PAIN

Persistent postsurgical pain may be predictable with sensory testing and preventable with a prolonged regimen of oral pregabalin: a randomised, double blind, controlled trial and mechanism study

--Manuscript Draft--

Manuscript Number:	
Full Title:	Persistent postsurgical pain may be predictable with sensory testing and preventable with a prolonged regimen of oral pregabalin: a randomised, double blind, controlled trial and mechanism study
Article Type:	Research Paper
Keywords:	Persistent postsurgical pain; preventive analgesia; perioperative sensory testing; conditioned pain modulation; temporal summation; wound hyperalgesia; catastrophising; state anxiety; poor quality of life
Corresponding Author:	Sibtain Anwar, MD PhD NIHR Biomedical Research Centre at Barts London, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	NIHR Biomedical Research Centre at Barts
Corresponding Author's Secondary Institution:	
First Author:	Sibtain Anwar, MD PhD
First Author Secondary Information:	
Order of Authors:	Sibtain Anwar, MD PhD
	Jackie Cooper, PhD
	Junia Rahman, MD
	Chhaya Sharma, MD
	Richard Langford, MD
Additional Information:	
Question	**Response**
Have you posted this manuscript on a preprint server (e.g., arXiv.org, BioXriv, PeerJ Preprints)?	No

Dear Editor,

We are delighted to submit our manuscript to PAIN, the leading journal for research in our specialty.

Our study is unique in combining a quantitative study of sensory changes in the nervous system that can lead to persistent postsurgical pain with an efficacy study of pregabalin to try and prevent this process.

While a clinical trial of only 150 patients would not be worthy of publication in an eminent journal, we have phenotyped every patient prior to surgery and following intervention. This provides objective evidence of the powerful protective effect of pregabalin as well as de novo signs of the transition from acute to persistent pain states. We also identify patient-specific risk factors which predispose individuals to pain persistence, including a failure of the ability to engage descending inhibitory pathways to modulate acute surgical pain.

All the authors have read and approved the paper. Drs. Anwar and Langford conceived the study design. Drs. Anwar, Rahman and Sharma recruited patients and collected all outcomes data. Drs. Anwar and Cooper contributed to the analysis, while all authors interpreted the findings and prepared this manuscript.

We thank the editorial tem and journal reviewers for considering our submission.

Yours faithfully,

Dr Sibtain Anwar
Consultant and Senior Lecturer in Pain Medicine
St. Bartholomew's Hospital

Persistent postsurgical pain is common and has long-term effects on quality of life. Surgical incision is believed to sensitise the central nervous system and neuromodulation of this process may be possible.

We randomised adults without chronic pain and undergoing elective cardiac surgery patients to either usual care, 14 days of perioperative pregabalin alone or in combination with a 48-hour postoperative infusion of ketamine. The primary endpoints were prevalence of moderate to severe sternotomy pain at three and six months following surgery, following three maximal coughs. Experimental pain responses before and following surgery were used to test nervous system function and screen for the transition from acute to chronic pain states. The study was registered on clinicaltrials.gov (NCT01480765.)

Pregabalin alone, and in combination with ketamine, reduced the development of persistent pain at three months [Odds Ratio = 0.13 (0.02 to 0.49), number needed to treat (NNT) =3.6 and 0.04 (0.0 to 0.28), NNT=3.1 respectively] and at six months following surgery [Odds ratio = 0.16 (0.03 to 0.66), NNT=4.5 and 0.00 (0.00 to 0.20), NNT=3.6]

Preoperative measures of state anxiety, pain catastrophising and poor quality of life were associated with poor outcomes as were reduced responses to the challenge of conditioned pain modulation. Postoperative de novo signs of temporal summation and hyperalgesia were also predictive.

The prolonged use of pregabalin in the perioperative period should be considered as a means to preventing the development of new chronic pain following surgery.

Quantitative assessment of responses to experimental pain may predict long-term outcomes.

Persistent postsurgical pain may be predictable with sensory testing and preventable with a prolonged regimen of oral pregabalin: a randomised, double blind, controlled trial and mechanism study

Sibtain Anwar [123], Jackie Cooper [2], Junia Rahman [3], Chhaya Sharma [3], Richard Langford [3].

1. Department of Perioperative Medicine, St. Bartholomew's Hospital
2. NIHR Biomedical Research Centre at Barts
3. Pain and Anaesthesia Research Centre, St Bartholomew's Hospital

Manuscript composed of 39 pages (including 3 figures and 6 tables)

Correspondence address:
Dr. Sibtain Anwar
Department of Perioperative Medicine
King George V Building
St. Bartholomew's Hospital
London. EC1A 7BE

Email: s.anwar@qmul.ac.uk
Tel: 02034658054
Fax: 02037658054
https://www.qmul.ac.uk/whri/people/academic-staff/items/sibtainanwar.html

Introduction

Persistent postsurgical pain (PPP) is common and has long-term effects on quality of life [17]. Defined as a new pain, developing postoperatively in and around the incision site, and persisting for at least three months following surgery, it is difficult to treat once established. Prevention of this phenomenon therefore seems attractive given the considerable impact on quality of life.

Up to half of all patients undergoing any type of surgery to the chest may be at risk of developing PPP, and over half of these cases will demonstrate features of neuropathic pain [14]. Postoperative pain can persist for many years - for at least five years, for example following breast surgery, with significant effects on quality of life [8; 20]. Long-term data for PPP following cardiac surgery is lacking but level-one clinical trial data reveals a prevalence of 27-41% at three postoperative months[5; 23; 26].

Surgical incision is believed to cause hyperalgesia and sensitise the central nervous system [17]. The gabapentinoids are effective in neuromodulating these processes during the treatment of established neuropathic pain [27]. They have also been shown to suppress central sensitisation in other centrally driven processes, such as chronic cough, leading to improved symptoms as well as quality of life [24].

Studies of the preventive effects of gabapentinoids have been limited in terms of duration of perioperative administration, rarely extending beyond a few days [18]. Pregabalin has improved bioavailability, efficacy and tolerability, as compared to gabapentin, which may be important when considering its prolonged and prophylactic use in pain-free surgical patients [9]. The concept of preventive or *protective* analgesia is better established with some neuromodulating analgesics, such as ketamine, [4] but surprisingly few studies have taken the approach of combining agents, even in established neuropathic pain - although the exceptions have stood out for their efficacy[10-12].

Not all patients are destined to develop PPP. Predicting a patient's susceptibility to the development of PPP may inform the risk: benefit evaluation of any preventive strategy or medication especially if the latter has potential for side effects. Preoperative challenges to the nervous system with experimental pain may predict the subsequent development of pain persistence [15]. Sensory testing can also be repeated following surgery to examine putative mechanisms for the transition to persistent pain states.

No study has yet tested a regimen to prevent PPP alongside sensory testing of pain pathways as biomarkers, for efficacy as well as individual patient susceptibility to pain persistence. The aim of this study was to assess the effect of a prolonged regimen of preventive analgesia on pain pathways and PPP outcomes but also to determine risk factors and predictors for this phenomenon.

Methods

Study design

Heart PPPAIN – Heart surgery and Persistent Postsurgical PAIN - was a prospective, double blind, randomised, parallel 3-group, placebo-controlled trial of preventive analgesia alongside a mechanistic study for PPP. We screened patients, aged 18 to 80 years, scheduled to undergo elective cardiac surgery via sternotomy, at the two London Heart Centres of St. Bartholomew's Hospital and The London Chest Hospital.

Study participants

We excluded patients who had undergone sternotomy previously, if they gave a history of chronic pain, or if they regularly used pain medication (other than paracetamol and non-steroidal anti-inflammatory drugs.) As pregabalin is renally cleared, we used an estimated glomerular filtration rate < 60 ml/min to exclude patients or to withhold single postoperative doses, based on twice-daily blood testing. If values were <30ml/min or renal replacement therapy was required, we withdrew patients from the study.

All participating patients gave written, informed consent for this clinical trial, conducted as per the protocol approved by the National Research Ethics Service (NRES) and the Medicines and Healthcare Products Regulatory Authority (MHRA.) The study was registered on clinicaltrials.gov (NCT01480765.)

Randomisation and blinding

As set out in figure one, 150 patients were recruited and block randomised (in groups of thirty) to one of the following three treatment groups, using a computer-generated randomisation sequence, created and managed in a blinded manner by the Barts Trials Pharmacy:

1. **Usual Care (UC group) paracetamol and morphine patient controlled analgesia:** received one preoperative and fourteen postoperative days of placebo capsules, as well as 48 postoperative hours of placebo ketamine (normal saline) intravenous infusion.
2. **UC + Pregabalin (P group):** received one preoperative and fourteen postoperative days of 150mg pregabalin capsules, as well as 48 postoperative hours of placebo ketamine (saline) infusion.
3. **UC + Pregabalin and ketamine (PK group):** received one preoperative and fourteen postoperative days of 150mg pregabalin capsules, as well as ketamine infusion 0.1mg/kg/hour for 48 hours postoperatively.

Allocation concealment was achieved by the use of study capsules and intravenous infusions with identical appearance for active and placebo drug. Pregabalin study capsules were supplied by Pfizer with no other contribution to the design, conduct, analysis or publication of this trial. Sealed 50ml syringes containing clear ketamine or placebo (0.9% saline) solution were prepared in a blinded manner by the clinical trials unit at St. Bartholomew's Hospital, with no other involvement in patient care.

Patients, healthcare providers and research staff collecting outcomes data all remained blinded to treatment allocation until all follow up assessments were

completed and the data sets were locked and submitted to the trials pharmacy for release of the randomisation code.

Study Procedures and drug administration

All patients completed baseline questionnaires of EQ-5D Quality of Life (EuroQOL, Rotterdam, The Netherlands), Spielberger State Anxiety and Pain Catastrophising Scale, as potential risk factors for the development of PPP[16; 25].

On the day prior to surgery, we tested sensory responses to painful stimuli as set out below. This was done in a quiet environment with patients in a comfortable semi-reclined position and with both eyes closed. Four reference points were used for sensory testing of the planned incision site (five centimeters from the midline of the sternum, at the level of the second and third rib bilaterally - marked as X on Figure One.) Remote sensory testing was performed on the right forearm at the mid point between the wrist and the elbow as a surrogate measure of central processing of pain.

Pressure pain measures

This test measures sensitivity of pain pathways to increasing mechanical pressure. We used a handheld pressure algometer (Figure Two) (Somedic AB, Stockholm, Sweden) to measure pain pressure threshold (PPT) at the same four standardised testing points on the chest as well as the remote site. The diameter of the contact tip was $1cm^2$. A standard pressure of 30 Kilopascals per second

was applied perpendicular to the skin until the patient defined the pressure as pain. We took the mean of four, random-ordered, measurement points as PPT.

Conditioned pain modulation (CPM) is the physiological engagement of the endogenous analgesic system to reduce pain intensity or increase threshold to pain detection[30]. We calculated the CPM effect as the difference in algometer-derived PPT readings, with and without the application of a conditioning remote noxious stimulus.

Ischaemic arm pain was used as the conditioning stimulus. A blood pressure cuff was manually inflated to 250mm Hg to achieve an arm pain score on the numeric rating scale (NRS) of 5/10. In refractory cases, after 15 minutes of inflation, the cuff was further inflated in 10mm Hg increments to attain this pain score. PPT measurements were repeated at this point to record the CPM effect.

Tactile pain measures

We used twenty, progressively stiffer monofilament von Frey fibres (Ugo Basile, Gemonio, Italy) to determine tactile pain detection thresholds (TPT) at the sites described above. Ascending fibres were applied perpendicular to the skin for one second, to the point of deformation of the fibre, until the patient described pain, with the TPT defined as the least force that elicits a sensation of pain on buckling of the standardised filament. This was determined by repetitive testing of ascending fibre sizes, until the same von Frey fibre elicits two similar responses

in succession. All measurements were repeated at the remote site on the right arm.

Temporal summation (TS) to tactile stimulation is an indicator of a sensitised pain system [29]. We used the von Frey fibre one reading below the TPT, and stimulated at a frequency of 2HZ for 60 seconds on all test points. NRS score increases of more than one point were reported as positive TS, as described in the literature [1; 28].

We retested pain responses at the sternotomy site as well as remotely on postoperative day four to assess for new postsurgical TS as well as changes in PPT. In addition, a dynamic assessment of spreading sensitisation was carried out to give an indication of zone of secondary hyperalgesia (ZoH.) We used the TPT fibre but starting from an area free of pain - the lateral chest – moved towards and perpendicular to the midline sternotomy. The von Frey fibre was advanced in one-centimeter increments until the first sensation of pain was achieved. This distance from the midline sternotomy was measured using a disposable tape measure and we used the sum of the four recordings as a measure of ZoH[29].

Clinical management of perioperative care

Nursing staff administered the first study capsule (containing either 150mg pregabalin or matched placebo lactose) to all patients two hours prior to surgery.

Anaesthesia was induced with propofol and fentanyl (restricted to a total intraoperative dose of 7.5- 20mcg/kg) and maintained with Isoflurane, prior to cardiopulmonary bypass, before converting to intravenous infusion of propofol for the remainder of the perioperative period. Remifentanil was prohibited in this study.

Cardiopulmonary bypass was established on all patients using moderate hypothermia (30– 34 degrees Celsius), a membrane oxygenator and a centrifugal pump. The intravenous infusion of ketamine or placebo was started at the end of cardiac surgery, once sternal closure with wires had commenced.

All patients remained sedated and ventilated for transfer to the Cardiac Intensive Care Unit (CICU) following surgery, and extubation took place as per unit protocol. In addition to the trial regimen, all patients received (usual care) patient controlled analgesia (PCA) in the form of morphine 1mg/ml/bolus with a lockout period of five minutes alongside regular paracetamol.

During the recovery from surgery, study capsules were continued twice daily for ten continuous days, followed by a dose reduction to 75mg for days 11 and 12, and then 50 mg for days 13 and 14.

Chest drains were removed, as per usual care, with provision of patient controlled morphine analgesia up to this point. Supplementary regular oral codeine was provided following drain removal, and in addition, oral tramadol on demand for breakthrough pain.

If patients were discharged from hospital prior to completion of the 14-day capsule regimen, any remaining doses were dispensed by the trials pharmacy for the patients to complete the course at home. Any unused capsules were returned to the trial pharmacy and recorded. Details of any missed doses during in patient stay or early withdrawal from either drug were also recorded. We assessed pain and health-related quality of life assessments with structured questionnaires at three and six postoperative months.

Outcomes

The primary outcome was the proportion of patients with clinically meaningful pain at three and six months following cardiac surgery. This was defined as a NRS greater than three out of a maximum score of ten - indicating moderate to severe pain intensity - following a functional assessment of three maximal coughs[22] .

Secondary outcomes included clinically meaningful acute pain scores at the sternotomy and saphenectomy sites (NRS>3, following three maximal coughs and dorsiflexion respectively) alongside total morphine consumption, both measured at 24 hours following surgery. Recovery from surgery was assessed in terms of sedation and nausea scores at 24 hours (Likert scale of 0=none, 1=mild, 2=moderate, 3=severe), time to extubation, times to readiness for discharge from the CICU and hospital, as well as safety measures of respiratory rate and arterial carbon dioxide partial pressure at 24 hours following surgery and any episode of inpatient diplopia – a common transient side effect of pregabalin use

in naïve patients. Changes in sensory testing following surgery were also recorded as secondary outcomes, as well as potential biomarkers of drug efficacy.

During the final study assessment at six months following cardiac surgery, we assessed the presence of neuropathic PPP (S-LANSS score above 12), EQ-5D based quality of life index, as well as any medication use or sleep disturbance attributable to PPP, over the previous seven days.

In addition to baseline anxiety and catastrophising scores, we also collected patient age, sex, weight, baseline EQ-5D quality of life index, duration of surgery and the need to harvest the left internal mammary artery (LIMA) as biologically plausible risk factors for the development of PPP.

Statistical analysis

This study was powered to detect a two-thirds reduction in the percentage of patients with PPP. Pilot observational data from 312 consecutive patients undergoing elective sternotomy in our centre over a six-month period revealed a PPP prevalence of 39.7%. Based on an alpha of 5% and power of 80%, we therefore calculated a sample size per group of 43 patients. To allow for early withdrawals and loss to follow up, we recruited 50 patients per group

Patients were included in the final analysis of outcomes and safety on an intention to treat basis, with imputation of missing data on the basis of average values for the group. Sensitivity analysis for the primary outcome was also undertaken assuming patients lost to follow-up had pain at three and six months which is the most conservative possible outcome. All data was entered using

two-pass verification and analysis was performed using Stata (version 14, StataCorp Texas).

We descriptively compared the baseline characteristics across the three treatment groups. All primary and secondary outcomes are reported as frequency and percentages or medians and interquartile range [IQR]. In the case of the primary outcome, this is also reported as number needed to treat (NNT) (inverse of the absolute risk reduction.) Where the number of patients experiencing pain was small, we used exact logistic regression to estimate odds ratios and confidence intervals comparing each active treatment group to the UC group. For ordinal score data we used an ordinal logistic regression model, with the proportional-odds assumption tested by an approximate likelihood ratio test. If the continuous secondary outcomes were not normally distributed, we used quantile regression to compare medians between the groups, estimating the difference in medians along with bootstrap confidence intervals. As the groups were balanced in terms of covariates, and as sparse data may result in bias if too many variables are included in the model, the main analysis focused on unadjusted results. For the primary outcome we also ran a model to adjust for age, gender, weight, preoperative EQ-5D index, state anxiety, pain catastrophising as well as the duration and type of surgery as a sensitivity analysis to the main result. A Firth logistic regression model was used for this in order to obtain bias corrected estimates.

The association of each predictor variable with pain was examined using Firth logistic regression with adjustment for randomization group. To examine whether the effect of any predictor was stronger in the treatment groups we

tested for interaction. We used NRS score as a continuous dependent variable for this to increase the power and an ordinal logistic regression model was fitted for each predictor along with treatment group and the interaction term.

The reported p values have not been adjusted for multiple comparisons. Results from all tests are shown allowing secondary outcome results to be interpreted in light of the number of tests made.

Results

We screened 362 patients to recruit 150 patients for the Heart PPPAIN study (Figure Three.) Three and six month assessments were completed on 148 patients. Two patients were lost to follow up: one due to death on day seven following surgery and one patient emigrated. Data was imputed for these two patients assuming no pain at follow-up, as this was the most likely outcome for the treatment groups.

Additional withdrawals from treatment also took place for delayed recovery from cardiac surgery, drug intolerance or patient choice, as set out in figure one. All patients were approached for three and six month follow-up and any missing data for unresponsive patients was imputed on an 'average for the group' basis, allowing analysis for all 150 patients.

Baseline patient characteristics were similar among the three groups (Table One).

Primary outcome

As set out in Table Two, pregabalin alone and in combination with ketamine reduced the likelihood of developing PPP at three postoperative months from 34% in the control group to 6% and 2% respectively (Odds Ratio (OR) = 0.13 (0.02 to 0.49), NNT=3.6 and 0.04 (0.00 to 0.28), NNT=3.1 respectively) and at six months from 28% to 6% and 2% (Odds ratio = 0.16 (0.03 to 0.66), NNT=4.5 and 0.00 (0.00 to 0.20), NNT=3.6).

These effects remained significant after adjustment for possible confounders (supplementary table). Confidence intervals for the two active arms for the primary outcome reveal no difference in efficacy. No further comparison is therefore made between the active arms.

Sensitivity analysis assuming both patients who withdrew from the treatment arms went on to experience pain at three and six months demonstrated that the findings were robust with odds ratios (95% CI) for P and P+K groups respectively of 0.17 (0.04 to 0.59) p=0.003, 0.08 (0.01 to 0.39) p=0.0002 at 3 months and 0.22 (0.05 to 0.80) p=0.017 and 0.05 (0.00 to 0.38) p=0.0004 at 6 months.

Secondary outcomes:

Both pregabalin alone and the combined PK group reduced the likelihood of clinically meaningful acute pain scores at 24 postoperative hours, for sternotomy [OR=0.24 (0.09 to 0.62), NNT=3.1 and 0.21 (0.08 to 0.53), NNT=2.8 respectively] as well as saphenectomy [OR=0.11 (0.02 to 0.41), NNT= 2.4 and 0.28 (0.09 to 0.83), NNT=3.4 respectively.] At this time point, these were associated with median reductions in morphine requirement of 29mg (IQR=8-50) and 33mg (12-54) respectively for the P and PK groups compared to a median of 52mg (33-830 for patients receiving usual care, with improved nausea scores in both active arms (table three).

We found an increase in PPT in both active arms but only when tested at a site remote to the incision (table four). By contrast, the control group showed a decrease in the PPT, indicating hyperalgesia. When we tested at the site of sternotomy there were no significant postoperative changes in PPP following surgery.

New temporal summation was significantly reduced in both active arms, at the incision site as well as remotely. Likewise, ZoH was reduced in groups P and PK compared to UC.

In terms of the potential sedating effects of the pregabalin and ketamine in the active arms, there were no significant differences in time to extubation or length of stay on the CICU. Safety was assessed in terms of the occurrence of inpatient

diplopia, revealing an increased likelihood in both active arms with numbers needed to harm of 6.3 for pregabalin alone and 4.5 for the combined PK group. This was transient in all cases and resolved with omission of a single capsule dose. Median sedation scores were 2 in all groups but with statistically significant increases in sedation in both active arms, although respiratory rate and arterial carbon dioxide tension revealed no clinically meaningful differences.

Length of stay in the hospital was significantly shorter in groups PK as compared to usual care (UC). Confidence intervals indicated no significant difference between both active arms with a median difference of 0.5 days.

At the final study assessment, at six postoperative months, patients in both active arms demonstrated significant differences in EQ-5D indices of quality of life, as well as in the likelihood of developing neuropathic pain, requiring analgesics or describing sleep disturbance as a result of PPP (table three.)

Associations with PPP

Analysis of risk factors for PPP was carried out for all 150 patients with adjustment for randomisation group to allow assessment of the relationship between patient or surgical factors and PPP outcomes (independent of treatment allocation.)

Preoperative measures of anxiety, catastrophising and poor quality of life were associated with poor PPP outcomes (Table Five) as were reduced responses to CPM. Surgical duration and technique seems to have less impact. Postoperative reductions in PPT remote to the sternotomy were associated with PPP alongside the development of new TS, either at the sternotomy site or remotely. While ZoH may indicate efficacy of preventive analgesia it is not independently associated with PPP in this study. No significant interactions with treatment group were found, but the study has low power to detect these effects.

Discussion

This is the first study to describe the potential to improve pain and quality of life at three and six months following cardiac surgery. We found that the use of a prolonged regimen of pregabalin during the entire perioperative period protected patients from pain persistence.

Over and above the cost of this additional medication, not all patients will tolerate centrally acting analgesic drugs, pre-operatively or for a prolonged postoperative period, and side effects such as somnolence or dizziness have the potential to limit mobilisation and return to functioning. It may be optimal to identify the patients most at risk of developing PPP, and hence we evaluated patient phenotypes, namely those with poor preoperative quality of life, state anxiety and pain catastrophising. In addition, it may be possible to predict

susceptibility by challenging patients to experimental pain before surgery with the CPM platform.

Countering the argument for using drugs these drugs in high-risk patients only, is the potential to spare the use of high dose opioids, in all patients. Perioperative opioid use may delay recovery as well as increase the risks of long-term use and dependence in the postoperative period [3; 6]. In other surgical models, such as thoracic surgery, local anaesthetic techniques (e.g. thoracic epidural or paravertebral block) are frequently used as part of a multimodal analgesic regimen. In contrast, cardiac surgery has traditionally relied on large doses of intra- and post-operative opioids, as the mainstay of analgesic treatment. Given that non-steroidal anti-inflammatory drugs are also avoided in this group of patients, an alternative opioid sparing regimen such as in this trial, may reduce sensitisation of the CNS [7; 19] and confer long-term outcomes benefits.

Opioid sparing properties of pregabalin are well known [21] but the potential to reduce length of stay in hospital and provide lasting improvements in quality of life to six months are new findings, requiring corroboration in large multicentre trials. The latter is particularly surprising given the large improvements in quality of life index of over 0.2. This suggests more than a simple reduction in pain intensity and more likely a system-wide benefit of opioid sparing, perhaps even a neurocognitive effect.

There is some debate in the non-cardiac surgery literature regarding the preventive effects of pregabalin where smaller doses or shorter durations of

treatment are used, especially for less painful incisions, or where treatment is started late in the postoperative period once sensitisation of the CNS has begun[4; 13]. Other plausible explanations for the differences in outcomes between studies in the literature and our clinical trial are the varying tissue injury, pain intensity and pain mechanisms underlying these different procedures. This has led to consensus agreement on the need for procedure specific studies of PPP [18].

This is the first trial of pregabalin specifically for the prevention of PPP following surgical incisions on the chest, an area where PPP is highly prevalent. Pesonen and colleagues conducted a randomised trial of low dose pregabalin and only for five days, in order to primarily assess acute pain scores and opioid requirement. They demonstrated opioid sparing as well as reduced confusion on the CICU following cardiac surgery [23]. While not powered for long-term outcomes, they did report improved pain scores on movement at three months in the pregabalin arm compared to usual care but not at earlier time points.

Identifying the patient at risk of developing PPP is particularly important given the possibility of diplopia and sedation following initiation of pregabalin in pain free patients. Our study suggests that preoperative assessments of quality of life, state anxiety, pain catastrophising, combined with CPM response, could potentially predict high-risk patients. With this in mind, simplified scoring and tests suitable for routine care should be evaluated. Another putative risk factor for PPP in other studies is young age but we failed to corroborate this -

likely as a result of the small numbers of younger patients in this relatively elderly population (median age of 66 years.)

The relationship between pre-existing anxiety and catastrophising and both acute and chronic pain is established for other surgical incisions [16; 25]. Further study is required to determine whether these risk factors are fixed or some (e.g. state anxiety) can be modified, for example, by pregabalin.

A unique opportunity exists to translate the findings of this study into clinical practice, as cardiac surgery is the only adult discipline that still routinely administers anxiolytic premedication to patients prior to transfer to the operating room. Currently these are benzodiazepine or opioid-based but, with pregabalin ranked first in terms of patient tolerability in a recent meta-analysis of anxiolytics [2], our study could strengthen the case for such a change in clinical practice.

Study limitations

This study has several limitations. Identical dose oral pregabalin was administered to all patients rather than titrating for body weight. While the multivariate model included weight, there remains a possibility of under or over-dosing in some subjects. This may explain the sedation and diplopia in both active arms and justifies a dose-finding study with smaller doses than the 300mg per day of pregabalin used in this trial.

While there was a statistically significant difference in sedation between usual care and both active arms, it could be argued that is unlikely to be of clinical significance (median differences of 0.38 and 0.26.) The use of a limited four-point Likert scale may have reduced the sensitivity of measurement for this important side effect.

The powerful effect of pregabalin in preventing PPP in cardiac surgical patients made the combined pregabalin-ketamine arm of this trial redundant. A ketamine only arm may have proved useful in determining the contribution of ketamine to this effect.

Conclusion

Surgical outcomes are improving with the key exception of PPP, which is now widely recognised and studied following, for example, inguinal hernia repair and orthopedic surgery. In the former, it is recognised as the most serious complication whereas following most other surgical procedures, it is the most common longer term complication[17].

We provide evidence for the protective effect of a prolonged regimen of perioperative pregabalin on PPP at three and six months time points following cardiac surgery. We also present data suggesting that patients with state anxiety,

feature of pain catastrophising, low preoperative quality of life or reduced response to CPM may be at increased risk of PPP. This may warrant focused discussion during informed consent as well as the use of pregabalin, in spite of its potential for short-term side effects.

In addition, postoperative de novo signs of new temporal summation and decreased pain thresholds at a site remote to incision, may be early warning signs of hyperalgesia and CNS sensitisation. These signs could also trigger early intervention to prevent pain persistence. Further studies should screen and target these features as a potential means of risk identification and reduction in all surgical patients.

Funding

This study was funded by a research grant from the European Association of Cardiothoracic Anaesthesiologists, independent of study design, data collection, analysis and preparation of this manuscript.

No conflict of interests is declared

References

[1] Aasvang EK, Gmaehle E, Hansen JB, Gmaehle B, Forman JL, Schwarz J, Bittner R, Kehlet H. Predictive risk factors for persistent postherniotomy pain. Anesthesiology 2010;112(4):957-969.

[2] Baldwin D, Woods R, Lawson R, Taylor D. Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. Bmj 2011;342:d1199.
[3] Brat GA, Agniel D, Beam A, Yorkgitis B, Bicket M, Homer M, Fox KP, Knecht DB, McMahill-Walraven CN, Palmer N, Kohane I. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. Bmj 2018;360:j5790.
[4] Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. Cochrane Database Syst Rev 2013;7:CD008307.
[5] Choiniere M, Watt-Watson J, Victor JC, Baskett RJ, Bussieres JS, Carrier M, Cogan J, Costello J, Feindel C, Guertin MC, Racine M, Taillefer MC. Prevalence of and risk factors for persistent postoperative nonanginal pain after cardiac surgery: a 2-year prospective multicentre study. CMAJ 2014;186(7):E213-223.
[6] Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. Bmj 2014;348:g1251.
[7] Colvin LA, Fallon MT. Opioid-induced hyperalgesia: a clinical challenge. Br J Anaesth 2010;104(2):125-127.
[8] Gartner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H. Prevalence of and factors associated with persistent pain following breast cancer surgery. Jama 2009;302(18):1985-1992.
[9] Gilron I. Gabapentin and pregabalin for chronic neuropathic and early postsurgical pain: current evidence and future directions. Curr Opin Anaesthesiol 2007;20(5):456-472.
[10] Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. Lancet 2009;374(9697):1252-1261.
[11] Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med 2005;352(13):1324-1334.
[12] Gilron I, Jensen TS, Dickenson AH. Combination pharmacotherapy for management of chronic pain: from bench to bedside. Lancet Neurol 2013;12(11):1084-1095.
[13] Gilron I, Kehlet H. Prevention of chronic pain after surgery: new insights for future research and patient care. Can J Anaesth 2014;61(2):101-111.
[14] Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. Pain 2013;154(1):95-102.
[15] Johansen A, Schirmer H, Stubhaug A, Nielsen CS. Persistent post-surgical pain and experimental pain sensitivity in the Tromso study: Comorbid pain matters. Pain 2014;155(2):341-348.
[16] Kalkman CJ, Visser K, Moen J, Bonsel GJ, Grobbee DE, Moons KG. Preoperative prediction of severe postoperative pain. Pain 2003;105(3):415-423.
[17] Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. The Lancet 2006;367(9522):1618-1625.

[18] Kehlet H, Rathmell JP. Persistent postsurgical pain: the path forward through better design of clinical studies. Anesthesiology 2010;112(3):514-515.
[19] Martinez V, Fletcher D. Prevention of opioid-induced hyperalgesia in surgical patients: does it really matter? Br J Anaesth 2012;109(3):302-304.
[20] Mejdahl MK, Andersen KG, Gartner R, Kroman N, Kehlet H. Persistent pain and sensory disturbances after treatment for breast cancer: six year nationwide follow-up study. Bmj 2013;346:f1865.
[21] Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. Br J Anaesth 2015;114(1):10-31.
[22] Moore RA, Straube S, Aldington D. Pain measures and cut-offs - 'no worse than mild pain' as a simple, universal outcome. Anaesthesia 2013;68(4):400-412.
[23] Pesonen A, Suojaranta-Ylinen R, Hammaren E, Kontinen VK, Raivio P, Tarkkila P, Rosenberg PH. Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: a randomized placebo-controlled trial. Br J Anaesth 2011;106(6):873-881.
[24] Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. The Lancet 2012;380(9853):1583-1589.
[25] Theunissen M, Peters ML, Bruce J, Gramke HF, Marcus MA. Preoperative anxiety and catastrophizing: a systematic review and meta-analysis of the association with chronic postsurgical pain. Clin J Pain 2012;28(9):819-841.
[26] Turan A, Karimi N, Zimmerman NM, Mick SL, Sessler DI, Mamoun N. Intravenous Acetaminophen Does Not Decrease Persistent Surgical Pain After Cardiac Surgery. J Cardiothorac Vasc Anesth 2017;31(6):2058-2064.
[27] Turk DC, Wilson HD, Cahana A. Treatment of chronic non-cancer pain. Lancet 2011;377(9784):2226-2235.
[28] Weissman-Fogel I, Granovsky Y, Crispel Y, Ben-Nun A, Best LA, Yarnitsky D, Granot M. Enhanced presurgical pain temporal summation response predicts post-thoracotomy pain intensity during the acute postoperative phase. J Pain 2009;10(6):628-636.
[29] Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011;152(3 Suppl):S2-15.
[30] Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. Curr Opin Anaesthesiol 2010;23(5):611-615.

Figure One. Sensory testing sites

X marks four testing sites at 5cm from the midline on the second and third rib bilaterally. Arrows indicate lateral starting points for zone of hyperalgesia testing, followed by 1cm incremental steps towards the X point.

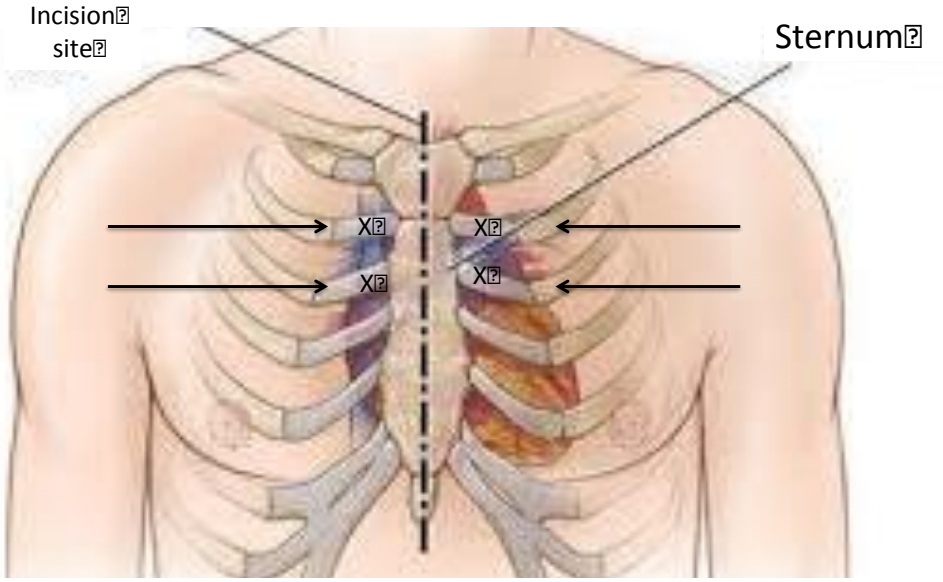
Figure Two. Pressure algometer (Somedic AB, Stockholm, Sweden)

Figure Three. CONSORT Diagram

Twenty-five word summary for TOC:

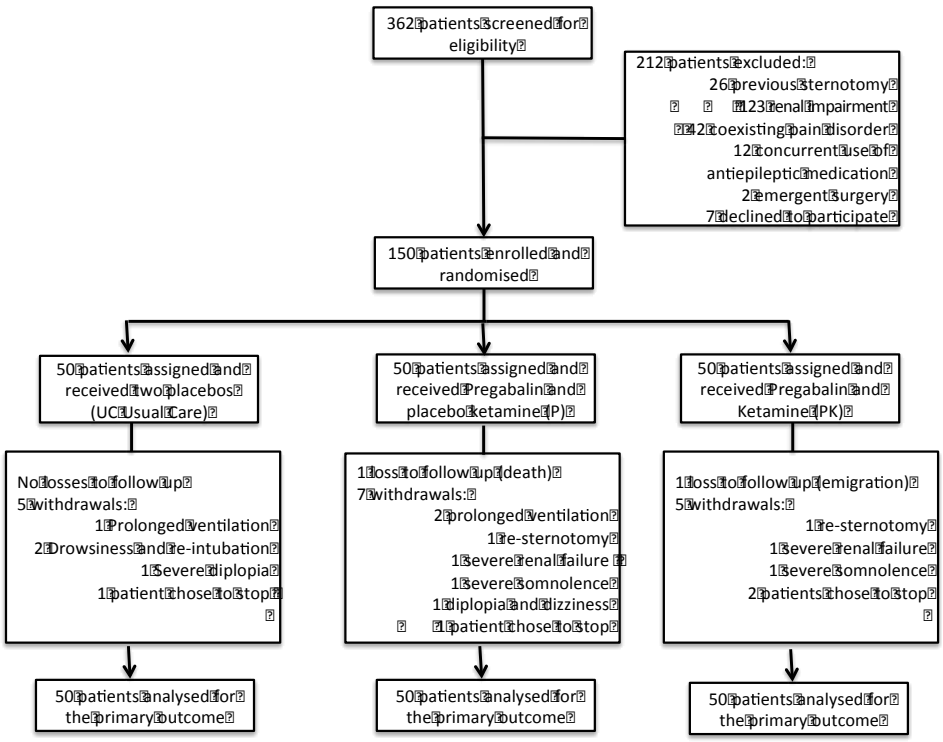
Persistent postsurgical pain is predictable with tests of preoperative conditioned pain modulation as well as postoperative new hyperalgesia and summation. Prevention is challenging but possible

Figure



Figure

Figure


362 patients screened for eligibility
212 patients excluded:
26 previous sternotomy
123 renal impairment
42 coexisting pain disorder
12 concurrent use of antiepileptic medication
2 emergent surgery
7 declined to participate
150 patients enrolled and randomised
50 patients assigned and received two placebos (UC Usual Care)
50 patients assigned and received Pregabalin and placebo ketamine (P)
50 patients assigned and received Pregabalin and Ketamine (PK)
No losses to follow up
5 withdrawals:
1 Prolonged ventilation
2 Drowsiness and re-intubation
1 Severe diplopia
1 patient chose to stop
1 loss to follow up (death)
7 withdrawals:
2 prolonged ventilation
1 re-sternotomy
1 severe renal failure
1 severe somnolence
1 diplopia and dizziness
1 patient chose to stop
1 loss to follow up (emigration)
5 withdrawals:
1 re-sternotomy
1 severe renal failure
1 severe somnolence
2 patients chose to stop
50 patients analysed for the primary outcome
50 patients analysed for the primary outcome
50 patients analysed for the primary outcome

Table

	Intervention arm		
	Usual care (UC)	Pregabalin (P)	Pregabalin & ketamine (P+K)
Male sex n/N (%)	36/50 (72%)	41/50 (82%)	40/50 (80%)
Age (years), median [IQR]	67.5 [52-72]	67.5 [59-73]	64 [54-72]
Weight (Kilograms)	81 [70-92]	76 [68-84]	77 [66-89]
Pre op EQ-5D quality of life index	0.721 [0.395-0.784]	0.687 [0.395-0.768]	0.686 [0.382-0.776]
Anxiety: Spielberger score	38 [31-47]	39 [32-44]	40 [33-50]
Catastrophising: Pain Catastrophising Scale score	14.5 [6-26]	14 [5-24]	13 [7-28]
Duration of surgery (minutes)	285 [225-320]	275 [245-330]	287.5 [250-315]
LIMA dissection	35/50 (70%)	39/50 (78%)	37/50 (74%)

Table one. Baseline characteristics of patients as per randomisation group
Data is presented as portion (percentages) or median [IQR: Interquartile Range] PPT= pressure pain threshold, CPM= conditioned pain modulation, LIMA= left internal mammary.

Table

	Intervention arm		
	Usual care (UC)	**Pregabalin (P)**	**Pregabalin & ketamine (PK)**
PPT Sternotomy site (KPa)	214 [160-294]	266 [214-337]	243 [193-363]
PPT remote (KPa)	208 [180-312]	289 [215-352]	264 [176-397]
Percent change in PPT with CPM	19.4 [-1.8 – 67.0]	23.8 [2.1 – 47.8]	16.3 [-2.5 – 48.6]
Presence of preoperative temporal summation at sternotomy site	17/50 (34%)	15/50 (30%)	14/50 (28%)
Presence of remote temporal summation (forearm)	10/50 (20%)	9/50 (18%)	9/50 (18%)

Table two Baseline sensory measurements
Data is presented as median (IQR) or proportions (%.) PPT = pressure pain threshold, CPM = conditioned pain modulation.

Table

		Intervention arm		
		Placebo = Usual care (UC)	Pregabalin (P)	Pregabalin & ketamine (P+K)
PRIMARY OUTCOMES:				
Prevalence of moderate to severe PPP at 3 months following surgery	N (%) Odds Ratio (95% CI) P value	17/50 (34%) 1.00 -	3/50 (6%) 0.13 (0.02 to 0.49) P=0.0008	1/50 (2%) 0.04 (0.00 to 0.28) p<0.0001
Prevalence of moderate to severe PPP at 6 months following surgery	N (%) Odds Ratio (95% CI) P value	14/50 (28%) 1.00 -	3/50 (6%) 0.16 (0.03 to 0.66) P=0.006	0/50 (0%) 0.00 (0.00 to 0.20) P<0.0001

SECONDARY OUTCOMES:				
Prevalence of moderate to severe acute sternotomy pain at 24hours following surgery	N (%) Odds Ratio (95% CI) P value	39/50 (78%) 1.00 -	23/50 (46%) 0.24 (0.09 to 0.62) P=0.002	21/50 (42%) 0.21 (0.08 to 0.53) P=0.0004

Prevalence of moderate to severe acute saphenectomy pain at 24hours following surgery	N (%) Odds Ratio (95% CI) P value	19/36 (53%) 1.00 -	4/37 (11%) 0.11 (0.02 to 0.41) P=0.0002	9/38 (24%) 0.28 (0.09 to 0.83) P=0.019

Total morphine consumption at 24hrs (mg)	Median [IQR] B (95% CI)[2] P value	52 [33-83] 0.00 -	25.5 [15-36] -29 (-50 to -8) P=0.007	21.5 [14-31] -33 (-54 to -12) P=0.002
Extubation time (minutes)	Median [IQR] B (95% CI)[2] P value	372.5 [245 -540] 0.00 -	365 [270- 540] -15 (-107.3 to 77.3) P=0.749	397.5 [235-555] 25 (-82.6 to 132.6) P=0.647
Length of stay in Cardiac Intensive Care (hours)	Median [IQR] B (95% CI)[2] P value	18 [14-24] 0.00 -	15 [10-20.5] -3 (-6.6 to 0.6) P=0.097	14.5 [10-23.5] -3 [-6.5 to 0.5] P=0.093
Sedation score at 24 hours (none/ mild/ moderate/ severe)	Median [IQR] Odds Ratio (95% CI)[3] P value	2 [2-2] 1.00 -	2 [2-2] 0.38 (0.15 to 0.97) P=0.042	2 [1-2] 0.26 (0.10 to 0.66) P=0.005
Nausea score at 24	Median [IQR]	2 [0-2]	0 [0-0]	0 [0-1]

hours (none/ mild/ moderate/ severe)	Odds Ratio (95% CI)[3] P value	1.00 -	0.08 (0.03 to 0.21) P<0.0001	0.23 (0.10 to 0.50) P=0.0002
Prevalence of diplopia throughout inpatient stay	N (%) Odds Ratio (95% CI) P value	4/50 (8%) 1.00 -	12/50 (24%) 3.58 (0.98 to 16.52) P=0.054	15/50 (30%) 4.85 (1.38 to 21.87) P=0.010
Respiratory rate at 24 hours (breaths/min)	Median [IQR] B (95% CI)[2] P value	12 [9-15] 0.00 -	14.5 [12-18] 3 (0.80 to 5.20) P=0.008	14 [12-17] 2 (-0.17 to 4.17) P=0.071
Arterial carbon dioxide partial pressure at 24 hours (KPa)	Median [IQR] B (95% CI)[2] P value	5.79 [5.05-6.43] 0.00 -	5.14 [4.8-5.6] -0.57 (-1.04 to -0.10) P=0.019	5.28 [4.54-5.8] -0.52 (-0.99 to -0.05) P=0.032
Length of stay in hospital (days)	Median [IQR] B (95% CI)[2] P value	7.5 [6-14] 0.00 -	6.5 [5-9] -1 [-4.9 to 0.9] P=0.180	6 [5-8] -1.5 [-5.8 to -0.2] P=0.034
Quality of life at six month follow up (EQ-5D Index)	Median [IQR] B (95% CI)[2] P value	0.53 [0.01-0.72] 0.00 -	0.80 [0.58-0.81] 0.27 (0.07 to 0.44) P=0.011	0.77 [0.73-0.81] 0.24 (0.05 to 0.42) P=0.014

Prevalence of neuropathic pain at six month follow up	N (%) Odds Ratio (95% CI) P value	8/38 (21.1%) 1.00 -	2/43 (4.7%) 0.19 (0.02 to 1.03) P=0.055	0/41 (0%) 0 (0.00 to 0.46) P=0.003
Analgesics required for persistent postsurgical pain at six month follow up	N (%) Odds Ratio (95% CI) P value	21/50 (42.0%) 1.00 -	5/50 (10.0%) 0.18 (0.06 to 0.50) P=0.0004	1/50 (2.0%) 0.02 (0.00 to 0.16) P<0.0001
Sleep disturbed as a result of persistent postsurgical pain at six month follow up	N (%) Odds Ratio (95% CI) P value	18/50 (36.0%) 1.00 -	4/50 (8.0%) 0.16 (0.04 to 0.54) 0.001	1/50 (2.0%) 0.04 (0.00 to 0.26) P<0.0001

Table three: Primary and secondary outcomes

Data is presented as proportion, or median (interquartile range.)

[1]Odds ratio from exact logistic regression model

[2]B (95% CI) from quantile regression represents group differences in medians.

[3]Odds ratio from ordinal logistic regression model representing the odds of having a higher score category.

Table

		Intervention arm		
		Placebo = Usual care (UC)	Pregabalin (P)	Pregabalin & ketamine (P+K)
Change in PPT sternotomy site from baseline	Median [IQR] B (95% CI)[2] P value	-38.25 [-88.5 – 10.5] 0.00 -	-2.1 [-84 – 36.5] 42.9 (-7.8 to 93.6) P=0.097	-42 [-93.5 – 8.75] 7.8 (-32.2 to 47.8) P=0.701
Change in PPT remote from baseline	Median [IQR] B (95% CI)[2] P value	-46 [-112 – 15] 0.00 -	16 [-12 – 57] 91.4 (24.9 to 157.9) P=0.008	27.5 [-2 – 86] 82.7 (18.5 to146.8) P=0.012
New TS at sternotomy site	N (%) Odds Ratio[1] (95% CI) P value	16/50 (32.0%) 1.00 -	3/50 (6.0%) 0.14 (0.02 to 0.54) P=0.002	2/50 (4.0%) 0.09 (0.01 to 0.42) P=0.0004
New TS at remote site	N (%) Odds Ratio[1] (95% CI) P value	16/50 (32.0%) 1.00 -	5/50 (10.0%) 0.24 (0.06 to 0.77) P=0.013	3/50 (6.0%) 0.14 (0.02 to 0.54) P=0.002
Loss of TS at sternotomy site	N (%) Odds Ratio[1] (95% CI) P value	4/50 (8.0%) 1.00 -	4/50 (8.0%) 1.00 (0.18 to 5.71) P=1.00	7/50 (14.0%) 1.86 (0.44 to 9.30) P=0.52
Loss of TS at remote site	N (%) Odds Ratio[1] (95% CI) P value	2/50 (4.0%) 1.00 -	6/50 (12.0%) 3.24 (0.54 to 34.4) P=0.269	5/50 (10.0%) 2.64 (0.41 to 29.1) P=0.436
Zone	Median	37.5 (14.8-	12.3 [9.5-	10.3 [6.5-20]

hyperalgesia	[IQR] B (95% CI)[2] P value	48] 0.00 -	29] -21.3 (-28.4 to -14.2) P<0.0001	-23.8 (-31.2 to -16.4) P<0.0001

Table four: Postoperative sensory changes dependent on treatment arm.
Data is presented as portion (percentages) or median [IQR: Interquartile Range]. PPT= pressure pain threshold, TS= temporal summation.

[1] OR (95% CI) from exact logistic regression model

[2]B (95% CI) from quantile regression adjusted for baseline PPT.

Table

PREDICTOR		OR (95% CI) adjusted for randomization group	P value
Age	Per 10 year increase	0.75 (0.50-1.11)	p=0.146
Sex	M:F	1.14 (0.36 -3.59)	p=0.825
Weight	per 1 SD increase (15kg)	1.08 (0.67-1.75)	p=0.743
Pre op Eq-5D quality of life index	Per 1SD increase (0.3)	0.51 (0.32-0.82)	p=0.005
Spielberger state anxiety	Per 1 SD increase (11 units)	1.98 (1.18-3.34)	p=0.010
Catastrophising	Per 1 SD increase (12 units)	3.80 (1.99-7.29)	P<0.0001
PPT Change with CPM	Per 1 SD increase (42)	0.33 (0.15-0.72)	p=0.005
Preoperative presence of TS Sternotomy site	Yes: No	2.35 (0.85-6.50)	p=0.099
Preoperative presence of TS remote	Yes: No	2.09 (0.66-6.57)	p=0.208
Duration of surgery (minutes)	Per 1 SD increase (85mins)	1.37 (0.88-2.13)	p=0.167
Surgical technique	LIMA Absent: present	0.54 (0.19-1.54)	p=0.247
Postoperative change in PPT at sternotomy site	Per SD increase (106)	0.52 (0.24-1.12)	p=0.097
Postoperative change in PPT at remote site	Per SD increase (146)	0.04 (0.00-0.58)	p=0.018

New TS Sternotomy site	Yes: No	3.20 (1.04-9.82)	p=0.043
New TS remotely	Yes: No	3.94 (1,33-11.68)	p=0.01
Zone of hyperalgesia	Per SD increase (18)	1.61 (0.96-2.69)	p=0.071

Table five: Association of factors with persistent pain at three months.
Odds ratios with 95%CI, derived from Firth logistic regression modelling (p value.) SD= standard deviation. LIMA= left internal mammary artery. PPT=pain pressure threshold. CPM=conditioned pain modulation. TS= temporal summation.

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	2
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	13
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
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	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	13-14
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	14
	13b	For each group, losses and exclusions after randomisation, together with reasons	15
Recruitment	14a	Dates defining the periods of recruitment and follow-up	14
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	26
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure three and page 13
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)	15
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 3
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Tables 3-5 and supplementary
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Table 3
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14 and 21-22
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	21
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	20-22
Other information			
Registration	23	Registration number and name of trial registry	NCT01480765.) clinicaltrials.gov
Protocol	24	Where the full trial protocol can be accessed, if available	Included in submission

Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	7 and 23

*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.

Supplementary table: Adjusted analysis of primary outcomes (Penalized Firth logistic regression model)

*Comparison adjusted for age, gender, weight, preoperative EQ-5D quality of life index, state anxiety, pain catastrophising, duration and type of surgery

		Group allocation		
		Placebo = Usual care (UC)	Pregabalin (P)	Pregabalin & ketamine (P+K)
PRIMARY OUTCOMES:				
Prevalence of moderate to severe PPP at 3 months following surgery	Odds Ratio (95% CI) P value	1.00 -	0.05 (0.01 to 0.29) P=0.001	0.01 (0.00 to 0.14) P=0.001
Prevalence of moderate to severe PPP at 6 months following surgery	Odds Ratio (95% CI) P value	1.00 -	0.13 (0.02 to 0.68) P=0.016	0.01 (0.00 to 0.24) P=0.004