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Efficacy of avoiding chest drains after video-assisted thoracoscopic surgery wedge resection: protocol for a randomised controlled trial

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ABSTRACT

Introduction The use of routine postoperative chest drains after video-assisted thoracoscopic surgery (VATS) of the lung is a practice based on tradition with the aim of draining fluid and air. However, new evidence suggests that chest drains can be avoided in selected cases. With this randomised controlled trial, we wish to establish the efficacy and safety of avoiding postoperative chest drains compared with routine postoperative chest drains.

Methods and analysis This is a two-centre randomised controlled trial without allocation concealment, but where randomisation occurs after the end of procedure leaving operative personnel blinded during surgery. The sample size is calculated to show a difference in pain measurements using the Numeric Rating Scale under different circumstances and at different time points to show superiority of the intervention. The trial is pragmatic by design to reflect the daily clinical scenario and with the aim of increasing the external validity of the results.

Ethics and dissemination Approval by the local ethics committees has been obtained for both sites. The study was registered with ClinicalTrials.gov (NCT05358158) prior to inclusion. The results of the trial will be disseminated by publication in an international journal and presentation at major international thoracic surgical meetings.

Article summary This is a randomised controlled trial estimating the effects of avoiding a chest drain after VATS wedge resection of the lung on pain, total morphine use, quality of life and complications.

Trial registration number NCT05358158.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ First randomised study of drain omission with pain measurements as primary endpoint.
⇒ Detailed set-up with multiple dynamic pain measurements for 2 weeks postoperatively.
⇒ Analysis of cumulative opioid use.
⇒ Standardised approach using video-assisted thoracoscopic surgery.
⇒ Pragmatic trial design from two inclusion sites with potentially high degree of generalisability.

INTRODUCTION

Background and rationale

Chest drains are traditionally used to drain air and fluid in the postoperative period after pulmonary resection,[1] however, their routine use is not based on evidence.[2 3] Chest drains are associated with pain, nerve damage, increased risk of infections, delayed mobilisation and increased length of stay (LOS).[4–7] Shortening or avoiding postoperative drainage, therefore, seems to benefit patients. Previous studies indicate that the omission of chest drains is safe and feasible in selected cases,[2 8–10] however, with the majority of evidence based on observational studies. Only a few randomised controlled trials have been published on the subject, but evidence on benefits and safety is still limited.[2 11 12]

A landmark trial from 2007 comparing 60 patients randomised to drain or no drain after video-assisted thoracoscopic surgery (VATS) wedge resection for benign or malignant reasons showed shorter LOS in the group without drain but without a difference in pain.[2] The authors also found an increased rate of clinically non-significant pneumothorax in the group without drain but no difference in complications. In the trial, the majority of patients underwent diagnostic resection for benign conditions, which may limit the applicability of the results on a broader population. The trial was conducted prior to the publishing of the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[13]

One recent trial from 2020 demonstrated shorter LOS (mean 1.2 vs 2.6 days, p<0.001), shorter surgery duration (mean 59 vs 74 min, p=0.001) and reduced pain on postoperative day (POD) 1 (mean 0.9 vs 1.2, p=0.011).[12] The trial is, however, limited by issues in the

methodology. The primary outcome was LOS, and the trial was powered to show a reduction in LOS of 1 day, but the authors did not define which criteria were used to discharge patients. The specific discharge criteria are of interest since patients in the drain groups stayed for a mean 1.4 days after drain removal although patients underwent a simple wedge resection with no air leak. Drain management may also have prolonged drainage duration, since the maximum tolerated fluid production was 200 mL per day. Of interest, the trial scores pain and neuralgia in participants with and without drain showing a mean score of 0.9 on the visual analogue scale in the drainless group compared with 1.2 in the drain group (p=0.011). In the trial, however, rescue analgesics and planned analgesics are not detailed, limiting the interpretation of the results.

Another recent trial from 2019 randomising 74 patients without air leak after wedge resection to drain or no drain showed shorter LOS, reduced pain and reduced analgesic intake in the group without drain.[14] This trial was well conducted but applied a long list of exclusion criteria rendering the trial explanatory in nature, as opposed to pragmatic, with limited external validity and applicability of the results.[15]

There are, however, issues with the methodology in the trials from 2019 and 2020. In the trial from 2019, multiple pain measurements are compared using the Wilcoxon test[14] and in the trial from 2020 by Liao *et al* they are compared using the Student's t-test.[12] Both tests are based on the assumption that data are independent, not correlated. Since repeated pain measurements are correlated, it should be analysed in a repeated measures design.[16 17] Furthermore, data such as LOS are not normally distributed, and therefore, not suitable for comparison using Student's t-test, unless data are transformed.[18 19] Skewed data, such as LOS, should be summarised using medians and IQR and compared using non-parametric statistics.[16]

A fourth trial from 2018, analysing the effects of drain avoidance (n=58) compared with standard drain (n=61) after VATS wedge resection.[11] The authors claim to have conducted a randomised controlled trial, but patients were assigned treatment according to odd or even consecutive numbers, which potentially introduces bias from lack of randomisation and allocation concealment. Adding this to unavoidable risks of bias from the nature of using chest drains in one group and avoiding them in the other, that is, lack of blinding, results are not interpreted further.

The results of the mentioned randomised controlled trials together with several observational studies comparing the outcomes of chest drain versus no chest drain after lung surgery, have been summarised in a systematic review and meta-analysis from our group.[20] So far, no previous trial reported pain as primary endpoint or used this measure for sample size estimation. Furthermore, there is a lack of studies with well-defined pain assessment during function.[20]

Generally, previous studies reported a low risk of drain reinsertion with a risk of up to 1% in the chest drain group compared with 3%–4% in the no chest drain group.[20 21] There are, however, between-study differences which need to be taken into account, where one observational study from 2017 reported 3 of 28 patients (11%) with reinsertion of a chest drain due to pneumothorax, subcutaneous emphysema or hemopneumothorax.[22] These three patients experienced rather complicated and long admissions of 4–10 days. There are notable differences between this study and our previous observational study in selection of eligible patients, and the details of the air leak test which may explain the high rate of complications.[10 22]

Overall, with limitations of previous studies and a low-risk profile, there is a need to conduct a new trial with the aim of detailed comparisons of postoperative pain scores to assess the potential benefits of avoiding a chest drain.

Aims and hypotheses

Our aim is to determine whether avoidance of a chest drain is an efficient and safe alternative to routine chest drain placement after VATS wedge resection.

We hypothesise that patients treated without a postoperative chest drain compared with patients treated with a routine chest drain:

- Have reduced pain.
- Require fewer analgesics.
- Recover faster leading to potential earlier mobilisation and discharge.
- Are not at increased risk of complications including pneumothorax and drain insertion.

METHODS: DESIGN, PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Trial design

This trial is a two centre, open-label, parallel-group, pragmatic randomised, controlled trial with a 1:1 allocation ratio powered for superiority.

This trial is not designed to show whether the intervention may work under ideal settings, which is largely the aim of a trial designed with an explanatory approach, and which has already been shown internationally and by this research group.[10 15 23] This trial is designed to take a pragmatic approach, answering the question 'Does this intervention work under usual conditions?', with the goal of maximising applicability of the intervention to usual care across a varied range of settings. The rationale behind the scores is given in table 1 using the PRagmatic-Explanatory Continuum Indicator Summary-2 toolkit,[15] and the score is illustrated in figure 1.

Study setting

The trial is planned as a multicentre trial with the following centres and a possibility for additional centres.
The Department of Cardiothoracic Surgery.
Centre for Heart, Vessels, Lung and Infectious Diseases.
Copenhagen University Hospital Rigshospitalet.

Table 1 PRagmatic-Explanatory Continuum Indicator Summary-2 (PRECIS-2) scoring table

	Domain	Score	Rationale
1	Eligibility criteria	4	Some selection occurs, however, with no difference from usual clinical practice.
2	Recruitment path	5	Recruitment during standard preoperative meetings in at least two regional thoracic surgical centres (of four existing nationally).
3	Setting	5	No difference from the usual care setting.
4	Organisation intervention	4	Trial staff will remind surgeons of the steps in the intervention to ensure they are followed. All steps are managed by the surgical personnel and do not differ from usual clinical practice.
5	Flexibility of experimental intervention-Delivery	4	Some instructions need to be followed, however, with no difference from usual care.
6	Flexibility of experimental intervention-Adherence	NA	Single surgical intervention without patient involvement. Scoring of adherence is, therefore, not possible.
7	Follow-up	5	Follow-up occurs during routine outpatient visit and using electronic health records. No additional meetings are scheduled.
8	Primary outcome	5	Primary outcomes (pain, complications) are highly relevant to patients and clinicians and will guide future management.
9	Analysis	5	Intention-to-treat analysis will be conducted.

The trial design is scored using the PRECIS-2 toolkit on a 5-point Likert scale: 1. Very explanatory, 2. Rather explanatory, 3. Equally pragmatic and explanatory, 4. Rather pragmatic, 5. Very pragmatic.
NA, not available.

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Central Region of Denmark, Denmark.

Eligibility

Inclusion criteria

- Age ≥18 years.
- Patients referred for elective three port VATS wedge resection of the lung for suspected or confirmed malignant nodules.

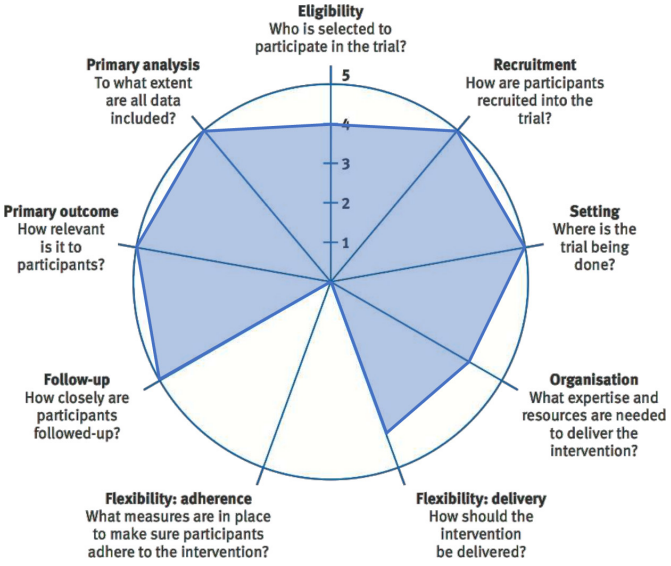

Figure 1 PRagmatic-Explanatory Continuum Indicator Summary-2 wheel.

- Forced expiratory volume in the first second (FEV1)≥60% of expected.
- No increased bleeding risk (eg, preoperative international normalised ratio (INR)>2, overdue discontinuation of anticoagulants according to guidelines by the Danish Society for Thrombosis and Haemostasis, known coagulopathy).
- Not scheduled for frozen section pathology of wedge resection and subsequent lobectomy.
- Able and willing to give informed consent.

Exclusion criteria

- Increased risk of postoperative air leak assessed perioperatively by the surgeon (eg, severe adhesions, bullous/emphysematous lung tissue, defects of the visceral pleura due to iatrogenic or other reasons, suturing in the lung tissue, deep lung resection).
- Increased risk of postoperative bleeding assessed perioperatively by the surgeon (eg, intraoperative bleeding or oozing).
- Air leak during intraoperative air leak test.

Interventions

Intervention groups

Currently, applying a chest drain or not is up to the surgeon's discretion. If no chest drain is applied, an air leak test is performed at the end of the surgical procedure. In case of chest drain application, it is inserted through the anterior inferior port (ie, the camera port) with the tip at the apex verified thoracoscopically and tied using a standard non-resorbable suture. Thereafter all patients will be submitted to an air leak test (described in detail below) by the operating surgeons to confirm the

lung is completely sealed. If the lung is sealed, patients will be randomised to one of the following groups:

- A standard postoperative chest drain (control group).
- Intraoperative chest drain removal (intervention group).

Patients with continued air leak during the sealing test will be excluded, but followed prospectively in a separate observational study, and treated with a routine chest drain until air leak cessation. Air leak data from the drainage device will be used to assess the quality of the air leak test in comparison with the patients randomised to a standard postoperative chest drain.

Air leak test

At the end of the operation, in theatre, with the patient still fully anaesthetised, an air leak test is performed to determine the need for pleural drainage. An active air leak from the lung precludes participation in this trial.

A Ch. 20 chest drain (made from bio-compatible PVC, Redax, Italy) is inserted through the anterior inferior port (the camera port) with the tip at the apex of the lung, away from the fissure, and attached using a standard U-suture. The operated lung is ventilated at a maximum pressure of 20 cmH_2O and the complete expansion of the lung is confirmed thoracoscopically. Ventilation pressures above 20 cmH_2O increases the risk of barotrauma and air leak on the lung without an increased benefit. Double lung ventilation is maintained while closing the remaining two portholes and the operating table is reset to flat position.

The exterior tip of the chest drain is submerged in a water basin outside the patient to act as a one-way valve to avoid air entering the thoracic cavity. It is important not to keep the water basin too high to avoid a syphon effect pulling water into the thoracic cavity. Air is evacuated from the thoracic cavity using manual ventilation with pressures up to 20 cmH_2O while applying abdominal pressure below the ribs with a flat hand. Afterwards for a period of 3–5 min the oscillation in the chest drain is observed for signs of continued air leak. During this period, the surgeon can suture the skin to avoid delays. The details of the air leak test have been described by our group previously.[10] See figure 2 for a schematic illustration of the set-up.

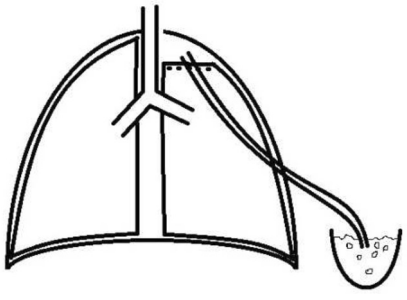

Figure 2 Schematic illustration of the set-up for the air leak test.

If the air leak continues, the patient will need a postoperative chest drain and will therefore not be randomised.

If the air leak ceases the patient does not need a postoperative chest drain and will be randomised to a standard postoperative chest drain (control group), where the drain is left in the cavity, or to intraoperative chest drain removal (intervention group), where the chest drain is removed, and the U-suture tied while keeping a positive inspiratory pressure on the ventilator.

Standard treatment protocol

Chest drains are connected to a digital drainage device (Thopaz$^+$, Medela) and will be removed at earliest on the morning of POD 1 if the trend curve shows air leak below 20 mL/min for at least 12 consecutive hours. Preset pressure on the Thopaz$^+$ is −2 cmH_2O (≈−0.2 kPa, Rigshospitalet) or −10 cmH_2O (≈−1 kPa, Aarhus University Hospital). A standing chest X-ray with lateral and posterior–anterior projections is taken approximately 2 hours after drain removal to check for pneumothorax and fluid. All patients in the trial will be discharged at the earliest on POD 1.

Interventional treatment protocol

Patients in the intervention group will have their chest drain removed after randomisation (and prior air leak test showing sealed lung). A standing chest X-ray with lateral and posterior–anterior projections is taken approximately 6 hours after surgery.

Surgical and anaesthetic treatment pathway

Patients included in the trial will be treated according to the respective department's standards, and deviations from standard treatment may take place at the discretion of the surgical team according to the pragmatic trial design.

Surgical access for VATS wedge resection is performed via a standardised anterior approach with three ports.[24 25] Anterior to the latissimus dorsi muscle level with the papilla a 3 cm upper port is made and used with a soft wound protector (SurgiSleeve wound protector, Medtronic or Alexis O Wound Protector-Retractor, Applied Medical) and two lower ports level with the diaphragm placed after thoracoscopic guidance. A 5 mm camera is introduced through a rigid camera port in the anterior basal incision. The posterior port for instruments is 1–1.5 cm and used without a wound protector unless suspicion of sarcoma. The size and location of the ports do not change according to the location of the planned resection. All patients will be operated by an experienced surgeon specialised in cardiothoracic surgery with subspecialty in general thoracic surgery as either the primary or the supervising surgeon. When the thoracic surgeon is the supervisor, the primary surgeon will be a trainee.

Intraoperative intercostal nerve block with 20 mL bupivacaine 5 mg/mL (eg, Marcain) administered under thoracoscopic vision from the thoracic cavity.

Table 2 Anaesthesia and analgesia in the two participating centres

	Rigshospitalet	Aarhus university hospital
Preoperative analgesics (min. 2 hours before surgery)	► 1000 mg paracetamol (oral) ► 800 mg Brufen Retard (oral, sustained release ibuprofen)	► 1000 mg paracetamol (oral)
Anaesthesia, induction	► Fentanyl 0.1 mg intravenous before induction ► Propofol doses of 0.5–1.0 mL/kg/hour (20–30 mL/hour) ► Ultiva (remifentanil) doses of 0.5–1.0 mL/kg/hour (20–30 mL/hour) ► Propofol bolus 1–2 mg/kg until anaesthesia ► Esmeron (rocuronium) 0.6–1.0 mg/kg	► Fentanyl 0.1–0.2 mg intravenous before induction ► Propofol doses of 0.5–1.0 mL/kg/hour (20–30 mL/hour) ► Ultiva (remifentanil) doses of 0.5–1.0 mL/kg/hour (20–30 mL/hour) ► Propofol bolus 1–2 mg/kg until anaesthesia ► Esmeron (rocuronium) 0.6–1.0 mg/kg
Anaesthesia, maintenance	Reduced rates of (based on BP and BIS): ► Propofol ► Ultiva (remifentanil) ► Option of esmeron single dose 0.15 mg/kg	Reduced rates of (based on BP): ► Propofol ► Ultiva (remifentanil) ► Option of Esmeron single dose 0,15 mg/kg
Anaesthesia, before wake-up	► 1000 mg paracetamol ► 30 mg ketorolac trometamol ► 5–10 mg oxycodone	► 1000 mg paracetamol ► 30 mg ketorolac trometamol ► 0.05–0.15 mg fentanyl
Postoperative	► 1000 mg paracetamol (oral) four times daily usually for up to 2 weeks ► 800 mg Brufen Retard (oral) two times daily usually for up to 2 weeks ► 5 mg Oxynorm (oral, oxycodone hydrochloride) only if necessary, during the first week	► 1000 mg paracetamol (oral) four times daily usually for up to 2 weeks ► 400 mg ibuprofen (oral) three times daily usually for up to 1 week ► 5 mg Oxynorm (oral, oxycodone hydrochloride) only if necessary, during the first week

BIS, bispectral index; BP, blood pressure.

All patients are intubated using a double lumen endotracheal tube (35 F for female patients, 37 F for male). Total intravenous anaesthesia is used for all patients, as described below.

Anaesthetic and analgesic treatment pathways are summarised in table 2.

Monitoring

All patients will be observed for approximately 2 hours in the postanaesthesia care unit (PACU) and thereafter moved to the ward. At the PACU, invasive blood pressure is monitored using the arterial line from surgery. Heart rhythm is monitored continuously using a 4-point ECG. Patients are allowed sugary fluids, food and encouraged to be mobilised. No patient receives a routine bladder catheter. When moved to the ward, all continuous monitoring is removed, and patients will have their vitals measured at least once daily until discharge.

All patients included in the study are scheduled for routine standing chest X-ray in two projections after drain removal. Patients in the intervention group will have a chest X-ray taken 6 hours after surgery, whereas patients in the control group will have the X-ray taken 2 hours after drain removal, usually on POD 1. Any other chest X-ray is performed on clinical indication.

Intervention providers

The surgical team will be responsible for conducting the air leak test and intraoperative chest drain removal. The procedure is simple and will be performed by the surgical team of which at minimum one surgeon has received video demonstration and supervision on at least two procedures, or by supervision of the surgical team by a third adequately trained surgeon.

Endpoints

The primary endpoints are to test the superiority of avoiding a chest drain vs a routine chest drain after VATS wedge resection on:

- Postoperative pain at 3 and 6 hours after surgery, and on the morning of POD 1 at 8:00 hours assessed in three different situations (at rest, both arms lifted and during cough) by questionnaire, see Pain and rehabilitation diary 1 and 2 (online supplemental materials 1 and 2, Danish).
- The amount of rescue analgesics given during the first 24 hours assessed as cumulative amount of morphine milligram equivalents (MME) as defined by pro.medicin.dk hosted by the Danish Association of the Pharmaceutical Industry, see equianalgesic conversion table for selected opioids (online supplemental table 1).

Secondary endpoints are as follows:

- Number and size of pneumothorax at first standing chest X-ray after drain removal.
- Number and size of pneumothorax at postoperative 2-week control.
- Pulmonary complication after drain removal leading to drain reinsertion (progressive pneumothorax, progressive subcutaneous emphysema, haemothorax requiring intervention, chylothorax, hydrothorax).
- Pain on POD 2–6 (see patient diary).
- Pain on POD 7–14 (see patient diary).
- Postoperative complications according to the Clavien-Dindo Classification.[26]
- Number of patients who did not receive planned postoperative analgesics according to the standards at their institution.
- Quality of recovery (QoR-15)-score.
- Time to fulfilled discharge criteria.
- Number of complications after fulfilled discharge criteria, which would have led to readmission, had the patient been at home.
- LOS.

Definitions

Pain

Patients are scored in the patient diary using an 11-point Numeric Rating Scale (NRS) ranging from 0 to 10, where 0 is no pain and 10 is the worst imaginable pain.

Patients are scored under well-defined circumstances (resting, with arms lifted and while coughing) at the following time points:

- Before surgery to establish a baseline, important in patients with chronic pain and for validation of the score.
- 3 and 6 hours after surgery, and on POD 1 at 8 am in the morning, see the patient diary (online supplemental material 1).
- Daily at midday/12:00 hours on POD 2–POD 14, see the patient diary (online supplemental material 2).

Morphine milligram equivalents

Patients are instructed to ask for supplementary opioid analgesics if they feel they are unable to cough due to pain but are not given opioids regularly as part of a multi modal opioid-sparing analgesic treatment. Patients are regularly asked to cough to ensure they are sufficiently covered. Opioid doses are converted and recorded as daily oral MME using equianalgesic conversion table for selected opioids (online supplemental table 1).

Standard analgesic treatment

The total doses of standard analgesics are quantified using the patient diary. If patients do not receive standard postoperative analgesic treatment according to table 2 during the pain scoring follow-up period (POD 0–POD 6), it is counted as an event.

Use of other analgesics

Additional non-opioid analgesic treatment is recorded. For pragmatic reasons these are defined as:

QoR is measured according to the Danish version of the QoR 15-score[27 28] before surgery and the day after surgery at noon (online supplemental material 1).

Complications

Pneumothorax is defined as air in the pleural cavity and is measured on the first standing X-ray after drain removal (6 hours after surgery in the drain-free group, 2 hours after drain removal in the drain group) and on 2-week postoperative control. The size of pneumothorax is measured as the vertical height (in mm) from the thoracic cupola to the apex of the lung.

A non-symptomatic pneumothorax which is stationary or regressing on repeated chest X-rays is not counted as a complication. However, a pneumothorax which leads to an intervention is counted as a complication. Selected complications are defined in table 3. Complications will furthermore be classified according to the Clavien-Dindo grading system for postoperative complications (online supplemental table 2).[29] Patients are followed up until POD 30. Any complication will receive its final grading according to the Clavien-Dindo system by this time, and the suffix 'd' will not be used.

Discharge criteria

When the following criteria are fulfilled, the patient is considered to have reached short-term postoperative recovery and should be considered ready for discharge. Discharge may take place as soon as the patient has adequate post discharge support (family at home, nursing or rehabilitation facility) and is willing to leave the hospital. The discharge criteria are defined in table 4.

Other data collection

Data collection is done by passing on information from electronic patient records (Epic, MidtEPJ, ThopEasy drain data).

- Name.
- Social Security number.
- Height (cm) and weight (kg).
- Smoking status (never/current/previous (ie, ceased less than 6 months ago)).
- Pack-years.
- Lung function (FEV1, FEV1/Forced vital capacity (FVC), diffusing capacity of the lungs for carbon monoxide (DLCO)).
- Comorbidities and analgesics
- Previous thoracic procedures.
- Previous chemotherapy or radiotherapy.
- Procedure including date and time.
- Bleeding.
- Drain data including air leak, fluid production, suction, pressure.
- Date and time of drain removal.
- Discharge date.
- Pathology result.

Table 3 Definitions of selected postoperative complications

Complication	Definition
Drain reinsertion	Drain reinserted in the pleural cavity on the side of the operation. Reasons for drain reinsertion: ► Symptomatic or progressive pneumothorax (including tension pneumothorax) ► Symptomatic or progressive subcutaneous emphysema ► Symptomatic or progressive pleural effusion ► Symptomatic or large haemothorax ► Empyema ► Chylothorax
Pneumothorax	Air in the pleural cavity. A non-symptomatic pneumothorax which is stationary or regressing on repeated chest X-rays is not counted as a complication but still quantified on: ► First standing X-ray after drain removal (6 hours after surgery in the drain-free group, 2 hours after drain removal in the drain group) ► 2-week postoperative control The size of pneumothorax is measured as the distance (in mm) from the apex of the lung to the thoracic cupola, the apex-cupola distance[32 33] Only a pneumothorax which leads to an intervention (drain reinsertion, needle aspiration, surgery, etc) is counted as a complication.
Subcutaneous emphysema	Subcutaneous emphysema is not counted as a complication, however, drain reinsertion because of progressive subcutaneous emphysema is.
Pleural effusion	Chest radiograph demonstrating blunting of the costophrenic angle, loss of sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows
Haemothorax	Blood in the pleura. Only a symptomatic or large (estimated >200 mL) haemothorax is counted as a complication, as all patients are expected to have some degree of non-symptomatic haemothorax after surgery.
Empyema	Pus or verified microbiologic agent in the pleural fluid.
Chylothorax	Chyle in the pleural space.
Respiratory infection	The patient has received antibiotics for a suspected respiratory infection and met one or more of the following criteria: new or changed sputum, new or changed lung opacities, fever, white cell count >12×10^9/L
Respiratory failure	Postoperative PaO_2<8 kPa (60 mm Hg) on room air, a PaO_2:F-ratio<40 kPa (300 mm Hg) or arterial oxyhaemoglobin saturation measured with pulse oximetry <90% and requiring oxygen therapy. However, in patients with a preoperative pulse oximetry <95%, a 5% decrease in pulse oximetry and requiring oxygen therapy is counted as respiratory failure.
Reoperation	Any reoperation of the operated lung/hemithorax in general anaesthesia.
Death	Death by any cause during the follow-up period of 30 days.

FIO_2, the fraction of inspired oxygen; PaO_2, the partial pressure of oxygen in arterial blood; P/F-ratio, the ratio between PaO_2 and FIO_2 (expressed as a fraction).

Data generated from collected data

- Age (date difference between date of surgery and date of birth).
- Date of birth (using social security number).
- Gender (using social security number).
- Body mass index (kg/m^2).

Participant timeline

Patients are informed and enrolled during the preoperative visit 1–4 days before surgery, or in the outpatient clinic 1–4 weeks before surgery, depending on local preferences. During anaesthesia, but after the pulmonary VATS wedge resection, an air leak test is performed, and patients are randomised if there is no air leak. Patients are followed in the department until discharge and in the outpatient clinic approximately 2 weeks after surgery. Patients are followed for 30 days after surgery for complications in the patient records. The timeline is depicted in figure 3.

Trial duration

Planned start of inclusion will be 1 April 2022 or after necessary permissions have been obtained, and expected final inclusion and follow-up are expected by 31 March 2024.

This trial has been approved by two different Regional Ethical Committees (Capital Region for Rigshospitalet and Central Region for Aarhus University Hospital).

Sample size

Sample size is based on a previous observational study of 48 patients treated with multimodal, non-opioid analgesia

Table 4 Criteria to determine readiness for hospital discharge

Criteria	Endpoints to determine
Adequate pain control using oral analgesia	Patients should be able to rest and mobilise (sit up and walk, unless unable preoperatively) without significant pain (ie, patient reports pain is controlled or pain score ≤4 on a scale from 0 to 10) while taking oral analgesics.
Tolerance of oral intake	Patients should be able to tolerate at least one solid meal without nausea, vomiting, bloating or worsening abdominal pain. The patient should drink liquids actively (ideally >2000 mL/day) and not require intravenous fluids infusion to maintain hydration.
Recovery of pulmonary function	Patients should be able to breathe freely without the need for supplementary oxygen, chest drain or intravenous antibiotics.
Recovery of lower gastrointestinal function	The patient should have passed flatus.
Ability to mobilise and self-care	Patients should be able to sit up, walk and perform activities of daily living (eg, go to the toilet, dress, shower and climb stairs if needed at home) unless unable preoperatively.
Postdischarge support	Self-supported or adequately supported by family at home, nursing or rehabilitation facility.

Patients are evaluated for readiness for discharge on the day of surgery at 18:00 hours and thereafter twice daily at 9:00 hours and 15:00 hours until discharge.

with intercostal catheter after thoracoscopic lobectomy,[7] with no data on local pain following prior thoracoscopic wedge resections. Patients who undergo VATS wedge resection are operated using the same surgical approach originally developed for lobectomies.[24] Patients in the study had a mean pain score at rest of 3.2 (SD 1.6) on POD 1. A difference of 30% corresponding to 1 point on the NRS scale is set as the minimal relevant clinical difference. The sample size calculation is performed only for POD 1 during only one of the planned activities, as correlations between the 12 measurements are unknown. This approach ensures the power calculation is conservative. In other words, the actual study, as described above, will have a higher power although it cannot be estimated by how much.

With 80% power and a significance level of 5 %, 82 patients are required to show a difference from mean pain score of 3.2 in the control group to 2.2 in the intervention group. To account for a possible 15% drop-out rate or other loss of data a total of 94 patients are planned to be included in this trial.

Missing data

In any case of missing data on the primary outcome, multiple imputation and a subsequent sensitivity analysis will be conducted with our primary outcome reported using an intention-to-treat analysis.

Recruitment

Information used in this project prior to patient consent will be transferred to the responsible scientist. The treating physician will approach the patients and ask if the patients are interested in participation when the patient is scheduled for an appointment in the clinic. The treating physician will then convey the name and social security number as well as the type of surgical procedure of suitable patients to the principal investigator responsible for the project. In screening, the patient data are gained from the surgical list. Trial personnel are given the name, Danish civil registration number and surgical procedure from the surgical list. The conveyed data (before consent) are from a period of up to 4 weeks before the procedure. We expect that approx. 200 patients will be screened to select the 94. All patients participating in the study must provide oral and written informed consent before being included in the study (online supplemental material 3). It will be made clear that consent will allow the principal investigator responsible for the project and relevant authorities direct access to collect information from the patients' medical records etc, including electronic records, to view information regarding the subject's health, which are necessary in completing the research projects and for control purposes, including self-monitoring, quality control and for monitoring purposes, that they are obliged to perform. After consent is given, the principal investigator responsible for the project will have direct access to the AOP, containing health information about the patient and the subsequent surgical data. These data are used for continuous analysis of safety in relation to the research project. The patient may withdraw his/her consent to attend the study at any time. If the patient decides to do so, it will not impair his or her relationship with investigators or other staff and the patient will continue to receive the best treatment the department can offer.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation sequence generation

Allocation sequence is generated in RStudio. Randomised permuted blocks of 4, 6 or 8 in random sequence are generated to ensure balanced inclusion, and the allocation sequence is uploaded to the online application Research Electronic Data Capture (REDCap) to ensure online access for all study investigators. Stratification for potential confounders is not planned.

Allocation concealment mechanism

The allocation sequence list in REDCap will be prompted during the final stages of surgery after placement of a

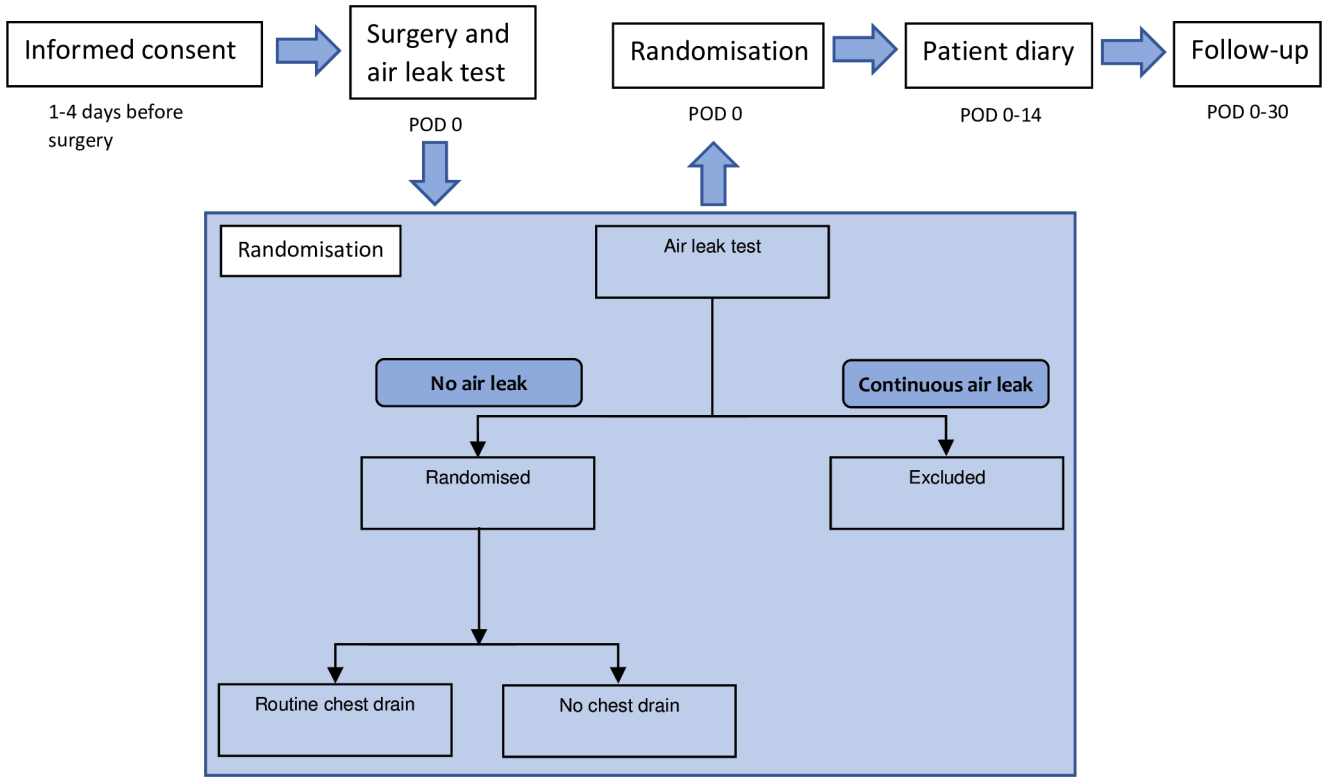

Figure 3 Flow diagram for patient inclusion. POD, postoperative day.

chest drain and confirmation of a completely sealed lung. This ensures allocation concealment up to the time of randomisation.

Implementation

Allocation sequence will be generated by a biostatistician using randomised permuted block randomisation in blocks of 4, 6 or 8 and stratified according to institution to control for confounding variables. This allocation sequence will be uploaded to REDCap for all investigators to be able to perform randomisation. Patients will be included by investigators, research nurses or surgical staff given adequate training in informed consent. Investigators, research nurses or surgical staff will access the randomisation list at the end of the procedure to assign patients to treatments.

Blinding

The placement of a sham-drain is not possible, and the study is, therefore, conducted as open label. However, because randomisation is performed after the pulmonary resection is completed during the last stages of the procedure, the surgeon, assistant and all other personnel are blinded to the allocation group before and during the procedure. This ensures uniform treatment during surgery and reduces the risk of bias during the steps leading up to the randomisation.

Furthermore, statistical analyses will follow a prespecified statistical analysis plan, where comparison of primary outcome and secondary outcomes will be conducted after treatment groups have been blinded to assessors. The manuscript will be formulated based on the initial blinded analyses, thereby ensuring blinding of trialists during data analysis and manuscript drafting. Hereafter data will be unblinded and the manuscript will be finalised based on the conclusions drawn while data were still blinded.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection methods

Data will be collected from electronic patient files on a daily basis by experienced research nurses or investigators. Data will be typed directly into REDCap. Data from surgeons and patients will be collected by research staff (research nurse or investigators) using the questionnaires 'Checklist for inclusion' and 'Patient diary' and typed directly into REDCap. All forms and questionnaires will furthermore be scanned into REDCap, and originals stored in a folder.

Assessment of data quality will be performed by an investigator, who will separately double check for errors of data entry using a random sample of 10% of the data. If error margin is below 10%, no further checks will be performed. If error margin exceeds 10%, a further random sample of 20% of the data will be accessed. Similarly, following an error margin below 10%, no further checks will be performed. If the error margin exceeds 10%, the whole dataset will be reassessed.

Data management

Data will be entered directly into REDCap on a daily basis, and progress will be monitored weekly. Data will be stored

on a server belonging to Region Hovedstaden according to a permission from the Data Protection Agency.

Adequate ranges for numerical values will be coded in REDCap to promote data quality.

Statistical methods

The primary endpoint consists of up to nine measurements per patient (measurements at three different time points and at three various movements). The two groups will be compared with a joint test of no group difference in a mixed effects model involving all nine measurements. The model allows for different treatment effects for each time point and for each movement but not for the interaction between them. The joint test for no group difference thus corresponds to simultaneously testing nine parameters to zero. In addition, the model will allow different pain levels for the different times and movements, but not interactions between them. Treatment effects will be quantified by the mean difference at each time point and movement estimated via the above mixed effect model.

For secondary outcomes, continuous data will be compared by parametric or non-parametric test depending on distribution. Categorical data are compared using χ^2 test or Fisher's exact test.

Statistical calculations are made using R. Significance level is set to p=0.05. Data processing is done by the investigator in collaboration with a biostatistician at the Biostatistics Department, University of Copenhagen.

METHODS: MONITORING

Data monitoring

This trial does not involve administration of medicine as part of the intervention, and the described intervention is part of the routine treatment in thoracic surgery. There are, therefore, no legal or ethical reasons to use a data monitoring committee. However, to reduce the risk of systematic and random data entry errors and to ensure the validity of the trial, data quality is assessed by the research group, as described in 'Data collection methods' section.

Benefits

This study will help shape the future treatment of thoracic surgery patients nationally and internationally. The study is unique based on the detail and combination of outcomes. As assessed by the steering committee, the potential risks and disadvantages are clearly outweighed by the benefits of the study.

The study will be conducted in accordance with the principles of the Declaration of Helsinki.

Participants may help clarify benefits and possible disadvantages of treatment without drainage after VATS wedge resection of the lung. Participants cannot be guaranteed personal gain from involvement but will receive the department's standard treatment as a minimum. The results of the trial can be used directly to patients after completion of the trial and will help future patients.

Harms

Patients undergoing thoracoscopic wedge resections are at risk of pleural effusion or pneumothorax requiring chest drainage. There are no data to support that patients are at increased risk in any of the two groups. Based on previous studies, the risk of drain reinsertion is <2%.

Patients may experience discomfort related to the drain insertion site, due to standard medications given or directly related to the surgery. There is, however, no indication of increased risk when participating in this study. Patients will furthermore have at least one chest X-ray taken but without increased risk due to radiation exposure.

Side effects, risks and disadvantages

Side effects are defined as any harmful and undesirable event, signs or symptoms that occur as a result of participation in the study and which cannot be attributed to the risks of the procedure. During the study, the chest drain is removed either in the operating room (intervention group), or at the surgical ward when the air leak is below 20 mL/min for at least 12 consecutive hours (control group). Both treatment modalities are performed on a routine basis in this patient population, and there are no known side effects to the treatment, which cannot be attributed to the risks of the surgery itself. Known risks of the operation include:

- Pneumothorax.
- Subcutaneous emphysema.
- Bleeding from the surgical site.
- Empyema.
- Drain reinsertion due to any of the above reasons.
- Surgical site infection.
- Pneumonia.
- Pain.

All patients included in the study will have one chest X-ray taken after drain removal as per department standard. Thus, there is no increased radiation risk among subjects.

Any patient operated in the lung will be at risk of having a chest drain reinserted after initial drain removal due to fluid or air in the pleura. Patients undergoing perioperative drain removal are not considered to be at greater risk for drain reinsertion.[2 8 10]

Patients included in the trial are asked to rate their level of pain during various movements (see 'Patient diary'). This may be considered a disadvantage for some but may for others be associated with a sensation of being at an advantage due to a higher level of attention from staff and generally a more detailed bodily insight.

Since both treatment options (chest drain and omission of chest drain) are used in daily clinics, it is considered reasonable to perform randomisation.

Limitations

This trial is an open-label trial with associated limitations. It has not been possible to develop a credible sham-drain to ensure blinding of participants, trialists

or staff. Therefore, outcomes in this trial are subject to potential bias. Measurements of pain and quantification of rescue analgesics are, therefore, subject to the same bias. However, owing to the pragmatic design, these issues contribute to the generalisability of the results, and therefore, also contribute to potential benefits of the results.

Auditing

There are no planned audits of this trial.

ETHICS AND DISSEMINATION

Research ethics approval

This protocol was approved by the Knowledge Centre for Data Reviews ('Videnscenter for Dataanmeldelser') at the Capital Region and Central Region, Denmark.

Protocol amendments

The study responsible investigator will inform the Scientific Ethics Committee of any major or major changes to the protocol and the study will be conducted in accordance with current rules for clinical studies in humans.

Consent

Patients meet in the surgical ward 1–2 weekdays before their planned surgery for preoperative workup. During this visit, the participant will be provided with written information about the trial and will be asked for a personal information meeting later that same day. The participant will be informed of his/her right to bring an assessor. If accepted, the time of the meeting will be planned for the patient and any assessor to participate, and adequate oral information will be provided on the purpose and structure of the study, as well as potential risks and disadvantages. The interview will be conducted by an investigator or research nurse, or by a person with delegated responsibility, and will take place in a quiet environment where the participant will be given the opportunity to ask questions.

Patients will be informed that it is voluntary to participate and that they can leave the study at any time without affecting their further treatment. They will also be informed that they may be excluded from the study at the discretion of an investigator or surgeon. Patients will be informed that randomisation will take place on the day of surgery itself. Patients will also be told what treatment they will receive if they choose to decline, as well as being informed that all data is treated confidentially and according to what is described below.

Once it is ensured that the patient understands the given information and has received answers to any questions, informed consent is sought. The patient will be offered reflection time before consent is given, at least 24 hours, and if necessary, until the morning of the day of surgery (normally at least 48 hours).

A copy of the information and signed consent statement will be provided to the patient.

It is the responsibility of the primary investigator to ensure that all patients receive oral information and ensure that the patient is fully aware of all aspects of study participation.

The trial is also registered prior to start of the international project database ClinicalTrials.gov.

Confidentiality

All information will be treated confidentially, and all data will be pseudonymised during the project. The persons responsible for this study are subject to professional confidentiality. Collected data will be recorded in a trial management system.

An investigator will keep an identification list of all patients included, containing full name, Danish civil registration number and assigned patient number. Furthermore, a screening list will be kept containing the screening date, the patient's initials (first and last name) as well as any cause for lack of inclusion for anyone screened.

Collected data will be recorded in an electronic case report form. This and the patient record will be made available to third parties in accordance with Danish law, that is, in connection with the inspection of authorised representatives of relevant authorities.

Patients are informed that the results will be stored and analysed in a database, that their data will be protected, and we will comply with the Data Protection Act and The General Data Protection Regulation.

The study investigator is responsible for handling and filing data in compliance with the Data Protection Act and The General Data Protection Regulation.

The project will be reported to the Capital Region's Videnscenter for Dataanmeldelser. After data processing is complete, all data will be anonymised and stored for 10 years.

Access to data

The steering committee will have access to the final trial data set. Furthermore, access will be given to biostatisticians and coauthors during the statistical analysis.

Ancillary and post-trial care

No ancillary or post-trial care will be given to participants as all procedures are performed on a routine basis. Any complications to treatment given will be treated as per the institution's standard.

Patient compensation

Patients are not compensated for their participation, since no experimental treatment is performed and both options (for randomisation) are considered standard treatment at the department.

Patient and public involvement

This trial was designed without direct involvement of patients or the public.

Dissemination policy

After completion of data collection and processing, the primary author will prepare a report on the basis of the results, which will be forwarded to the relevant authorities. The results will also be used to update the department's instructions so that future treatment is based on the latest evidence.

The results will form the basis of a manuscript which will be published in an international peer-reviewed scientific journal by the authors Lin Huang (first author), Bo Laksáfoss Holbek (second author), René Horsleben Petersen (last author) and Thomas Decker Christensen, Henrik Kehlet and Henrik Jessen Hansen as coauthors with the provisional working title: 'Efficacy of avoiding chest drains after video-assisted thoracoscopic surgery wedge resection: a randomised, controlled trial'. An additional coauthor from Aarhus University Hospital and a statistician are planned as additional coauthors. We will use the standard protocol items recommendations for interventional trials (SPIRIT) checklist when writing our report.[30] The results will have broad international interest and will be published regardless of positive, negative or inconclusive results. Authorships are awarded in accordance with the International Committee of Medical Journal Editors' recommendations.[31]

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Contributors This trial was initiated on behalf of HJH and principal investigator (PI) RHP. Co-PI, BLH, has designed the trial and authored and revised the protocol, and he is the corresponding author. LH, RHP, HK, TDC, MB and HJH have reviewed and revised the protocol.

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Competing interests BLH has received a speaker's fee from Medela Healthcare. HJH has received a speaker's fee from Medtronic and BD. TDC has been on the speaker bureaus for AstraZeneca, Boehringer-Ingelheim, Pfizer, Roche Diagnostics, Takeda, Merck Sharp & Dohme (MSD) and Bristol-Myers Squibb and has been in an Advisory Board for Bayer and Merck Sharp & Dohme (MSD). RHP has received a speaker's fee from Medtronic, AMU, AstraZeneca, Medela and is an advisory board member for AstraZeneca, Roche, MSD, BMS. LH, MB and HK have no conflicts of interest to report. This is an investigator-initiated trial with no ties to private industries.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

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