Comparison of the clinical benefits for non-small cell lung cancer patients between different volume of pleural lavage fluid following video-assisted thoracoscopic lobectomy and systematic mediastinal lymph node dissection: study protocol for a randomized controlled trial

CURRENT STATUS: ACCEPTED

Jian Zhou
Sichuan University West China Hospital

Chengwu Liu
Sichuan University West China Hospital

Shulei Man
West China School of Medicine

Mengyuan Lyu
Sichuan University West China Hospital

Hu Liao
Sichuan University West China Hospital

Nan Chen
Sichuan University West China Hospital

Yuhui Cheng
Sichuan University West China School of Medicine

Lunxu Liu
Sichuan University West China Hospital

Corresponding Author

lunxu_liu@aliyun.com

DOI:
10.21203/rs.2.10216/v4

SUBJECT AREAS
Integrative & Complementary Medicine
KEYWORDS
Pleural lavage fluid, Pulmonary surgery, Non-small cell lung cancer, Thoracic drainage, Randomized controlled trial
Abstract

Background: Pleural lavage is regularly performed before closing chest wall in pulmonary surgeries to prevent pleural implantation of tumor cells and postoperative infection. However, scant data could be found in the literature regarding the optimal regimen for performing pleural lavage. To establish a proper volume of pleural lavage, we herein designed a protocol for a randomized controlled trial.

Methods: A total of 400 participants with non-small cell lung cancer (NSCLC) undergoing video-assisted thoracoscopic surgery (VATS) lobectomy and systematic mediastinolymph node dissection (MLND) will be randomly assigned into 2 groups: Group A (500ml pleural lavage fluid) and Group B (3000ml pleural lavage fluid). The primary outcomes include the levels of leukocytes, neutrophils, inflammatory factors on the first postoperative day. The secondary outcomes include: (i) the levels of leukocytes, neutrophils, inflammatory factors on the second and third postoperative day; (ii) the incidence of postoperative fever on the first, second and third postoperative day; (iii) the volumes of chest drainage within the first 3 operative days, the duration of drainage, and postoperative hospitalization; (iv) the incidence of postoperative complications (incision infection, pain, atelectasis, hemorrhage, etc.), and the incidence of pleural effusion requiring thoracic puncture or drainage within 30 days after surgery. The main content of the analysis includes effectiveness and safety analysis. We will perform subgroup analyses to identify potential influence factors. Discussion: As far as we know, this will be the first randomized controlled trial is expected to compare the clinical outcomes between different volumes of pleural lavage fluid following VATS and MLND. Findings from this trial will determine the appropriate amount of pleural lavage before chest wall closure. Trial registration number: This study has been registered with the Chinese Clinical Trial Registry (ChiCTR1900021950) on 17 March 2019. The URL of the trial registry record is http://www.chictr.org.cn/showprojen.aspx?proj=37003.

Background

In pulmonary surgery, pleural lavage is routinely performed before closing chest wall, to rinse off residual tumor cells and tissues and ideally prevent pleural implantation of tumor and postoperative infection [1]. It was known decades ago that even if there were no obvious malignant pleural effusion
or pleural implants, tumor cells can be found in as much a third of postoperative pleural lavage [2]. Since then, accumulating data has indicated the presence of tumor cells in intraoperative pleural lavage as an independent prognostic factor [3-5]. Intra-operative pleural lavage cytology detected before closure could present a higher prognostic value than pleural lavage cytology detected before thoracotomy. Further, it could guide the choice of adjuvant chemotherapy for lung cancer patients after surgery.

While there is no guideline regarding how pleural lavage should be conducted [6], usually it involves irrigating the thoracic cavity with 0.9% sodium chloride injection varying from 20 to 2000 ml [2, 7-9] at 38~40 °C [10]. However, there are no determinant criteria on the volume of pleural lavage fluid. If the volume of pleural lavage is too small, the residual tumor cells and tissue cannot be washed away, which may result in increased absorption of inflammatory mediators, fevers, and even severe inflammatory reactions [11]. And it could affect prognosis and prolong hospitalization [12]. Furthermore, the residual tumor cells may increase the risk of recurrence [13] and metastasis [14-16]. And if the volume of pleural lavage is excessive, it will cause waste of resources and prolongation of operation time. Kaneda M et al. [9] found that the doses of over 500 ml could cause false negative results of pleural lavage cytology. Based on clinical practice and literatures[7, 8], we decided to test two volumes of pleural lavage, at 500 ml or 3000 ml.

We will prospectively enroll non-small cell lung cancer (NSCLC) patients undergoing video-assisted thoracoscopic surgery (VATS) for lobectomy and systematic mediastinal lymph node dissection (MLND). After enrollment, we will randomly allocate patients into 2 groups: Group A (500ml pleural lavage fluid) or Group B (3000ml pleural lavage fluid). Blood samples will be collected to test for leukocytes, neutrophils and inflammatory factors. Postoperative complications, the volume of pleural drainage and length of hospital stay will be also recorded. We aim to compare the clinical benefits for NSCLC patients between different volumes of pleural lavage fluid following VATS lobectomy and MLND.

Methods/design

Trial design
This is a single-blind, single-center, randomized controlled trial (Fig. 1). This study protocol adheres to the Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) statement. The SPIRIT figure (Fig. 2) summarizes the items of enrollment, intervention and follow-up. The detailed SPIRIT checklist is also provided (see Additional file 1).

**Study objective**

This study aims to identify the effects of different volumes of pleural lavage fluid on perioperative outcomes of NSCLC patients following VATS lobectomy and MLND.

**Study location**

This study will be conducted in NSCLC patients undergoing VATS lobectomy and MLND in the Department of Thoracic Surgery, West China Hospital, Sichuan University.

**Recruitment**

**Recruitment of Participants**

Patients eligible for this trial must comply with all the inclusion criteria and must not meet any exclusion criteria. To achieve adequate enrollments, all surgeons in the thoracic department of the hospital are informed of this trial. Each included patient will sign an informed consent form. The consent form at least contains: (i) the detailed explanation of the study design, including backgrounds and aims of this trial; (ii) the benefits and risks of participating; (iii) the strategy and compensation for the participants if they experience any harm as a result of trial participation.

**Inclusion criteria**

Patients who, at the start of the treatment, meet all the following criteria, are eligible for this study: (i) patients aged between 18 and 75 years; (ii) patients undergoing planned VATS lobectomy and MLND; (iii) be American Society of Anesthesiologists (ASA) grades I-II; (iv) essential materials were complete such as clinical staging of lung cancer and medication; (v) confirmed diagnosis of NSCLC through pathological examination after surgery; (vi) willing to participate after reading and signing an informed consent form.

**Exclusion criteria**

Patients who, at the start of treatment, meet any of the following criteria are excluded from this
study: (i) last smoked <2 weeks prior to surgery for current smokers; (ii) preoperative hydrothorax of patients was predominant; (iii) patients were pregnant or breastfeeding women (females aged 18 to 55 should receive pregnancy test); (iv) patients with preoperative severe mental illness; (v) patients with preoperative gastrointestinal or blood system disease; (vi) patients underwent cardiac ischemia; (vii) patients receiving preoperative radiotherapy or neoadjuvant chemotherapy; (viii) intraoperative accidents happened to the patients, such as hemorrhage (>500ml), conversion to open surgery, or cardiac arrest; (ix) patients with severe postoperative bleeding or persistent air leakage, which require reoperations.

**Randomization and blinding**

Randomization of trial participants will be based on computer-generated random numbers prior to the surgery. The random numbers will be printed, and placed in consecutively numbered and separate sealed opaque envelopes, which will be only opened when a patient is enrolled and meets all inclusion criteria. Based on the number, the principal doctor (CL) will assign the participant to a group. The research assistant should receive the notification timely and assign patients to their study group strictly as required. This study will be single-blind. The participants will be blinded to the allocation of the participants, while the investigators and project manager will be unblinded. If an unexpected emergency occurs, allocation will be disclosed to the investigators, the participant will be withdrawn from this study and a detailed explanation will be recorded if unblinding happens.

**Sample size**

This is the first study which focuses on the effect of different volume of pleural lavage on the clinical outcomes following VATS lobectomy and MLND, and no reference is available to estimate the sample size. We estimated the power based on Student’s t test of the levels of leukocytes on the first postoperative day in each group. We estimate an effect size of 0.5 from our experience. A total of 400 participants will be recruited in this study with 200 in each group. We set the dropout rate as 10% to account for inability to complete the treatment, data errors, loss to follow-up and other unanticipated study problems based on our experience. Assuming a type I error rate of 5%, this study could provide a power of 99.72% by using G*Power (Software Version 3.1.3, University of Düsseldorf, Germany).
**Intervention**

A total of 400 NSCLC patients aged 18-75 years, who are undergoing VATS lobectomy and MLND, will be recruited in our study based on the inclusion and exclusion criteria. All the patients will be divided into 2 groups:

Group A (experimental group): 500 ml pleural lavage fluid

Before closing the chest wall, we will perform careful hemostasis and then flush the thoracic cavity with 500 ml 0.9% sodium chloride injection at 38-40 °C. A 28F catheter will be indwelled for chest drainage.

Group B (experimental group): 3000 ml pleural lavage fluid

We will use 3000 ml 0.9% sodium chloride injection at 38-40 °C to flush the thoracic cavity in this group. All other procedures are the same as that of group A.

**Study dropouts**

All recruited participants have the right to quit this study at any time for any reason based on the ethical consideration, without any negative effects on their further therapy. Meanwhile, all researchers have the right to terminate the enrollment of any patients at any time within reasonable circumstance. All the changes and reasons will be recorded immediately in the case report form (CRF). If dropout rate is higher than 10%, we will apply multiple imputation to avoid pitfalls involved with listwise deletion of cases. Intention-to-treat (ITT) principle will be applied to analyze the data.

**Data management**

All the data recorded in CRF will be checked twice by two independent researchers. A data management safety committee (DMSC) comprised of 3 independent investigators will be needed. They will supervise the study protocol adherence, participants recruitment, and confirm that the CRF is correctly completed and consistent with the original data. All the data can only be acquired by the study investigators who have signed the confidential disclosure agreement. We do not plan to collect personal information about potential and enrolled participants beyond what is collected during normal hospitalization. After the trial, personally identifiable information will be omitted and placed in a separate database before any data analysis will be performed. All participants’ data collected in this
trial will not be used for other ancillary studies. The adherence to the study protocol, data collection, statistical analysis and publication issue, as well as related safety issues will be strictly monitored by the Institutional Ethic Committee of West China Hospital, Sichuan University.

**Statistical analysis**

The main content of the analysis is effectiveness analysis and safety analysis. The analysis of all continuous variables will be presented as mean, standard deviation (SD), median, quartile spacing, maximum and minimum values. The analysis of all dichotomous variables will be presented as rate, constituent ratio and hazard ratio. We will use the t-test and $\chi^2$ test, analysis of variance, univariate and multivariate logistic regression analysis to describe our data. The factors ($p<0.15$) in univariate analysis will be analyzed in multivariate analysis. All the data will be checked twice by two independent statisticians. The two independent statisticians will also be blinded to treatment assignment. We will perform post-hoc subgroup analysis to identify potential significant factors based on age, sex, tumor location, clinical stage of tumor, resection scope, duration of surgery, the volume of intraoperative bleeding, and pathological stage of tumor. Demographics and clinical characteristics of the subjects are summarized as mean ± SD for continuous variables and number (%) for categorical variables. The difference between groups will be considered statistically significant if $P<0.05$. All data will be analyzed using SPSS (software version 25.0, Chicago, IL).

**Study organization**

**Data collection and outcomes**

We will collect blood sample of patients to test leukocytes, neutrophils and inflammatory factors. Sample collection will be performed by trained nurses. Samples will be sent to the Department of Laboratory Medicine immediately after collection. The laboratory evaluation will be conducted by technicians, which will be blinded to treatment groups. Laboratory results will be placed in an electronic chart. Specimens will be destroyed and not stored for any ancillary studies. Preoperative data will be collected within 3 days after recruitment. Surgery data will be collected within 2 days after operation. Postoperative data will be collected within 3 days after discharge. For patients discharged home, we will conduct follow-up information by phone calls, and these data will be
recorded within 3 days after follow-up. If there are any errors or omissions in the electronic chart, the investigator will correct them immediately. The raw data will be marked clearly when revising, and signed by the investigator with date when the modifications are made. All the data can only be obtained by the study researchers who have signed the confidential disclosure agreement.

**Complications**

Some postoperative complications, such as bleeding, pain at the incision site, postoperative air leak, prolonged air leak, and atelectasis, will be treated according to clinical guidelines. During every ward round, conducted at least twice a day, the doctors in charge will solicit the patients’ feedback and perform specific physical examination to monitor any adverse events. All adverse events will be recorded timely in CRF. Postoperative follow-up will be conducted for all participants. Participants with any serious harms experienced as a result of trial participation will receive adequate compensation.

**Primary and secondary outcomes**

All the outcomes will be defined according to two previous studies[17, 18].

**Primary outcomes:**

The levels of leukocytes, neutrophils, inflammatory factors [interleukin-1β (IL-1β), IL-6, IL-8, IL-2, tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), prostaglandin E2 (PGE2), and 5-hydroxytryptamine (5-HT)] on the first postoperative day. On the first postoperative morning, a trained nurse will collect blood samples and then send samples to test. The mean difference of the levels of leukocytes, neutrophils, and inflammatory factors will be compared between the 2 groups.

**Secondary outcomes:**

(i) the levels of leukocytes, neutrophils, inflammatory factors (IL-1β, IL-6, IL-8, IL-2, TNF-α, CRP, PGE2, and 5-HT) on the second and third postoperative day; (ii) the incidence of postoperative fever on the first, second and third postoperative day; (iii) the volumes of chest drainage within the first 3 operative days, the duration of drainage, and postoperative hospitalization; (iv) the incidence of postoperative complications (incision infection, pain, atelectasis, hemorrhage, etc.) and the incidence of pleural effusion requiring thoracic puncture or drainage within 30 days after surgery.

**Protocol amendments**
The current protocol is version 1.0 (25 September 2018). Any amendment to the protocol that may affect the process of study or the benefits and risks to participants will required the agreement of the Ethics Committee.

Discussion
It is essential to flush the thoracic cavity before chest wall closure. However, scant data could be found in the literatures. The most frequently used method is to flush the thoracic cavity with 0.9\% sodium chloride injection heated nearly to the temperature of the human body at 38~40\^\circ C. No determinant criteria on volume of pleural lavage fluid has been built. If the volume of pleural lavage is too less, the residual tumor cells and tissue cannot be washed away, which may result in increased absorption of inflammatory mediators, fever, and even severe inflammatory reactions. And it will affect prognosis and prolong hospital stay. Furthermore, the residual tumor cells may increase the risk of recurrence and metastasis. If the volume of pleural lavage is too high, it will cause waste of resources and prolongation of operation time.

The study will enroll 400 NSCLC patients undergoing VATS lobectomy and MLND, and divide them into 2 groups. We will change the volume of 0.9\% sodium chloride injection to find out whether different volumes of pleural lavage fluid have different effects on prognosis of NSCLC patients measuring by some important clinical indices such as the plasma levels of leukocytes, neutrophils, inflammatory factors, and the incidence of fever after operation were observed 1 to 3 days after operation.

However, the study has some limitations. First, it is a single-center trial which will restrict its generalizability, so a multiple-center large-sample clinical trial is warranted in the future. Second, the anesthesiologist and surgeons in charge of the intraoperative part of the study cannot be blinded to this study group regarding the safety. Third, the hospitalization time may be different across participants, which may bring effects on the prognosis of NSCLC patients. Fourth, larger patients may need different volumes of pleural lavage.

In conclusion, this study is the first randomized controlled trial aiming to compare the clinical benefits for non-small cell lung cancer (NSCLC) patients between different volumes of pleural lavage fluid following video-assisted thoracoscopic lobectomy and systematic lymph node dissection. This study
may help to develop a standardized procedure of pleural lavage before closing the thoracic cavity in patients undergoing lung cancer surgery.

**Trial Status**
This study is not yet open for recruitment. This trial is scheduled to begin in July 2019 and to end in July 2021.

**Lists Of Abbreviations**
NSCLC: non-small cell lung cancer; VATS: video-assisted thoracoscopic surgery; MLND: mediastinal lymph node dissection; SPIRIT: Standard Protocol Items: Recommendation for Interventional Trials; ASA: American Society of Anesthesiologists; CRF: case reported form; ITT: intention-to-treat; DMSC: data management safety committee; SD: standard deviations; IL: interleukin; TNF-α: tumor necrosis factor-α; CRP: C-reactive protein; PGE2: prostaglandin E2; 5-HT: 5-hydroxytryptamine.

**Declarations**

**Ethics approval and consent to participant**
Ethic approval has been obtained from the Institutional Ethic Committee for Clinical Research of West China Hospital, Sichuan University (NO. 2018-417). This study has been registered with the Chinese Clinical Trial Registry (ChiCTR 1900021950) on 17 March 2019. The URL of the trial registry record is http://www.chictr.org.cn/showprojen.aspx?proj=37003 (see Additional file 2). Only participants who read and write inform consent will be recruited.

**Consent for publication**
Not applicable.

**Availability of data and materials**
The results of this trial will be published in an international peer-reviewed journal and presented at international scientific meetings. No later than 3 years after the publication of the results of this trial, we will deliver a completely deidentified data set to an appropriate data archive for sharing purposes. Any data request will be sent to the corresponding author and considered carefully.

**Competing interests**
The authors declare that they have no competing interests.
**Funding**

This work was supported by Key Science and Technology Program of Sichuan Province, China (2016FZ0118) (to Dr. Lunxu Liu). The study funders played no role in the study design, writing of the protocol or the decision to submit the report for publication. The study funders will play no role and have no authority over the collection, management, analysis or interpretation of data.

**Authors’ Contributions**

LL, JZ and CL conceived of the study, finished its design and coordination. JZ, CL, SM and ML developed the protocol and collected data. JZ, CL, HL, and LL are responsible for the operations. NC and YC participated in statistics analysis. JZ and CL drafted the manuscript. LL financially supported this study. All authors read and approved the final manuscript.

**Acknowledgements**

We give sincere thanks to Weelic Chong from Sidney Kimmel School of Medicine, Thomas Jefferson University Philadelphia, PA, USA, for his help with the English language editing of this manuscript.

**References**

1. Toufektzian L, Sepsas E, Drossos V, Gkiozos I, Syrigos K. Pleural lavage cytology: where do we stand? Lung Cancer. 2014;83:14-22.

2. Enatsu S, Yoshida J, Yokose T, Nishimura M, Nishiwaki Y, Shirakusa T, et al. Pleural lavage cytology before and after lung resection in non-small cell lung cancer patients. Ann Thorac Surg. 2006;81:298-304.

3. Shoji F, Yamazaki K, Kouso H, Mori R, Takeo S. The impact of pleural lavage cytology both before and after lung resection on recurrence of non-small cell lung cancer. Ann Thorac Surg. 2016;101:2141-6.

4. Yanagawa N, Shiono S, Abiko M, Abe M, Watanabe K, Watanabe I, et al. Positive intraoperative pleural lavage cytology is a predictive marker of disease recurrence in stage I lung adenocarcinoma. Interact Cardiovasc Thorac Surg. 2014;18:621-5.

5. Nakamura T, Otsuki Y, Nakamura H, Funai K. Pleural lavage cytology after lung
resection in patients with non-small cell lung cancer and the feasibility of 20 mL saline solution. Asian J Surg. 2019;42:283-9.

6. Noppen M, De Waele M, Li R, Gucht KV, D'Haese J, Gerlo E, et al. Volume and cellular content of normal pleural fluid in humans examined by pleural lavage. Am J Respir Crit Care Med. 2000;162:1023-6.

7. Shintani Y, Ohta M, Iwasaki T, Ikeda N, Kanou T, Tomita E, et al. Intraoperative pleural lavage cytology after lung resection as an independent prognostic factor for staging lung cancer. J Thorac Cardiovasc Surg. 2009;137:835-9.

8. Nakao M, Hoshi R, Ishikawa Y, Matsuura Y, Uehara H, Mun M, et al. Prognosis of non-small-cell lung cancer patients with positive pleural lavage cytology. Interact Cardiovasc Thorac Surg. 2015;20:777-82.

9. Kaneda M, Yokoi K, Ito S, Niwa H, Takao M, Kondo R, et al. The value of pleural lavage cytology examined during surgery for primary lung cancer. Eur J Cardiothorac Surg. 2012;41:1335-41.

10. Hooper CE, Edey AJ, Wallis A, Clive AO, Morley A, White P, et al. Pleural irrigation trial (PIT): a randomised controlled trial of pleural irrigation with normal saline versus standard care in patients with pleural infection. Eur Respir J. 2015;46:456-63.

11. Ts'Ai YC, Keng CC, Fan YS. Intrapleural irrigation for reducing postresectional fever and pleural reaction. Chin Med J. 1959;78:313-21.

12. Higashiyama M, Doi O, Kodama K, Yokouchi H, Tateishi R, Horai T, et al. Pleural lavage cytology immediately after thoracotomy and before closure of the thoracic cavity for lung cancer without pleural effusion and dissemination: clinicopathologic and prognostic analysis. Ann Surg Oncol. 1997;4:409-15.

13. Satoh Y, Hoshi R, Ishikawa Y, Horai T, Okumura S, Nakagawa K. Recurrence patterns in patients with early stage non-small cell lung cancers undergoing positive pleural
lavage cytology. Ann Thorac Surg. 2007;83:197-202.

14. Kameyama K, Okumura N, Miyaoka E, Asamura H, Yoshino I, Tada H, et al. Prognostic value of intraoperative pleural lavage cytology for non-small cell lung cancer: the influence of positive pleural lavage cytology results on T classification. J Thorac Cardiovasc Surg. 2014;148:2659-64.

15. Mazza F, Ferrari E, Maineri P, Dozin B, Ratto GB. Pleural lavage cytology predicts recurrence and survival, even in early non-small cell lung cancer. Surg Today. 2015;45:322-8.

16. Hanagiri T, Takenaka M, Oka S, Baba T, Shigematsu Y, Nagata Y, et al. Pleural lavage cytology immediately after thoracotomy in patients with completely resected non-small cell lung cancer. Int Surg. 2011;96:171-5.

17. Saldanha IJ, Dickersin K, Wang X, Li T. Outcomes in Cochrane systematic reviews addressing four common eye conditions: an evaluation of completeness and comparability. PLoS One. 2014;9:e109400.

18. Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database--update and key issues. N Engl J Med. 2011;364:852-60.

Figures
Figure 1

Standard protocol items: recommendation for interventional trials (SPIRIT) figure.
### STUDY PERIOD

| TIMEPOINT                          | Enrollment            | Allocation | Follow up (postoperative) |
|-----------------------------------|-----------------------|------------|---------------------------|
|                                   | 3-7 days before surgery | surgery   | 1 day | 2 days | 3 days | 30 days |
| ENROLMENT:                        |                       |            |     |     |        |        |
| Eligibility screen                |                       | x          |     |     |        |        |
| Medical history                   | x                     |            |     |     |        |        |
| Obtaining informed consent        | x                     |            |     |     |        |        |
| Allocation                        | x                     |            |     |     |        |        |
| INTERVENTIONS:                    |                       |            |     |     |        |        |
| 500 ml pleural lavage fluid       | x                     |            |     |     |        |        |
| 3000 ml pleural lavage fluid      | x                     |            |     |     |        |        |
| ASSESSMENTS:                      |                       |            |     |     |        |        |
| Postoperative complications       |                       |            | x   |     |        |        |
| Blood test                        |                       |            |     | x   |        |        |
| Thoracic drainage                 |                       |            |     |     |        |        |
| Postoperative hospitalization     | x                     |            |     |     |        |        |

**Figure 2**

Flowchart for participants identification, assessment, enrollment, randomization, intervention, and follow-up.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- Additional file 1-SPIRIT Checklist.doc
- EQUATOR Network Reporting Checklist.doc
- IRB approval-original file.pdf
- support-original file.pdf
- Additional file 2-WHO Trial Registration Data Set.docx
- translation of support.pdf
- translation of the IRB.pdf
