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Perioperative anaesthesia by local infiltration following median sternotomy – a study protocol

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ABSTRACT

INTRODUCTION. Post-operative pain following open heart surgery is a clinical challenge usually requiring significant amounts of opioids. Long-acting local infiltration anaesthesia may effectively reduce post-operative opioid consumption and improve recovery. The trial is a publicly funded, double-blinded, randomised, placebo-controlled trial evaluating the effect of long-acting local infiltration anaesthesia in open heart surgery.

METHODS. Two Danish centres are planning to randomise 100 patients undergoing coronary artery bypass grafting to treatment with long-acting infiltration anaesthesia or placebo. We compare an active solution of bupivacaine, adrenaline, clonidine and dexamethasone with saline placebo. The primary outcome measure is the accumulated opioid use within the first 24 post-operative hours. Secondary outcome measures include evaluation of respiratory function, patient-reported pain scores, mobilisation, opioid-associated side effects and long-term opioid consumption.

CONCLUSION. This trial will define whether the use of long-acting infiltration anaesthesia during heart surgery may reduce acute and prolonged post-operative opioid consumption. Reduction of opioid-related adverse effects may improve recovery.

FUNDING. The trial is supported by public grants (Dansk Selskab for Anæstesiologi og Intensiv Medicin: 40,000 DKK; Regionernes Medicin og Behandlingspulje 2022: 686,000 DKK). The work of I. S. Modrau is supported by an unrestricted grant from the Health Research Foundation of the Central Denmark Region.

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Pain management following open heart surgery is challenging. Inadequate pain relief is associated with patient discomfort, increased pulmonary complications and prolonged recovery [1, 2]. Opioids offer effective treatment of post-operative pain but are associated with well-known and frequent side-effects such as nausea, obstipation, sedation and respiratory depression. The use of opioids after open heart surgery carries a significant risk of prolonged opioid consumption. Large Danish and American studies have found that 6-9% of opioid-naïve patients developed a chronic opioid use after open heart surgery [3, 4]. The amount of opioid consumption at discharge was found to be a strong predictor for the development of chronic opioid use.

A multimodal approach has been suggested in the pursuit of an opioid-sparring strategy. This strategy has proven to provide improved pain control, better oxygenation and faster extubation in cardiac surgery and other major surgeries [2, 5-7]. An essential modality is the use of regional anaesthesia. When performing heart surgery

through a median sternotomy, administering long-acting local wound infiltration and intercostal perineural anaesthesia is an easily accessible option to potentially improve post-operative pain management.

Three studies using a single dose of levobupivacaine or ropivacaine as a parasternal block administered at the end of surgery all found a significant reduction in opioid consumption within the first 24 post-operative hours [8-10].

One of these studies also found a significant reduction in patient-reported pain within the first six hours [9]. These three studies, however, all included a single local anaesthetic agent only. A major obstacle for the use of local infiltration anaesthesia in heart surgery has been the relatively short duration of the analgesic effect. Therefore, a longer lasting effect would be desirable to provide prolonged pain relief, particularly during early mobilisation.

Over the past few years, the use of and knowledge about local anaesthesia have improved. As regional block techniques have become widespread, the need for efficient and long-lasting local anaesthesia has been elucidated. Mixtures of various agents have been suggested, and adding vasoconstrictor [11] and clonidine [12] have been found particularly effective in prolonging durability. Furthermore, the addition of dexamethasone to peripheral nerve blocks may prolong the duration of local anaesthesia and is effective in reducing post-operative pain intensity and opioid consumption [13].

With the recent developments in long-acting local infiltration anaesthesia, a randomised trial is warranted that evaluates its efficacy and safety in open heart surgery compared with today's standard of care.

We hypothesise that the use of long-acting local infiltration anaesthesia in patients undergoing coronary artery bypass grafting (CABG) through a median sternotomy reduces opioid consumption within the first 24 post-operative hours. Secondary aims are to investigate whether the use of long-acting infiltration anaesthesia improves respiratory function and mobilisation and reduces the need for prolonged opioid use.

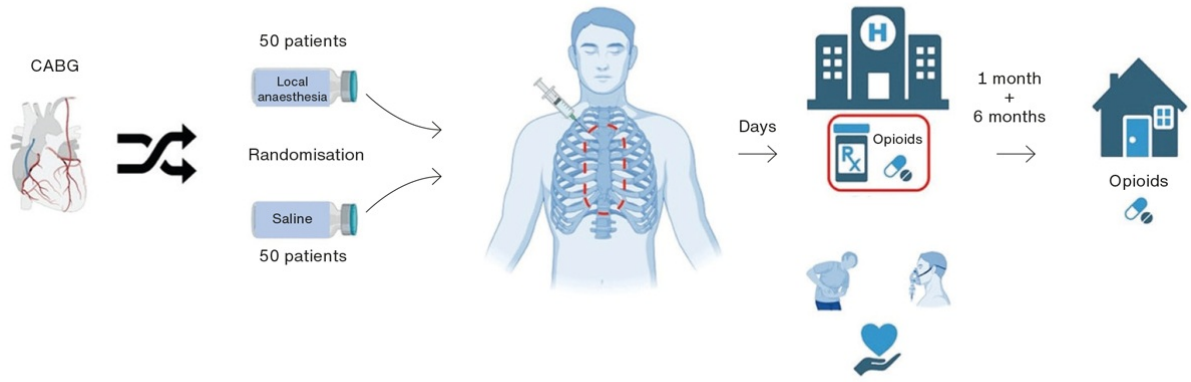
METHODS

Study design

This is an investigator-initiated, two-centre, double-blinded, randomised (1:1), placebo-controlled clinical trial with a superiority design. Adult patients scheduled for first-time elective CABG at two Danish heart surgery centres (Aarhus University Hospital and Aalborg University Hospital) are eligible for inclusion. The inclusion criteria are age > 18 years, CABG including harvest of left internal mammary artery (LIMA), surgical access through median sternotomy and informed consent. The exclusion criteria are prior sternotomy or cardiac surgery, concurrent surgical procedure other than lung vein ablation and/or left appendage closure, daily use of opioids and /or oral corticosteroids within the past six months prior to enrolment, known allergy or intolerance to any of the included drugs, any known condition that might interfere with the used drugs, impaired kidney function (estimated glomerular filtration rate < 30 ml/min), women of childbearing age without a negative pregnancy test and nursing women.

Participants are randomly assigned to receive active intervention or placebo. Participants, healthcare providers, researchers and outcome assessors are blinded to treatment assignment. Stratified permuted randomisation with an allocation ratio of 1:1 is used. Randomisation is stratified for two variables: 1) age < 60 years or age ≥ 60 years, and 2) inclusion site (hospital). This is based on our experience that younger patients generally have more procedure-related pain. The trial flow chart including study assessments is presented in **Figure 1**.

FIGURE 1 Study participation timeline.



CABG = coronary artery bypass grafting.

Study drugs

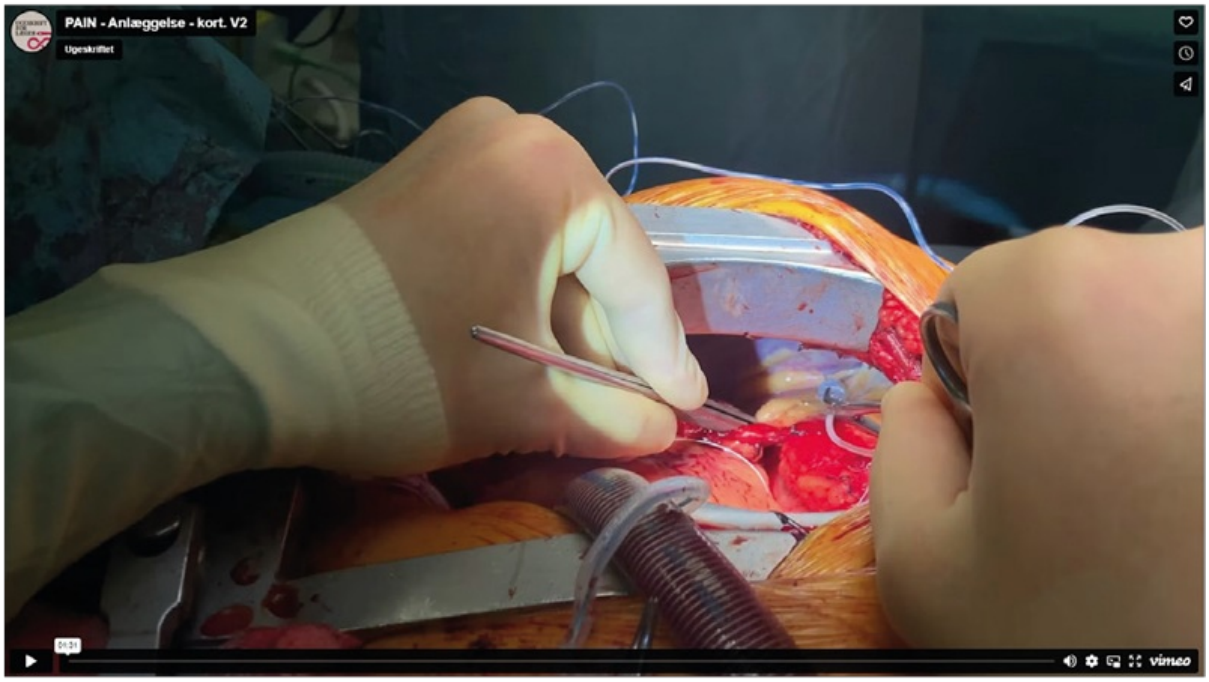
The intervention group receives local infiltration anaesthesia with the following mixture: 60 ml bupivacaine 2.5 mg/ml with adrenaline 5 µg/ml, 2 ml dexamethasone 4 mg/ml and 0.5 ml clonidine 150 µg/ml; a total of 62.5 ml. The control group will receive local infiltration with a placebo solution of 62.5 ml of 0.9% saline chloride.

All study drugs are handled and prepared by Hospital Pharmacy, Central Denmark Region. The drugs are packed in the correct amount in neutral vials. During surgery, the circulating nurse prepares the allocated drug package to be administered during surgery. It is not possible to visually or otherwise distinguish between the intervention and placebo mixtures.

Injection technique

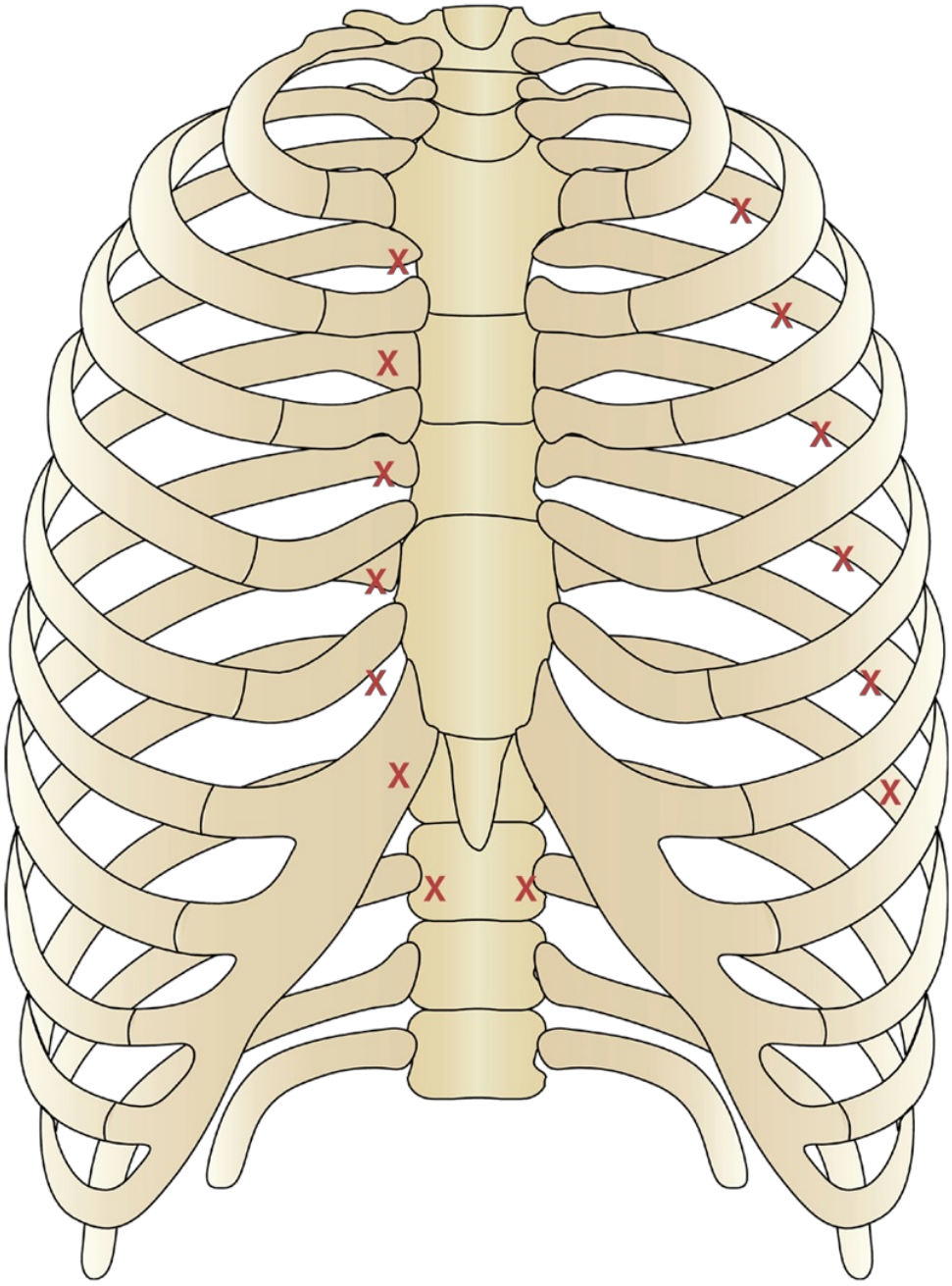
The drug infiltration will be administered at the end of surgery, immediately before sternal closure by the surgeon. On the left side the injection sites will be the intercostal space II-VII as far laterally from the sternum as possible reached through the sternotomy, and 5 ml will be injected in each intercostal space (total of 30 ml). On the right side, the pleura is not regularly opened. Injections will be administered as six single injections just to the right side of the sternum through the subcutaneous layers in the intercostal muscle layer with a total of 20 ml. This approach is performed regardless of the right pleura being incidentally opened during the surgery. The final 12.5 ml will be administered around the drain incisions. See **Video 1** and **Figure 2** for further details.

VIDEO 1 Video demonstrating the perioperative administration of the study drug. Link: https://vimeo.com/835340855



Link to video: https://vimeo.com/835340855

FIGURE 2 Schematic illustration of the injection sites.



Perioperative anaesthesia

All participants are treated according to the local anaesthesia protocols for heart surgery, pre-, peri- as well as postoperatively. At Aarhus University Hospital, 2 g of paracetamol and, optionally, midazolam 5 mg is used as premedication. Anaesthesia is induced using propofol, sufentanil and rocuronium. The dose of sufentanil is 0.7-1.5 µg/kg at induction and 1.5-2.0 µg/kg prior to skin incision. Analgesia may be supplemented by one or more doses of sufentanil 50 µg during surgery, on individual clinical indication. Anaesthesia is maintained with propofol.

At Aalborg University Hospital, patients are premedicated with 2 g of paracetamol and optionally midazolam 3.5-7.5 mg. Anaesthesia is induced using midazolam, fentanyl and rocuronium. The dose of fentanyl is 3.5-10 µg/kg at induction and 14-18 µg/kg prior to skin incision. Analgesia may be supplemented by one or more doses of fentanyl 100-250 µg during surgery, on individual clinical indication. Anaesthesia is maintained with sevoflurane.

Post-operative pain management

In Aarhus, patients are treated with paracetamol 1 g × 4 daily supplemented by oral oxycodone 5-10 mg × 4 daily and/or oral ibuprofen 200-400 mg × 3 daily. Intravenous (IV) oxycodone may be administered at doses of 2.5-5 mg, as needed.

In Aalborg, patients are also given paracetamol 1 g × 4 daily; however, along with oral ibuprofen 800 mg retard × 2 daily and oral morphine 5-10 mg either as needed or as standard treatment depending on the individual patient's requirements. Intravenous morphine 2.5-5 mg may be administered as needed.

At both sites, patients are discharged with a couple of weeks of oral paracetamol 1 g × 4 daily and, if needed, a few days of either ibuprofen or oxycodone (Aarhus)/morphine (Aalborg). If opioids are prescribed, a detailed step-down plan is made.

Outcome measures

The primary outcome measure is the accumulated opioid consumption within the first 24 hours after completion of surgery. This will be calculated in oral morphine equivalents.

Selected secondary outcome measures are listed in **Table 1**.

TABLE 1 Secondary outcome measures.

In hospital
Time to extubation
Patient-reported pain regarding the first and second post-operative days
Peripheral oxygen saturation and oxygen requirement 1 h after extubation
Time and extent of first and second mobilisation and pain during mobilisation
Post-operative peak flow compared with preoperative peak flow
Patient-reported assessment of whether they received the intervention or a placebo
ICU nurse assessment of whether the patient received the intervention or a placebo
Usage of antiemetic drugs within the first 24 h
Duration of need for oxygen supplementation
Length of stay
Follow-up
Opioid use 1 mo. after surgery
Opioid use 6 mos. after surgery
Safety measures
Sensitivity reaction
Bleeding
Adverse reactions to adrenaline administration
Requirement of transfusion
Deep sternal wound infection
Leg wound infection
Need for antibiotics
Pleural effusion
Pneumothorax
Atrial fibrillation
Bradycardia
Pneumonia

ICU = intensive care unit.

Finally, the use of opioid-containing drugs is evaluated one and six months after surgery.

To ensure the safety of the intervention, all patients are evaluated for a broad range of complications including but not limited to anaphylaxis, bleeding, infection and deep sternal infection.

Details regarding a sub-study using a mixed-method approach to describing chronic pain and opioid consumption after coronary surgery are outlined in a separate protocol.

Statistical considerations

Barr et al. 9 found that the use of infiltration anaesthesia with ropivacaine produced only approx. 50% less opioid use within the first 24 hours. Using their results, a power of 0.90 and a significance level of 0.05, 88 patients need to be enrolled in each group (totalling 176 patients). However, based on the studies by Kocabas et al. 8 and McDonald et al. 10, using the same power and significance levels, 26 and 30 patients, respectively, would need to be included in each group when using the results of opioid consumption within the first 24 hours. As ropivacaine was the only drug used in the study by Barr et al., we expect that our intervention will last longer and perform better. Based on this and the contradictive results of the mentioned studies, we aim to include 100 patients.

Categorical variables are presented as numbers and percentages. Continuous variables are presented as mean ±

standard deviation when distributed close to normal as assessed by quantile-quantile plots, otherwise as median (interquartile range). Intergroup comparisons are performed with Fisher's exact test for all binary outcomes, t-test for continuous outcomes following normal distributions, and otherwise with the Wilcoxon–Mann-Whitney test. A p value below 0.05 will be considered significant.

Approval and ethics

The study protocol was approved by the Danish Medicines Agency (Ref: 2022013814; 21-03-2022) and the Central Denmark Region Committees on Health Research Ethics (Ref: 1-10-72-27-22; 29-06-2022). The trial is registered in the EudraCT database (Number 2021-005886-41; 12-10-2021). In pursuance of the European Guidance on posting and publication of result-related information on non-paediatric clinical trials, the data supporting the findings of this study will be available on reasonable request from the corresponding author. The data will not be publicly available due to privacy restrictions. The perioperative anaesthesia by local infiltration following median sternotomy (PAIN) trial is conducted in accordance with the Declaration of Helsinki and monitored continuously by the Good Clinical Practice unit at Aarhus and Aalborg University, Denmark. All patients provide informed written consent before participating. Decisions on study design, acquisition, analysis, interpretation or publication of data are made exclusively by the authors who have initiated and designed the trial. Serious adverse events and suspected unexpected serious adverse events are adjudicated by an independent adverse clinical event committee. Trial enrolment began in November 2022 and is expected to be completed by December 2023. As of 29 March 2023, 31 patients have been randomised at Aarhus University Hospital and 18 patients at Aalborg University Hospital.

International Committee of Medical Journal Editors Data Sharing statement

Data sharing is not applicable to this article as no new data were created or analysed in this protocol article. The full protocol, statistical analysis plan, and the informed consent form are available upon reasonable request.

Trial registration: EudraCT 2021-005886-41.

DISCUSSION

Importance of the knowledge to be gained

Should the use of local infiltrative anaesthesia as proposed in the present trial prove efficient, it will be an easy, low-cost and low-risk treatment. Patients will benefit from this in terms of more comfort and fewer side-effects from opioids. This may potentially facilitate shorter admission times while reducing the number of adverse post-operative events. It will be possible to implement the use of local infiltrative anaesthesia across all cardiac surgery departments immediately. If the intervention proves to be opioid sparring, it will be very interesting to see if this translates into reduced long-term opioid use.

Strengths and limitations

In this trial, inclusion is restricted to patients undergoing CABG, including LIMA harvest, to ensure that all patients are exposed to a comparable surgical trauma and expected post-operative pain. How the intervention will perform in other open heart surgery procedures such as valve replacements may be debated. However, we believe that LIMA harvest is a major contributor to post-operative pain.

It may be argued that pre-emptive analgesia have the potential to be more effective than injection of the study drug at the end of surgery. The rationales behind our approach were 1) safety as the risk of pneumothorax is minimised, 2) longer duration of action and 3) feasibility and acceptability as the intervention is time-effective with no need for special training. The two-centre design implies both strengths and weaknesses. The two centres

have different anaesthesia protocols and different post-operative standards of treatment. Also, even though the CABG procedure is standardised, differences do exist between surgeons at the two units. However, if the trial favours the use of long-acting infiltrative local anaesthesia, the two-centre design will confer a higher external validity to the study findings. The possibility for single-centre sub-analysis depends on the inclusion rates of each site, keeping in mind that the trial is powered as a two-centre trial.

CONCLUSION

The PAIN trial is a randomised trial comparing the efficacy of long-acting infiltration anaesthesia to a saline placebo in patients undergoing open heart surgery. The goal of the trial is to determine if this strategy translates into reduced opioid consumption, enhanced recovery and reduced long-term opioid use.

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Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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