary outcome measures are at 24 hours with a minimal probability of drop out. However, enough participants will be recruited to attempt to ensure 65 participants per group are followed up at six months. As patients remain engaged with the breast service for clinical reasons, loss to follow-up is also expected to be low but there may be losses to the study because, for example, of the need for further surgery. Therefore, in order to achieve a study sample of 65 women per group at the six month follow-up, the aim is to recruit a total of 160 participants over a two year period, which allows for a loss to follow-up rate of just under 20%.

Statistical analyses

The primary analyses are all pre-specified and a detailed statistical analysis plan will be completed and agreed by the Data Monitoring Committee (DMC) prior to commencement of analyses. Data will be reported and presented according to the CONSORT statement [47]. Ninety five percent confidence intervals will be calculated and presented where possible. The trial statistician will be presented with a database by the CTU containing a group code for each participant but not identifying which group is which; only after final analysis will the individual groups be identified.

The primary statistical analysis will follow an intention-to-treat approach, with the intent-to-treat population defined as all trial participants who completed the baseline assessment and underwent surgery. A per protocol analysis may be undertaken as a sensitivity analysis. The analysis of adverse events will be presented on a per protocol basis.

The primary analysis will compare (i) total morphine consumption and (ii) 24 hour pain AUC at 24 hours post-surgery between the two groups using an analysis of covariance, including the stratification factors as covariates, with suitable transformation of total morphine consumption and pain AUC considered as necessary. The estimates of the differences in mean total morphine consumption and mean pain AUC will be presented, together with a 95% confidence interval for the difference. Secondary outcomes will be compared between groups in a similar way using analysis of covariance for continuous outcomes and logistic regression for binary outcomes such as incidence of post-operative nausea and/or vomiting and use of post-operative anti-emetics in the 24 hours following surgery. Comparisons of interest will be presented with 95% confidence intervals.

Interim analysis

An interim analysis will be undertaken after the 14 day follow-up data have been collected for the first 80 participants recruited. Given the nature of the study a stringent criterion has been set for early termination of the trial on grounds of efficacy, namely $p<0.001$ for both the primary outcomes, else continuation of the trial being recommended. Other outcomes to be included in the interim analysis will be agreed with the DMC but are likely to include pain and vomiting, as well as six month outcomes data available at the time of the interim analysis. The interim analysis will not influence the final statistical analyses; given the single interim analysis and the stringent stopping

criteria, any further adjustment is not considered to be necessary. Serious Adverse Events (SAEs) will be routinely reported to the DMC and discussed (by email/telephone) as considered necessary; they will be formally reviewed at the interim analysis within the context of any emerging evidence on efficacy.

Missing data

The nature of missing data will be examined to consider appropriate approaches such as multiple imputation. Where assumptions are necessarily made, alternative assumptions will also be used to conduct additional analyses examining how sensitive the results are to the baseline assumptions. For the joint primary outcome of pain VAS, the AUC can be calculated from available VAS scores even if some are missing, by using linear interpolation; but if one or more observations are missing at the end of the 24-hour period, the last observation recorded will be carried forward in the primary analysis.

Economic evaluation

The study will include an economic evaluation from an NHS perspective. Following the NICE reference case, the primary outcome for the economic evaluation will be the incremental cost per QALY gained. The study will collect resource use data for the main drivers of the marginal cost. Unit costs will be assessed using standard NHS reference costs and prices. Health related quality of life will be measured using the EQ5D-5L data collected at baseline, 14 days and six months and valued using the interim "crosswalk" value set [48]. QALYs will be estimated within trial by assuming a constant tariff value for days 0-14 and a straight line extrapolation between tariff scores at 14 days and six months.

The outcome of the economic evaluation will be the incremental cost effectiveness ratio (ICER) (the additional cost per QALY gained). Sampling variation for the ICER will be reported as the standard deviation, estimated by bootstrapping and illustrated on the cost-effectiveness plane. Sensitivity analysis will be undertaken as appropriate (depending on sampling variation and an analysis of relationships between QALY estimates and the other outcome measures) but it will include an analysis of the sensitivity of the estimated ICER to the functional form of the extrapolation between tariff scores at 14 days and six months.

Ethics and dissemination

Ethical and safety considerations

Post-operatively, all participants are provided with a morphine PCA system in addition to the sub-pectoral infusion of trial treatment and therefore it is not considered that there are any ethical issues in using a placebo control. The recommended maximum single dose of levobupivacaine is 150mg. The dose for post-operative pain management should not exceed 18.75mg/hour and the maximum recommended dose during a 24 hour period is 400mg. The maximum 24 hour dose in this study is 350mg which is therefore well within recognised safe limits.

Research governance

The protocol has been approved by the South West - Central Bristol Research Ethics Committee (REC reference 12/SW/0149) and follows the recent SPIRIT guidelines [49]. The Sponsor is responsible for judging the substantiality of any amendments to the study protocol. Important protocol modifications will be communicated to relevant parties by the Peninsula Clinical Trials Unit.

The study is conducted subject to the terms of a Clinical Trial Authorisation issued by the Medicines and Healthcare products Regulatory Agency (MHRA) and in compliance with the

principles of the Declaration of Helsinki, ICH GCP, the Data Protection Act 1988 and the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. The study has been adopted by the NIHR Clinical Research Network and has relevant local NHS Research & Development approvals. The study is sponsored by Royal Cornwall Hospitals NHS Trust and managed by the UKCRC-registered Peninsula Clinical Trials Unit at Plymouth University (Registration No.31).

A Trial Management Team meets regularly to monitor and discuss the progress of the trial and to address any issues that arise. A Trial Steering Committee (TSC), with an independent chair, meets approximately every six to nine months to oversee the overall conduct of the trial. A Data Monitoring Committee (DMC), comprising two independent clinicians and one independent statistician, meets approximately every nine to twelve months to monitor safety and ethics, including issues relating to attrition, overall data completeness and patient safety. The agreed role and responsibilities of both committees are set out in written charters and the DMC provides written recommendations to the TSC following each meeting. The CTU will conduct central and site monitoring in accordance with a risk-based monitoring plan and the study Sponsor may audit trial conduct as deemed appropriate.

Timelines and dissemination plans

The study start was delayed due to amendments to the study design, described earlier. Research Ethics Committee approval was obtained in June 2012. Recruitment and training of staff involved in the study commenced in autumn 2012, and participant recruitment started at the first study site in December 2012. Participant recruitment is due to be completed by the end of 2014, with the final six month follow-up visits in early summer 2015. Statistical analyses will commence once final data collection, monitoring and data cleaning is complete. The Chief Investigator will establish a writing committee comprising individuals who have made key contributions to study design and conduct and it is anticipated that the first publications will be ready for submission by early 2016. As well as the submission of research articles to appropriate peer-reviewed journals, research findings will be submitted for presentation at local, national and international scientific meetings including the European Society of Regional Anaesthesia annual scientific meeting.

The study team will prepare a plain English summary of the study results which will be sent to the study participants as soon as possible after the end of the trial. In addition, the final results of the study will be presented at meetings of the local breast cancer support groups.

Conclusions

The lack of good quality evidence regarding the effectiveness of a continuous local anaesthetic infusion on post-operative pain following mastectomy indicates the need for well-designed clinical trials to investigate this subject. This study has been designed to investigate whether the use of a continuous local anaesthetic infusion in the sub-pectoral tissue plane can improve post-operative analgesia and quality of life for patients undergoing mastectomy, with or without axillary surgery.

This is the first study to assess the use of such a continuous infusion in the sub-pectoral plane, as well as the first study to assess the effects on post-operative shoulder function or the development of chronic pain, and will therefore give a pragmatic answer to the question of whether continuous local anaesthetic infusion in the sub-pectoral tissue plane should be used in these patients.

Author's contributions

IB adapted the sub-pectoral catheter technique and originally conceived the study. RL and IB developed the trial with methodological advice from SC and CP, specialist pain advice from KM

and trial management advice from JV. SC is the trial statistician. JV is the trial manager. All authors helped to develop the study protocol to its final version.

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Competing interests
None

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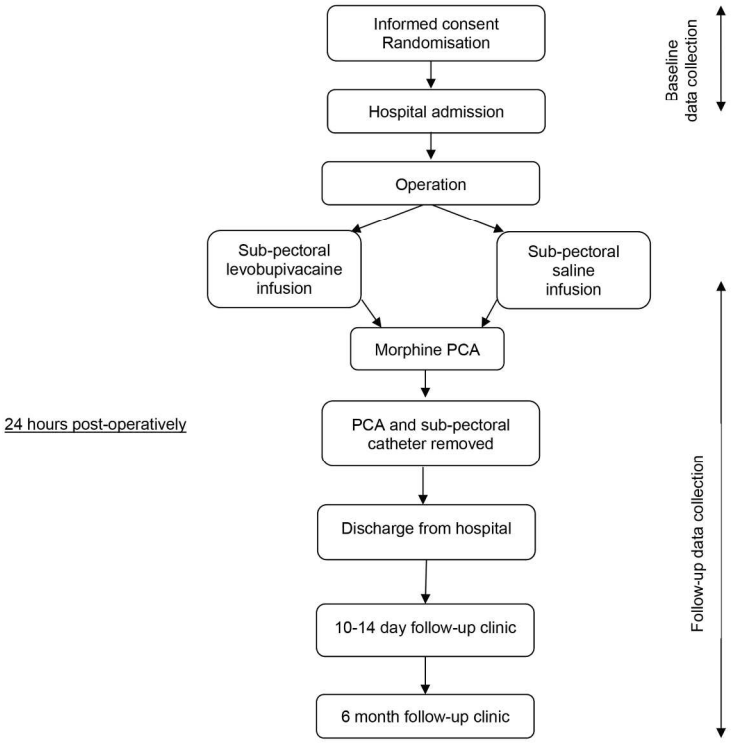
Figure legend

Figure 1: Trial schematic



SUBLIME protocol paper_4 September 2014_Figure 1

Trial schematic
233x319mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2,4,5,6,7,9,11,12
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,11,12
	5b	Name and contact information for the trial sponsor	11
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	10,11,12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10-11

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4-5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6, 16
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-7

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8-9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7,8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8,9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9-10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Study protocol for a~~A~~ double blind, randomised, placebo-controlled trial of continuous sub-pectoral local anaesthetic infusion for pain and shoulder function following mastectomy:

SUB-pectoral Local anaesthetic Infusion following MastEctomy (SUBLIME) study

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Keywords: mastectomy, local anaesthetic, anaesthetic infusion, pain, shoulder function

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Abstract

Introduction

Over 16,000 mastectomies are performed in England and Wales annually. Acute postoperative pain and nausea are common. The most frequently occurring long term complications are chronic pain (up to 50%) and reduced shoulder function (reported at 35%). Regional techniques that improve acute postoperative pain relief may reduce the incidence of these complications. This study assesses the effectiveness of a 24 hour continuous local anaesthetic in the sub-pectoral plane in improving post-operative pain and quality of life in patients undergoing mastectomy.

Methods and analysis

This is a randomised, double blind, placebo-controlled, two~~multi~~-centre, parallel group trial in females undergoing mastectomy with or without axillary involvement. One hundred and sixty participants will be randomised in a 1:1 ratio to receive either 0.25% levobupivacaine or 0.9% saline by sub-pectoral infusion post-operatively for 24 hours. All participants will be provided with an intravenous morphine patient-controlled analgesia (PCA) system. Participants will be followed-up for 24 hours in hospital and at approximately 14 days and six months post-operatively. Joint primary outcome measures are total morphine consumption and total pain score (captured via patient-recorded visual analogue scale (VAS) 4 hourly) during the first 24 hours post-operatively. Primary statistical analysis of total pain is based on the area under the curve of pain versus time graph. Secondary outcomes include PCA attempts in first 24 hours; VAS pain scores and shoulder function by goniometry at 24 hours, 14 days (approximately) and six months; VRS pain scores in first 24 hours; Brief Pain Inventory and Oxford Shoulder Score at six months; duration of hospital stay; incidence of post-operative nausea and vomiting; cost-effectiveness.

Ethics and dissemination

The study is approved by the South West England Research Ethics Committee (12/SW/0149). Results will be published in a peer-reviewed journal and presented at local, national and international scientific meetings.

Trial registration

ISRCTN46621916. EudraCT 2011-005775-16.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

- This is a double-blind, randomised, placebo-controlled trial.
- This is the first study to assess the use of a continuous local anaesthetic infusion in the sub-pectoral plane.
- This is the first study to assess the effects of continuous local anaesthetic infusion on post-operative shoulder function.
- The study includes an assessment of longer-term pain.

Limitations

- All instruments for measuring post-operative pain, including those used in this study, have limitations. We have attempted to address this by using two measures, morphine consumption and VAS scores, as joint primary outcomes.
- Changing surgical practice means that fewer simple mastectomies are being performed in comparison with breast conservation (wide excision) surgery and skin-sparing mastectomy with

immediate reconstruction. This study does not address whether any benefits demonstrated can be extrapolated to these procedures.

- The study does not assess the effects of surgeon variation or duration of surgery on pain and recovery outcomes for patients.
- The study does not assess the level of sedation in the post-operative period. Reduced sedation is a potential benefit of reduced morphine consumption.

INTRODUCTION

In 2010, the lifetime risk in women of developing breast cancer was estimated as 1 in 8, with the disease now the most commonly occurring cancer in the UK [1]. Surgery remains the treatment of choice, with around 43% of women with breast cancer opting for mastectomy [2]. A total of 16,595 mastectomies were performed in England and Wales in 2012-2013 [3]. The most common complications of mastectomy are post-operative acute and chronic pain and slow recovery of shoulder function. Acute pain in mastectomy patients is currently managed with systemic opiates, either by intramuscular injection or using an intravenous patient-controlled analgesia (PCA) device. Chronic post-operative pain is frequent (20–45%) [4-7] and requires significant use of NHS resources. Poor recovery of shoulder function, associated with initial poor analgesia, impacts on quality of life long after the initial recovery period [8,9]. These effects are all the more significant considering the young age at which many patients present.

Post-operative analgesia therefore remains a challenge for these patients despite a range of treatment options [10]. Most post-operative pain in mastectomy occurs within the first 24 hours of surgery. Inadequately managed pain in the acute post-operative phase is a major risk factor of chronic pain syndromes [11], which are present in up to 50% of patients six months after operation [12]. Impaired shoulder function also causes significant problems post-mastectomy [13-15] and it has been suggested that better post-operative analgesia may enhance the effects of early physiotherapy. There is no gold standard for pain relief following mastectomy surgery [10]. Morphine, the mainstay of therapy, is associated with vomiting and excessive drowsiness. Thoracic epidural and paravertebral blocks have been shown to provide adequate analgesia [10], but associated complications (e.g. pneumothorax), although rare, are severe and potentially life threatening. Local anaesthesia wound infiltration has not been adequately studied using randomised controlled trials [10]. An informal survey of current practice in the South West Peninsula of England suggested that its use is patchy and erratic, with a third of surgeons not using any at all and others reporting a range of different methods of administration and doses.

The use of wound catheters to deliver continuous local anaesthetic has been shown to reduce post-operative pain and analgesic requirements in cardiothoracic, orthopaedic and general surgery [6,16,17]. The nerve supply to the breast is predominantly from the lateral and anterior branches of the 2nd to 6th intercostal nerves and the supraclavicular nerves [18]. Nerves pass beneath the pectoral fascia before reaching the breast and it is here that local anaesthetic may be deposited via a catheter, as a bolus or sub-pectoral infusion. The ‘Pecs block’ was described in 2011 [19] as a technique for placing local anaesthesia in the sub-pectoral plane at the time of surgery. There have since been a number of similar descriptions of ultrasound-guided chest wall local anaesthetic techniques for use in breast surgery [20-22]. Case reports and small studies indicate that these techniques are efficacious in reducing post-operative pain, however there are, as yet, no large randomised controlled trials. So far these techniques have not been described with the use of continuous local anaesthetic infusion.

Current published research relating to post-mastectomy local anaesthesia infusion is scant. A meta-analysis of surgically placed wound catheters concluded that there was a trend towards improved analgesia in the immediate post-operative period, however studies were underpowered and often poorly designed [23]. One randomised study [24] of 42 patients found no significant difference in post-operative analgesia (as measured by PCA use and pain scores) between administration of 4-hourly 20ml bolus doses of 0.5% bupivacaine and placebo. However, the technique tested involved infiltration via wound drains which deposited local anaesthetic in a more superficial tissue plane than the sub-pectoral plane and did not use a continuous infusion. Non-randomised, non-blinded, retrospective and observational studies of local anaesthetic infusion [25-27] suggest more favourable results. Baroody et al. [26] demonstrated a five-fold reduction in analgesic requirement following local anaesthetic infusion after reconstructive breast surgery. Morrison et al. [25] compared post-operative opioid use ~~with placebo~~ in mastectomy patients receiving local anaesthetic infusion~~s~~ or no infusion and found a significant reduction in opiate use and hospital length of stay in the local anaesthetic arm. However, this was an unblinded retrospective analysis and made no attempt to investigate chronic pain or arm mobility. Lu et al. [27] compared local anaesthetic infusion to placebo in patients undergoing reduction mammoplasty and reconstruction. Results showed reductions in opiate use and pain scores in the local anaesthetic group but controls were historical and the study was unblinded and not randomised. Given the limitations of the study designs, it is currently difficult to make firm conclusions or recommendations for clinical practice. There are no published studies assessing the impact of local anaesthetic infiltration on post-operative shoulder function. There has recently been increased interest in post-operative local anaesthesia for the reduction of chronic pain. A 2012 Cochrane analysis pooled the results of two trials and concluded that paravertebral block may favour the reduction of chronic pain following mastectomy in one in five patients [28].

Levobupivacaine is the S(-)-isomer of bupivacaine. In common with other local anaesthetic agents, it is widely accepted that Levobupivacaine blocks nerve conduction in sensory and motor nerves by blocking voltage sensitive sodium channels in the cell membrane. Levobupivacaine exhibits fewer cardiovascular toxicity effects [29,30] than bupivacaine and, as such, is safer for use as an infusion. There appears to be no measurable difference in clinical effectiveness between the two agents [31].

The aim of this study is to establish whether the use of continuous local anaesthetic infusion in the sub-pectoral tissue plane can improve post-operative analgesia and quality of life for patients undergoing mastectomy with or without axillary surgery. If the use of this local anaesthetic infusion technique is shown to be more effective than current practice, the reduction of pain and opiate use in the immediate post-operative period would be a significant benefit to patients. The technique also holds the potential to improve patients' quality of life by reducing the longer term risks of chronic pain and impaired shoulder function.

METHODS AND ANALYSIS

Study design

The study is a double blind, randomised, placebo-controlled, two~~multi~~-centre, parallel group trial in 160 female patients undergoing mastectomy with or without axillary involvement. The study was originally designed as a single centre study in Cornwall, but audit data prior to the study start confirmed a significant reduction in the number of mastectomies being conducted locally, following changes in the surgical team and surgical practice. In order to achieve the required sample size, the study design was therefore amended to include two study sites. At the same time, an emerging trend for early discharge of patients post-mastectomy prompted a change in the timing of primary

outcome data collection from 48 hours to 24 hours post-operatively. These changes to the original study design eventually delayed the study start by approximately ten months.

Participants will be randomly allocated to receive either 0.25% levobupivacaine or 0.9% sodium chloride by sub-pectoral infusion post-operatively for 24 hours. All participants will be provided with an intravenous (IV) morphine PCA system. Participants will be followed up for 24 hours in hospital and at approximately 14 days and six months post-operatively as out-patients.

Setting and participants

The study is being conducted in breast surgery departments within two NHS Trusts in Cornwall and York, England. The second site was selected after expressing interest in the study and because of its similar mastectomy pathway compared with the lead site. Eligible patients comprise all women presenting for unilateral mastectomy, with or without planned axillary clearance, at one of the participating hospitals. Main exclusion criteria are: primary reconstructive surgery; hypotension or hypovolaemia; allergy or sensitivity to local anaesthetic agents, morphine, paracetamol, ondansetron or cyclizine; daily opioid analgesic use; pregnancy. Study participants are patients who meet the screening criteria and are willing and able to give informed consent.

Study recruitment

The recruitment process is designed to fit in with routine clinical practice. Potential participants are identified from those attending out-patient breast clinics for discussion of breast cancer diagnosis and treatment options. Surgery is usually scheduled within a month of the initial clinic appointment, following attendance at a pre-assessment clinic. Women attending clinic for discussion of prophylactic mastectomy may also be eligible to participate in the study.

Patients for whom mastectomy is a potential treatment option and who appear eligible for the study are given a brief verbal introduction to the study by a clinician or nurse at the initial breast clinic consultation and provided with either a brief written study summary or a full participant information sheet, as deemed appropriate. Patients are subsequently telephoned within a few days by the breast care nurse (or research nurse, depending upon local arrangements) and further information about the study is provided verbally and/or by post to patients who express further interest. Patients who are interested in participating in the study are invited to meet the research nurse at the routine pre-operative assessment clinic so that any further questions can be answered and eligibility for the study confirmed. Arrangements are made for the patient to discuss aspects of the study with the surgeon or anaesthetist if required. Written informed consent is obtained from patients willing and eligible to participate, by an appropriately trained member of the research team. Patients who decline to take part in the study are not obliged to give a reason for declining but the reason(s) are recorded by the research nurse if provided.

Study procedures

Figure 1 shows the participant pathway through the study. Following informed consent, each participant is assigned a unique study number. Baseline data are normally collected at the pre-operative assessment clinic, following consent. At this point the research nurse briefly explains use of the morphine PCA system and familiarises the participant with the visual analogue scale (VAS) pain scoring system. Each VAS score is recorded on a separate page of a mini flipchart. The participant turns the page of the flipchart after an entry is made, so that the previous score is not visible for comparison when the next score is recorded.

Interventions

The active investigational medicinal product is 0.25% levobupivacaine (Chirocaine), an established local anaesthetic infusion agent, prepared as a 2.5mg/ml solution and packaged by the manufacturer (Abbott) in ampoules for injection. The comparator solution, 0.9% sodium chloride, is sourced from standard NHS supplies at the participating sites. Active and comparator trial treatments are presented identically in infusion bags prepared by the local hospital pharmacy prior to the operation date and supplied on an individual patient basis according to treatment allocation. Bags are presented in heat-sealed outer packaging and labelled in accordance with current EU regulatory requirements for clinical trials. Each bag is assigned a unique code number and a seven day expiry date.

Anaesthesia and surgery

Study participants receive a standardised anaesthetic protocol with respect to analgesic and antiemetic medication (Appendix 1). Mastectomy is performed with/without sentinel lymph node sampling or clearance, as clinically indicated.

Delivery of trial treatment

Trial treatment is delivered by means of an infusion catheter and device, supplied as a sterile pre-packed kit and licensed for the delivery of local anaesthetic. At the end of the surgical procedure the surgeon inserts the infusion catheter percutaneously into the sub-pectoral plane under direct vision within the surgical field. After skin closure, a 20ml bolus of active or comparator treatment is given via the catheter, which is then connected to the infusion device to provide an infusion of trial treatment at a continuous rate of 5ml/hr for 24 hours. In the active treatment arm this equates to a 50mg bolus of levobupivacaine followed by an infusion of 12.5mg/hr.

Post-operative management and outcome assessment

In the Recovery Unit, post-operative pain is routinely managed with 2-3mg aliquots of IV morphine to achieve a Verbal Rating Scale (VRS) pain score of none-mild pain. All participants are provided with a PCA system set up to deliver IV morphine boluses of 1mg with a 5 minute lock-out and no background infusion. Once all other routine recovery discharge criteria have been met, the patient is transferred to the ward. A baseline VAS pain score is recorded prior to transfer to the ward.

Participants are asked to complete VAS pain scores at rest every four hours, with reminders from ward staff. The sub-pectoral infusion is discontinued after 24 hours and the catheter removed, together with the PCA system. Outcome measures are assessed at 24 hours and at routine follow-up visits, approximately 10-14 days and six months after the day of surgery (Table 1).

Table 1: Trial schedule

	Pre-operative		*Post-operative*		
	Baseline	OPERATION AND SET-UP OF TRIAL INFUSION	24hrs	14 days*	6 months
Screen/eligibility	x				
Consent	x				
BMI	x				
Concomitant medication	x			x	x
Oxford Shoulder Score (OSS)	x				x
Shoulder questions (from OSS)				x	
Shoulder goniometry	x		x	x	x
EQ-5D 5L	x			x	x

Randomisation	x				
VAS pain score			x	x	x
VRS pain score			x		
PCA attempts			x		
Total morphine consumption (oral/IV)			x		
Analgesia use			x	x	x
Adverse events			x	x	x
Brief Pain Inventory					x
Service use					x

*Approximately 10-14 days post-operatively according to local practice

Primary outcome measures

The joint primary outcomes are (i) total morphine consumption (mg) in the first 24 hours (defined as the 24 hours following commencement of the sub-pectoral infusion), including all morphine given in the Recovery Unit and cumulative PCA use as recorded by the PCA device and (ii) total pain over the first 24 hours, as defined by measurement of the area-under-the-curve of each participant's self-reported pain scores at rest, measured using a visual analogue scale (VAS). VAS pain scores are recorded in the Recovery Unit and then at four hourly intervals for the first 24 hours. The VAS is presented as a 100mm horizontal line with verbal anchors at each end of "no pain" and "worst pain possible". The study participant selects and marks with a pen the point along the line that reflects their current pain perception. Periods of sleep are recorded retrospectively by the participant.

Secondary outcome measures

Secondary outcome measures include the number of PCA attempts in the first 24 hours following commencement of infusion; VAS pain scores at rest at 24 hours, 14 days and six months after surgery; incidence of post-operative nausea and/or vomiting (PONV) and use of supplemental analgesics and post-operative anti-emetics in the first 24 hours; self-reported analgesia use at 14 days and six months; duration of hospital stay; shoulder movement assessed by goniometry at 24 hours, 14 days and six months following surgery; Brief Pain Inventory at six months; shoulder function (as measured by the validated Oxford Shoulder Score [32]) at six months. Items from the Oxford Shoulder Score are also assessed at the first follow-up visit in relation to the previous seven days. Following the participant's discharge, the length of stay in hospital is recorded by the research nurse.

Randomisation

Patients who consent to participate and fulfil the eligibility criteria are randomly allocated to receive either levobupivacaine or saline in a 1:1 ratio via a secure web-based randomisation system. The allocation sequence is computer-generated by the UKCRC-registered Peninsula Clinical Trials Unit (CTU) in conjunction with an independent statistician, using a random permuted block design, with blocks of varying sizes. The block sizes will not be disclosed, to ensure concealment. As post-operative pain is expected to differ between patients who are having simple mastectomy, mastectomy with sentinel lymph node sampling or mastectomy with axillary node clearance, randomisation is stratified by planned surgical procedure, and by recruiting centre. To ensure that the study team, including the study statistician, remain blind to participants' allocated study groups, randomisation is undertaken by the relevant hospital pharmacy department.

Blinding and emergency unblinding

This is a double blind study and therefore participants, the surgical/anaesthetic team and the research team are unaware of each participant's allocated treatment group. To help assess the success of blinding, participants and the research nurse completing the follow-up assessments are asked to guess the participant's treatment assignment, at both the 14 day and 6 month follow-up visits.

In the event of a potential suspected unexpected serious adverse reaction (SUSAR), unblinding will be undertaken by the Sponsor in accordance with the regulatory requirements for safety reporting in Clinical Trials of Investigational Medicinal Products (CTIMPs). Unblinding may also be performed at the request of a senior clinician responsible for the care of a trial participant but such requests are likely to occur only in the case of an adverse clinical event and are expected to be rare. Any request to unblind treatment allocation for clinical reasons will be made directly to the relevant hospital pharmacy and the treatment allocation will be reported to the relevant clinician according to an agreed procedure. The Chief Investigator and CTU trial manager will be kept informed of all instances of unblinding but remain blind to treatment allocations themselves wherever possible. The pharmacy and CTU will maintain a record of all requests for unblinding.

Data management

Data will be collected and stored in accordance with the Data Protection Act, 1998. Data will be recorded on study specific data collection forms and transferred to the CTU for double-data entry on to a password-protected database stored on a restricted access, secure server. Participants' anonymity will be maintained on all documents. Direct access to the trial data will be restricted to members of the research team and the CTU, with access granted to the Sponsor on request.

All participants will be encouraged to continue with follow-up as per protocol although they may withdraw from the study at any time without it affecting their care. Data collected prior to withdrawal will be included in the study analysis unless a participant specifically requests that their data are removed from the database.

Sample size

The study sample size was calculated to assess the joint aims of the effectiveness of a 24 hour continuous sub-pectoral local anaesthetic infusion on total morphine consumption and total pain over the 24 hour post-surgery period. Few studies have addressed the question of what reduction in total morphine use after breast surgery might be clinically important. A small number of studies have reported total morphine use after breast surgery, at varying end points [33-40]. Four have reported total morphine use at 24 hours post-surgery; three of these were comparative studies. Two of these three studies based their sample size calculations on the same prior belief that the minimum clinically important difference was 10mg (estimated standard deviation of 10mg, estimated mean 24 hour total morphine consumption of 40mg) [39,40]. Therefore the minimum clinically important difference in 24-hour total morphine consumption was set as 10mg. These studies also showed actual standard deviations in 24 hour post-operative total morphine consumption of 10 to 22mg. To allow for the variability in the total morphine consumption being at the upper end of this range, the sample size calculation for total morphine consumption assumed a standard deviation of 20mg. To detect a difference of 10mg between groups, with 80% power and at the 5% significance level, requires 65 participants per group.

Similarly, there is a lack of information on which to base a formal sample size calculation for pain as the (joint) primary outcome measure. With the sample size of 65 participants per group, there will be approximately 80% power to detect an effect size of around 0.5 standard deviations on the measure of pain. Such an effect size would be considered as being of "moderate" size [41]. From

studies using a single VAS pain measure, it has been suggested that clinically meaningful differences are of the magnitude of 20mm to 30mm on a 100mm VAS [42], whilst a recent review reported that at the group level the difference in pain levels varied from 4mm to 40mm for acute pain [43]. Assuming the standard deviation of the VAS is between 13mm [44,45] and 26mm [38,46], this suggests that clinically meaningful effect sizes are of the order of at least 0.8 standard deviations. To detect a difference of around 0.8 standard deviations would need 26 patients per group, assuming a two-sided significance level of 5%, with 80% power. Therefore, the sample size of 65 participants per group will be large enough to detect clinically relevant differences between groups, in terms of pain.

The primary outcome measures are at 24 hours with a minimal probability of drop out. However, enough participants will be recruited to attempt to ensure 65 participants per group are followed up at six months. As patients remain engaged with the breast service for clinical reasons, loss to follow-up is also expected to be low but there may be losses to the study because, for example, of the need for further surgery. Therefore, in order to achieve a study sample of 65 women per group at the six month follow-up, the aim is to recruit a total of 160 participants over a two year period, which allows for a loss to follow-up rate of just under 20%.

Statistical analyses

The primary analyses are all pre-specified and a detailed statistical analysis plan will be completed and agreed by the Data Monitoring Committee (DMC) prior to commencement of analyses. Data will be reported and presented according to the CONSORT statement [47]. Ninety five percent confidence intervals will be calculated and presented where possible. The trial statistician will be presented with a database by the CTU containing a group code for each participant but not identifying which group is which; only after final analysis will the individual groups be identified.

The primary statistical analysis will follow an intention-to-treat approach, with the intent-to-treat population defined as all trial participants who completed the baseline assessment and underwent surgery. A per protocol analysis may be undertaken as a sensitivity analysis. The analysis of adverse events will be presented on a per protocol basis.

The primary analysis will compare (i) total morphine consumption and (ii) 24 hour pain AUC at 24 hours post-surgery between the two groups using an analysis of covariance, including the stratification factors as covariates, with suitable transformation of total morphine consumption and pain AUC considered as necessary. The estimates of the differences in mean total morphine consumption and mean pain AUC will be presented, together with a 95% confidence interval for the difference. Secondary outcomes will be compared between groups in a similar way using analysis of covariance for continuous outcomes and logistic regression for binary outcomes such as incidence of post-operative nausea and/or vomiting and use of post-operative anti-emetics in the 24 hours following surgery. Comparisons of interest will be presented with 95% confidence intervals.

Interim analysis

An interim analysis will be undertaken after the 14 day follow-up data have been collected for the first 80 participants recruited. Given the nature of the study a stringent criterion has been set for early termination of the trial on grounds of efficacy, namely $p<0.001$ for both the primary outcomes, else continuation of the trial being recommended. Other outcomes to be included in the interim analysis will be agreed with the DMC but are likely to include pain and vomiting, as well as six month outcomes data available at the time of the interim analysis. The interim analysis will not influence the final statistical analyses; given the single interim analysis and the stringent stopping

criteria, any further adjustment is not considered to be necessary. Serious Adverse Events (SAEs) will be routinely reported to the DMC and discussed (by email/telephone) as considered necessary; they will be formally reviewed at the interim analysis within the context of any emerging evidence on efficacy.

Missing data

The nature of missing data will be examined to consider appropriate approaches such as multiple imputation. Where assumptions are necessarily made, alternative assumptions will also be used to conduct additional analyses examining how sensitive the results are to the baseline assumptions. For the joint primary outcome of pain VAS, the AUC can be calculated from available VAS scores even if some are missing, by using linear interpolation; but if one or more observations are missing at the end of the 24-hour period, the last observation recorded will be carried forward in the primary analysis.

Economic evaluation

The study will include an economic evaluation from an NHS perspective. Following the NICE reference case, the primary outcome for the economic evaluation will be the incremental cost per QALY gained. The study will collect resource use data for the main drivers of the marginal cost. Unit costs will be assessed using standard NHS reference costs and prices. Health related quality of life will be measured using the EQ5D-5L data collected at baseline, 14 days and six months and valued using the interim "crosswalk" value set [48]. QALYs will be estimated within trial by assuming a constant tariff value for days 0-14 and a straight line extrapolation between tariff scores at 14 days and six months.

The outcome of the economic evaluation will be the incremental cost effectiveness ratio (ICER) (the additional cost per QALY gained). Sampling variation for the ICER will be reported as the standard deviation, estimated by bootstrapping and illustrated on the cost-effectiveness plane. Sensitivity analysis will be undertaken as appropriate (depending on sampling variation and an analysis of relationships between QALY estimates and the other outcome measures) but it will include an analysis of the sensitivity of the estimated ICER to the functional form of the extrapolation between tariff scores at 14 days and six months.

Ethics and dissemination

Ethical and safety considerations

Post-operatively, all participants are provided with a morphine PCA system in addition to the sub-pectoral infusion of trial treatment and therefore it is not considered that there are any ethical issues in using a placebo control. The recommended maximum single dose of levobupivacaine is 150mg. The dose for post-operative pain management should not exceed 18.75mg/hour and the maximum recommended dose during a 24 hour period is 400mg. The maximum 24 hour dose in this study is 350mg which is therefore well within recognised safe limits.

Research governance

The protocol has been approved by the South West - Central Bristol Research Ethics Committee (REC reference 12/SW/0149) and follows the recent SPIRIT guidelines [49]. The Sponsor is responsible for judging the substantiality of any amendments to the study protocol. Important protocol modifications will be communicated to relevant parties by the Peninsula Clinical Trials Unit.

The study is conducted subject to the terms of a Clinical Trial Authorisation issued by the Medicines and Healthcare products Regulatory Agency (MHRA) and in compliance with the

principles of the Declaration of Helsinki, ICH GCP, the Data Protection Act 1988 and the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. The study has been adopted by the NIHR Clinical Research Network and has relevant local NHS Research & Development approvals. The study is sponsored by Royal Cornwall Hospitals NHS Trust and managed by the UKCRC-registered Peninsula Clinical Trials Unit at Plymouth University (Registration No.31).

A Trial Management Team meets regularly to monitor and discuss the progress of the trial and to address any issues that arise. A Trial Steering Committee (TSC), with an independent chair, meets approximately every six to nine months to oversee the overall conduct of the trial. A Data Monitoring Committee (DMC), comprising two independent clinicians and one independent statistician, meets approximately every nine to twelve months to monitor safety and ethics, including issues relating to attrition, overall data completeness and patient safety. The agreed role and responsibilities of both committees are set out in written charters and the DMC provides written recommendations to the TSC following each meeting. The CTU will conduct central and site monitoring in accordance with a risk-based monitoring plan and the study Sponsor may audit trial conduct as deemed appropriate.

Timelines and dissemination plans

The study start was delayed due to amendments to the study design, described earlier. Research Ethics Committee approval was obtained in June 2012. Recruitment and training of staff involved in the study commenced in autumn 2012, and participant recruitment started at the first study site in December 2012. Participant recruitment is due to be completed by the end of 2014, with the final six month follow-up visits in early summer 2015. Statistical analyses will commence once final data collection, monitoring and data cleaning is complete. The Chief Investigator will establish a writing committee comprising individuals who have made key contributions to study design and conduct and it is anticipated that the first publications will be ready for submission by early 2016. As well as the submission of research articles to appropriate peer-reviewed journals, research findings will be submitted for presentation at local, national and international scientific meetings including the European Society of Regional Anaesthesia annual scientific meeting.

The study team will prepare a plain English summary of the study results which will be sent to the study participants as soon as possible after the end of the trial. In addition, the final results of the study will be presented at meetings of the local breast cancer support groups.

Conclusions

The lack of good quality evidence regarding the effectiveness of a continuous local anaesthetic infusion on post-operative pain following mastectomy indicates the need for well-designed clinical trials to investigate this subject. This study has been designed to investigate whether the use of a continuous local anaesthetic infusion in the sub-pectoral tissue plane can improve post-operative analgesia and quality of life for patients undergoing mastectomy, with or without axillary surgery.

This is the first study to assess the use of such a continuous infusion in the sub-pectoral plane, as well as the first study to assess the effects on post-operative shoulder function or the development of chronic pain, and will therefore give a pragmatic answer to the question of whether continuous local anaesthetic infusion in the sub-pectoral tissue plane should be used in these patients.

Author's contributions

IB adapted the sub-pectoral catheter technique and originally conceived the study. RL and IB developed the trial with methodological advice from SC and CP, specialist pain advice from KM

and trial management advice from JV. SC is the trial statistician. JV is the trial manager. All authors helped to develop the study protocol to its final version.

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Competing interests
None

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APPENDIX 1

Standardised anaesthesia protocol for SUBLIME trial participants

Pre-op:
No specific premedication

Peri-op:
Paracetamol 1g IV
Ondansetron 4mg IV
Dexamethasone 3.3mg (+/- 0.1mg)* IV unless clinically contraindicated
Intubation and ventilation at anaesthetist's discretion - with muscle relaxant of anaesthetist's choice
Sevoflurane in air: depth of anaesthesia at anaesthetist's discretion
Fentanyl: 3-6 mcg/kg IV during surgery
Fluids: at anaesthetist's discretion
All other non-opiate and non-anti-emetic drugs: at anaesthetist's discretion

Post-op:
IV rescue morphine in recovery unit, 2mg increments
IV morphine PCA, 1mg bolus, 5 minute lockout
Paracetamol 1g 6-hourly orally
Ibuprofen 400mg 8-hourly orally unless contraindicated
PRN: ondansetron 4mg (IV) 8-hrly and cyclizine 50mg (IV) 8-hrly

**Dexamethasone concentration differs between manufacturers and is typically available as 8mg dexamethasone in 2mls (4mg/ml dexamethasone) or as dexamethasome phosphate 4mg/ml (equivalent to 3.3mg/ml dexamethasone). Either preparation is acceptable i.e. 1ml of 4mg/ml dexamethasone phosphate (3.3mg dexamethasone) or 0.8ml of 4mg/ml dexamethasone (3.2mg dexamethasone).*

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IV rescue morphine in recovery unit, 2mg increments
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Paracetamol 1g 6-hourly orally
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PRN: ondansetron 4mg (IV) 8-hrly and cyclizine 50mg (IV) 8-hrly

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