STUDY PROTOCOL ERASURE Study

Multicenter, international, prospective, randomized- controlled trial
Coordinating Center: Thoracic Surgery – Center for Thoracic Diseases, Mainz University, Germany

1. Project title, Version number/date

Title: ERASURE-Trial: Early autologous blood pleurodesis for postoperative air leaks - A randomized, controlled trial comparing prophylactic autologous blood pleurodesis versus standard watch and wait treatment for postoperative air leaks following thoracoscopic (VATS) anatomic lung resections.
Version number: 2.0
Version-date: 20.11.2022

2. Project summary

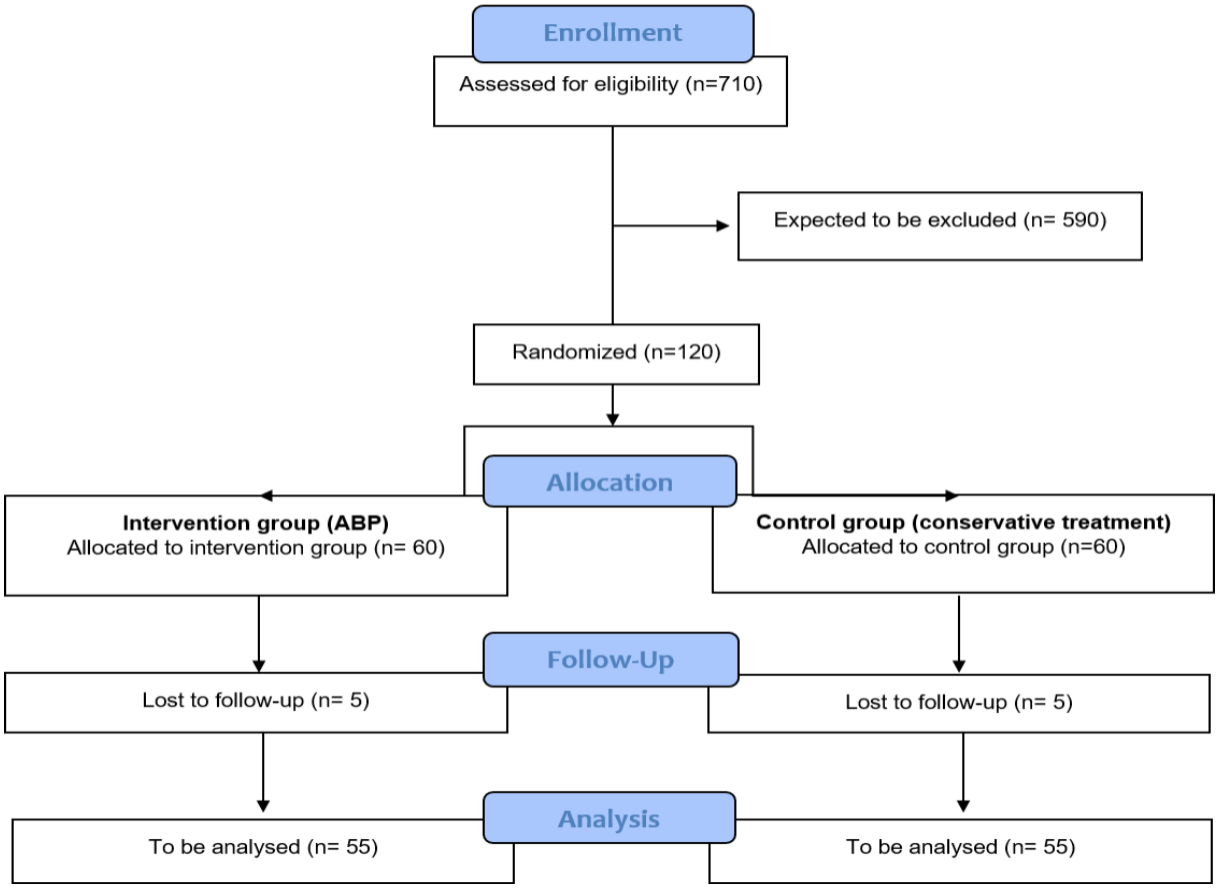
Background:
Every year around 1.8 million people are diagnosed and 1.6 million die of lung cancer (1). The morbidity associated with the disease is horrifying. In 2016 lung cancer was responsible for 36.4 million DALYs (disability adjusted life year) (1). The NLST trial showed significant reduction in the mortality of lung cancer after routine screening with low-dose CT scan of the chest (2). However, the screening has not been broadly implemented yet, expecting that the rate of patients being diagnosed with early stage lung cancer will substantially increase in the following years.

The most common complication following lung surgery is postoperative air leak. Air leaks result from incomplete closure of small airways during the division of lung tissue and can be monitored through the chest drain, which is placed at the end of an operation. Most air leaks heal within the first 24 hours after a lung procedure. However, 10-20% of the operated patients will eventually develop a prolonged air-leak (3).

The exact incidence of postoperative air leak widely varies, mainly due the absence of a commonly accepted definition. The traditional definition of a prolonged air leak is an air leak, which lasts over 7 days. This definition is based on studies using analog drain systems (underwater seal) to monitor the air leak. The expansion of the video-assisted thoracoscopic surgery, the modern anesthetic techniques and the evolution brought by the implementation of the ERAS pathway (4) have reduced the postoperative hospital stay after a lobectomy down to 2-3 days, making the definition of prolonged air leak clearly outdated. Furthermore, the modern electronic suction devices, that are nowadays used to monitor the air leak, enable a much more precise quantification of the air leak. It is therefore reasonable to expect that postoperative air leaks will soon become the most relevant complication in thoracic surgery.

The purpose of this trial is to investigate the impact of a prophylactic autologous blood pleurodesis in reducing the duration of the postoperative air leak and therefore the time that the drain needs to stay in the patient.

Design: Multicenter, international, prospective, randomized- controlled trial



Population:

- Study population: Patients undergoing an elective thoracoscopic anatomic lung resection for primary lung cancer or metastatic disease will be eligible for recruitment. Patients undergoing a segmentectomy, lobectomy or bi-lobectomy will be considered for this trial. The chest drain will be connected to an electronic suction device after the procedure to monitor the air leak. The commercially available electronic suction devices allow the retrieval of all data concerning the course of the air leak from the time that the patient was attached to the device by connecting the device to a PC. Patients with an air leak of > 100ml/min within 6 hours prior to the morning round on the second postoperative day will be eligible for inclusion in the study.

  We will not include patients undergoing open resections, since these usually are more complex procedures and might influence the homogeneity of the cohort. Furthermore, we will not include patients undergoing surgery for other pathologies than primary or secondary malignancies (emphysema/lung volume reduction surgery, infections) because the underlying pathology might have an impact on the quality of the lung tissue and might therefore represent a different patient population. We will also exclude patients undergoing complex resections (with angioplastic or bronchoplastic reconstructions) and patients with suspected or proven bronchial stump insufficiency because this type of air leak is not expected to resolve with the proposed intervention.
- Control(s): Patients in the control arm will not receive any specific treatment in order to reduce the postoperative air leak till the 7th postoperative day. This is the routine way to deal with postoperative air leaks in most thoracic centers worldwide. After the 7th postoperative day the patients of the control group can be treated according to the individual treatment algorithm of the participating center. In case the air leak amount is reduced to fulfill the drain removal criteria before the 7th postoperative day, the drain will be removed accordingly.

Treatments/Procedures

Patients who meet the eligibility criteria will be randomized. Patients who enter the interventional group will receive an autologous blood pleurodesis. A sterile bedside setup will be created for the procedure. A leur-lock connector will be attached to the chest drain in a sterile manner. 100-120 ml of patient blood will be obtained from a peripheral or central venous line. The blood will be then administered through the leur lock connector into the chest drain. The chest drain will be then flushed with 20 ml of sterile normal saline to avoid clotting of the drain. The tubing of the electronic suction system will be then raised 60cm above the level of the patient. The patient will be asked to change places and move while in bed in order for the blood to spread equally in the pleural cavity. After the two hours the patient will be free to mobilize and the electronic suction system will be turned on and set on gravity mode (-8 cm H20 or – 0.8 kPa). In case the air leak persists, the procedure will be repeated on the third postoperative day.

Patients who enter the control group will be treated conservatively. The electronic suction device will be set on gravity mode (-8 cm H20 or – 0.8 kPa). No interventions will be performed in order to speed up the healing of the air leak. After the 7th postoperative day, patients with persisting air leak will be treated according to each participating center's preference.

3. Applicant(s)/coordinating investigator(s)

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Financing

The trial has not received external financing so far and will be supported by institutional resources.

Registration

The study will be registered in the German Register for Clinical Trials (DRKS) after receiving a positive votum from the ethics committee.

4. Scientific Background

Search Strategy and Discussion of Evidence

A computer-based literature search was performed up until the 30th, July 2020 in the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR) from The Cochrane Library, MEDLINE (1966 to present), Cinahl (1981 to present) and Web of Science (1945 to present). Reference lists of retrieved articles were scanned for further eligible trials (backward search) and citations of identified trials were checked for inclusion (forward search). Search strategies included proper combinations of the MeSH terms 'lung/surgery', 'blood transfusion/autologous/autotransfusion/blood patch', 'air leak' and 'pleurodesis'. The search was not limited by publication type and there were no restrictions on language. The review was registered in the PROSPERO registry for systematic reviews and meta-analyses (CRD42021223388). The exact search strategy is available in the registry.

The database search provided 258 references. After removing duplicates, 245 references were available for reviewing. The citations of the initially included studies were hand-screened in order to identify further relevant publications, through which 8 additional references were found. Two hundred fifty-three abstracts and 30 full-text articles were assessed for eligibility. 10 articles were ultimately included in the analysis.

In order to assess the available literature in a systematic way we decided to perform a meta-analysis of the included references (5).Ten studies including a total of 198 patients (of which 159 underwent lung resections, the vast majority of which were lobectomies) were analyzed. Eight studies were retrospective, one was prospective and one was a randomized controlled trial. The pooled success rate of the blood pleurodesis for stopping the air leak within 48 hours after the intervention for all studies that were included was 83.7 % (95% CI 75.7 ; 90.3, fig. 2). Publication bias was excluded using the Egger's test (p= 0.825). In order to generate data for the sample size calculation for this trial, we performed a second analysis including only studies on patients who had undergone lung resections. The pooled success rate of the blood pleurodesis for stopping the air leak within 48 hours after the intervention was 85.7 % (95% CI 74.4; 94.0). The pooled empyema rate after the procedure was 1.5 % with an incidence of post-interventional fever of 8.6 %. All included studies were in favor of autologous blood pleurodesis for treating postoperative air leaks.

The literature research was repeated in order to include studies published between July 2020 and April 2021 (up until April 23, 2021). Another 32 references were reviewed, two of which as full-texts (6, 7). Both references were retrospective studies in favor of the autologous blood pleurodesis without adding any further evidence to the existing one.

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5. Purpose of the trial

The purpose of this trial is to investigate the impact of a prophylactic application of autologous blood on the healing of postoperative air leaks following minimally-invasive lung resections. The hypothesis of this trial is that an early blood pleurodesis would lead to a faster cessation of the air leak.

6. Endpoint(s)

Primary endpoint
Time to drain removal measured in full days

Secondary endpoint(s)
1. Time to cessation of the air leak (calculated in postoperative hours)
2. Length of postoperative stay measured in full days
3. Rate of (redo) interventions due to persistent air leaks
4. Rate of pleural empyemas

Outcome measures
Time to drain removal measured in full days was chosen as the primary endpoint for several reasons:

1) The intervention of this trial is a locally applied therapy enabling a more effective and faster sealing of the postoperative air leak. The efficacy of this treatment is more accurately evaluated by the time to drain removal. 2) It reflects the success or failure of the treatment directly, since removing the drain implies the cessation of the postoperative air leak. 3) It is a parameter, which is unique and irreversible throughout the patients' treatment and therefore not susceptible to interpretation bias from the medical team. 4) The parameter is clinically relevant and practical to use. The main reason is that chest drains are not usually removed overnight. Likewise, patients are not discharged overnight. 5) Several studies have analyzed the efficacy of the autologous blood pleurodesis using the time to drain removal as primary efficacy endpoint making it a widely accepted parameter to use as a primary outcome measure (8, 9).

The secondary outcomes include all relevant perioperative and patient-reported outcomes in thoracic surgery trials using widely accepted definitions. In order to assess the variability of the drain removal protocols among the participating centers, the shortest potential drainage time in postoperative hours will be calculated by retrieving the relevant data from the electronic suction device memory. Furthermore, in order to assess further complications associated with the procedure and potentially with the intervention (using the Clavien-Dindo grading system (10), the length of the postoperative stay calculated in full days will be evaluated. The rate of re-interventions due to persistent air leak after the initial removal of the drain will be also measured in order to detect treatment failures. The pleural empyema is the only well documented complication of the autologous blood pleurodesis with an incidence of 1.5% (5).

Study population

Key inclusion criteria

Adult patients undergoing a scheduled thoracoscopic (VATS) anatomic lung resection for primary or secondary lung tumors and presenting with an air leak > 100 ml/min within 6 hours prior to the morning round of the 2nd postoperative day will be eligible for enrollment.

Key exclusion criteria

1. Patients undergoing an open lobectomy
2. Patients undergoing complex lobectomies (bronchoplastic reconstructions etc.)
3. Patients requiring invasive or positive pressure non-invasive ventilation except in the first 6 hours following the operation
4. Patients undergoing re-operation during the same hospital admission
5. Suspected or proven bronchial stump leakage
6. Intraoperative use of sealants, pleural tents or talcum

Number of participants

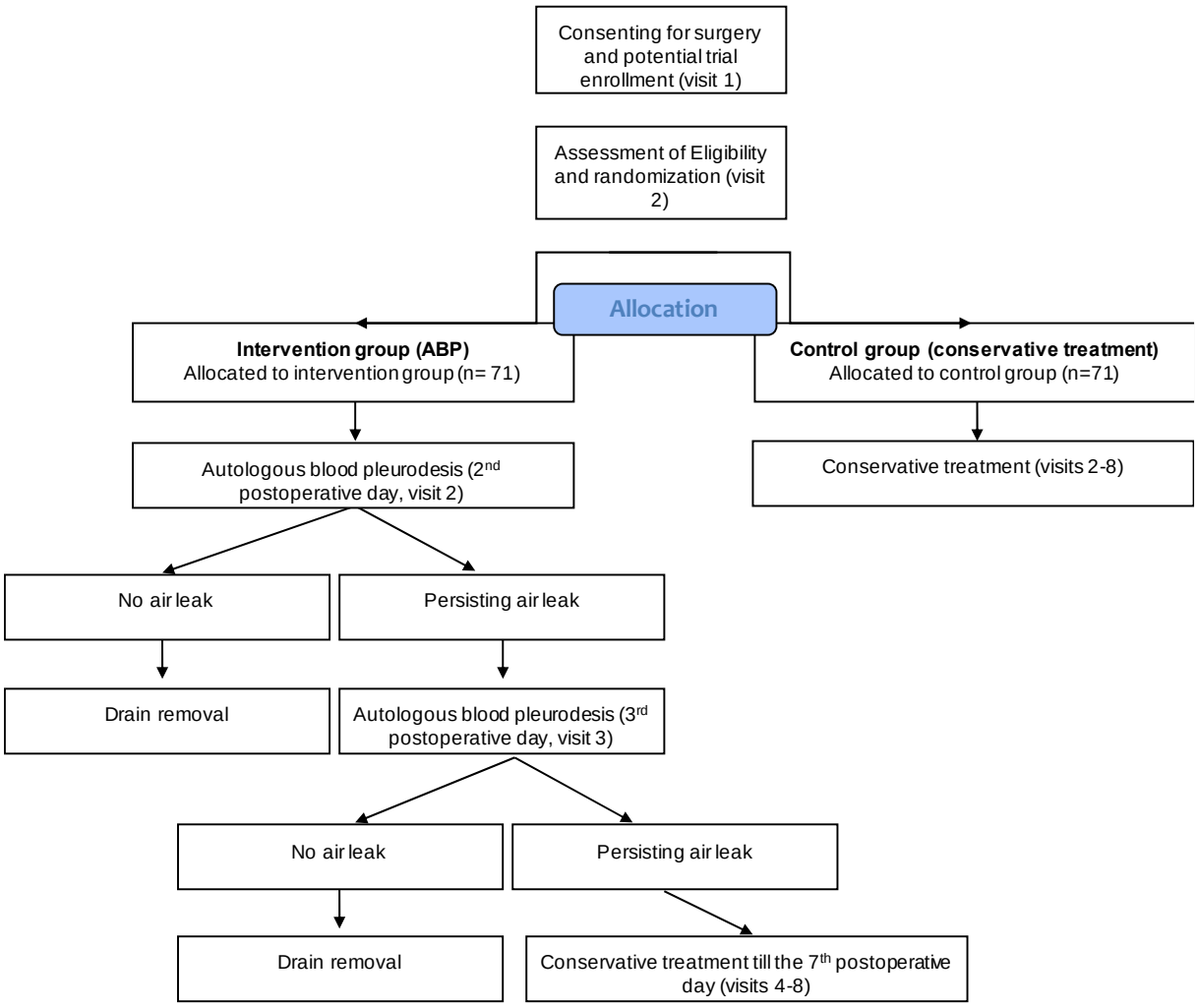
As presented in the flow diagram above, it is scheduled to randomize 120 patients in order to finally include and analyze 110 patients. For this purpose, over 700 patients need to be screened by the participating centers. The recruitment will take place at each participating center according to each centers' own workflow. Patients being recruited in the Academic Thoracic Center Mainz will be consented in the outpatient clinic.

7. Methods

Unicenter/Multicenter
This trial is planned as an international multicenter trial coordinated by the Division of Thoracic Surgery of the Center for Thoracic Diseases Mainz.

Consenting Process
All patients will be consented respecting the Good Clinical Practice guidelines. The legally foreseen interval for consideration of participation will be respected in every case. As reported previously, the consenting will be performed in written form along with the consenting for the surgical procedure. The process reported here reflects the process that will be followed in the coordinating center (Mainz). Each center and especially the international centers will adapt this algorithm in order to meet the local legal and ethical standards.

Treatment flowchart for each participant
The treatment of each particular patient will be based on the flowchart below.



8. Benefit-Risk-Assessment

Benefits associated with the trial

The early autologous blood pleurodesis could lead to a faster cessation of the air leak and therefore to a faster removal of the drain. A faster removal of the drain would relieve the patient from all the well-known drain associated complications (longer hospital stay, stronger postoperative pain, risk of drain-associated infection etc.).

Risks associated with the trial

The first and so far mostly reported risk of the procedure is the pleural empyema. Our recent metaanalysis has estimated the empyema rate following an autologous blood pleurodesis at 1.5%. However, it should be considered that the studies included in the metaanalysis reported outcomes on autologous blood pleurodesis which was performed after the 7th postoperative day, or even later. It is well known that the later the procedure is performed, the higher the risk of infection (and consequently of empyema) is. It is therefore reasonable to expect that the true incidence of empyema following a prophylactic blood pleurodesis is well under 1% which is medically acceptable. Furthermore, the drain itself harbors a certain risk of infection like every other foreign body penetrating the skin. The longer the drain stays, the higher the chances of a patient developing a drain-related infection. The empyema incidence for chest drains has not been reported but it is probably comparable with the empyema rate following an autologous blood pleurodesis. Based on these assumptions, we do not expect that performing an autologous blood pleurodesis is associated with more empyemas than needing to keep the chest drain for a longer period, due to a persisting air leak.

Second, performing the autologous blood pleurodesis requires the sampling of 100ml venous blood from the patient. Consequently, all the well-known risks of blood sampling are potential risks of the procedure (local pain, discomfort, hematoma, swelling, accidental arterial puncture etc.).

Statement of medical justification

The above mentioned trial is medically reasonable and is not associated with relevant risks for the study participants.

9. Biometrics

The sample size calculation was based on median drainage removal times of the study by Shackcloth (Ann Thorac Surg. 2006 Sep;82(3):1052-6 (2006)). This seems to be the study of highest quality on this topic so far. Shackcloth reported drainage removal times of 6.5 days in the control group and 12.0 days in the intervention group. The maximum observation time was set to 14 days and no accrual time is considered. For the sample size calculation we assumed a difference in the removal times of 2 days (compared with the 5.5 days reported by Shackcloth et al.). This is much more conservative and reflects more the current surgical practice than 18 years ago, when Shackcloths trial was published.
The sample size calculation was based on median drainage removal times of 4 days in the control group and 2 days in the experimental group. The maximum observation time was set to 7 days and no accrual time is considered. With a two-sided level of significance of 5% and a power of 90%, a sample size of 110 (=2x55) will be needed using a logrank-test for planning. When considering slightly less than 10% of dropouts, 120 patients (=2x60) should be randomized. The sample size was calculated with SAS Version 9.4.
The primary endpoint (the time to drain removal in full days) will be analysed within a Cox regression model with treatment as fixed factor and centre as covariate. Model assumptions will be checked by Schoenfeld residuals. The two-sided significance level is set to α= 5%. The primary analysis population is the ITT population consisting of all randomised patients. Treatment differences will be displayed by the estimate of the hazard ratio and the 95% confidence interval. Sensitivity analyses will be done by adding additional variables like smoking (yes/no) and sex in the regression model, although sex is not known as an influencing factor for time to drain removal.
Safety: Absolute and relative frequencies of adverse events.
Secondary endpoints: The length of postoperative stay will be analysed by the same model as the primary analysis. The rate of re-interventions and pleural empyemas will be analyzed by a logistic regression model.

10. Data management and confidentiality

The Interdisciplinary Center for Clinical Trials (IZKS Mainz) will be responsible for data management and data archive. Identifying information will be stored in anonymized form for 25 years. All data specified in the trial protocol will be documented in a clinical database. A case report form (CRF) will be used for data collection. All data will be pseudonymised. The investigator or the designated representatives are obliged to clarify and solve queries. If no further corrections are to be made in the database, it will be locked and used for statistical analysis. All data management procedures will be conducted according to written defined standard operating procedures (SOPs) of the IZKS that guarantee an efficient conduct complying with Good Clinical Practice (GCP) and under strict observance of national and EU regulations. Source data are to be stored for at least ten years after trial termination in center archive. At the end of the study, the data will be transformed into different data formats for archiving to ensure that it can be reused.
Dissemination of results: The trial will be registered at an international trial registry and the trial protocol will be published. International guidelines such as SPIRIT and CONSORT will be strictly adhered to. Results will be presented at national and international conferences. Publication in international open-access, peer reviewed journals is intended.

Signatures

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