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

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Study protocol

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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 propervolume of pleural lavage, we herein designed this 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 mediastinal lymph 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: This first randomized controlled trial is expected to compare the clinical outcomes between different volumes of pleural lavage fluid following VATS and MLND, and provide us evidence to develop a standardized procedure of pleural lavage before closing chest wall in lung cancer operation. 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/listbycreater.aspx.

Background

Pleural lavage is regularly performed before closing chest wall in pulmonary surgeries, by which some potentially residual tumor cells and tissues can be washed away, to prevent pleural implantation of tumor and postoperative infection [1]. It was early reported that even if there were no obvious malignant pleural effusion or pleural implants, the positive rate of tumor exfoliated cells in postoperative pleural lavage was as high as 33% in 1958 [2]. Various studies found that intraoperative pleural lavage was an independent prognostic factor of patients who underwent pulmonary surgery [3-5]. The positive results of pleural lavage cytology detected before closure not only could present higher prognostic value than pleural lavage cytology detected before thoracotomy, but also guide adjuvant chemotherapy for lung cancer patients after surgery.

Currently, no proper regimen of pleural lavage is available [6]. The most common liquid used for irrigating the thoracic cavity was 0.9% sodium chloride injection varying from 20 to 2000 ml [2, 7-9] nearly to the temperature of human body at 38~40 ℃ [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 PLC. In our study, we chose 500 ml pleural fluid or 3000 ml pleural fluid to wash thoracic cavity before chest closure based on clinical practice and literatures[7, 8].

To find a reliable procedure of pleural lavage, 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). And we will randomly divide them into 2 groups: Group A (500ml pleural lavage fluid) and 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 double-blind, single-center, randomized controlled trial (Fig. 1). This study protocol is conceived based on the Recommendation for Interventional Trials (SPIRIT). The SPIRIT figure (Fig. 2) summaries 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

Participants

Patients eligible for this trial must comply with all the inclusion criteria and do not meet any exclusion criteria before enrollment. To achieve adequate participant 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) ASA risk class of I-II; (iv) essential materials were complete such as clinical staging of lung cancer and medication; (v) confirmed with 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 received preoperative radiotherapy or neoadjuvant chemotherapy; (viii) intraoperative accidents happened to the patients, such as hemorrhage (>500ml), conversion to open surgery, and cardiac arrest; (ix) patients with severe postoperative bleeding or persistent air leakage, which require reoperations.

Randomization and blinding

We will perform the randomization to assign candidates into 2 groups based on computer-generated random numbers shortly 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 once a patient is deemed eligible. When receiving a patient who meets the inclusion criteria, the principal doctors will assign the newly participant to a group and inform the treatment group. The research assistant should receive the notification timely and assign patients to their study group strictly as required. This study will be double blind. The participants and investigators will be both blinded to the allocation of the participants, while the project manager will be unblinded. If an unexpected emergency circumstance happens, the allocation will be disclosed to the investigators. The participant will withdraw 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 could be available to estimate sample size. With respect to our experience, a total of 400 participants will be recruited in this study with 200 in each group. This should provide a power of 99.96% assuming this recruitment is met with no loss to follow up, a type I error rate of 5%, an estimated risk of 4% for outcome in the control group[17], and an anticipated effect of 0.5 based on clinical experience.

Intervention

A total of 400 NSCLC patients aged 18-75 years, who will undergo VATS lobectomy and MLND, will be recruited in our study according to 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 ℃. 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 ℃ to flush the thoracic cavity in this group. Other procedures are the same with that of group A.

Study dropouts

All the 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 the researchers have the right to terminate the enrollment of any patients at any time with reasonable circumstance. All the changes and reasons will be recorded immediately in the case reported 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-treatment (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 and only identical data will be published. 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 the 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 safe issues will be strictly monitored by the Institutional Ethic Committee of West China Hospital, Sichuan University.

Statistics analysis

The main content of the analysis is effectiveness analysis and safety analysis. The analysis of all continuous variable will be presented as mean, standard deviation (SD), median, quartile spacing, maximum and minimum values. The analysis of all dichotomous variable will be presented as rate,

constituent ratio and hazard ratio. We will use the t-test and χ^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 characteristic 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 test

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

Primary and secondary outcomes

All the outcomes will be defined according to two previous studies[18, 19].

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 amendments in the protocol during the trial which may affect the process of study, the benefit and risk of participants will be required a formal amendments agreement of Ethic Committee.

Discussion

It is essential to flush the thoracic cavity before closing the chest wall, 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℃. 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, patients of different somatotype may need different volumes of pleural lavage.

In conclusion, this study is the first randomized controlled trial aiming at comparison of 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 thoracic cavity in lung cancer operation.

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; CRF: case reported form; ITT: intention-to-treatment; SD: standard deviations.

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/listbycreater.aspx. 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 requests for acquiring the data will be sent to the corresponding author and be considered carefully.

Competing interests

The authors declare that they have no competing interests.

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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.

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Not applicable.

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Figures

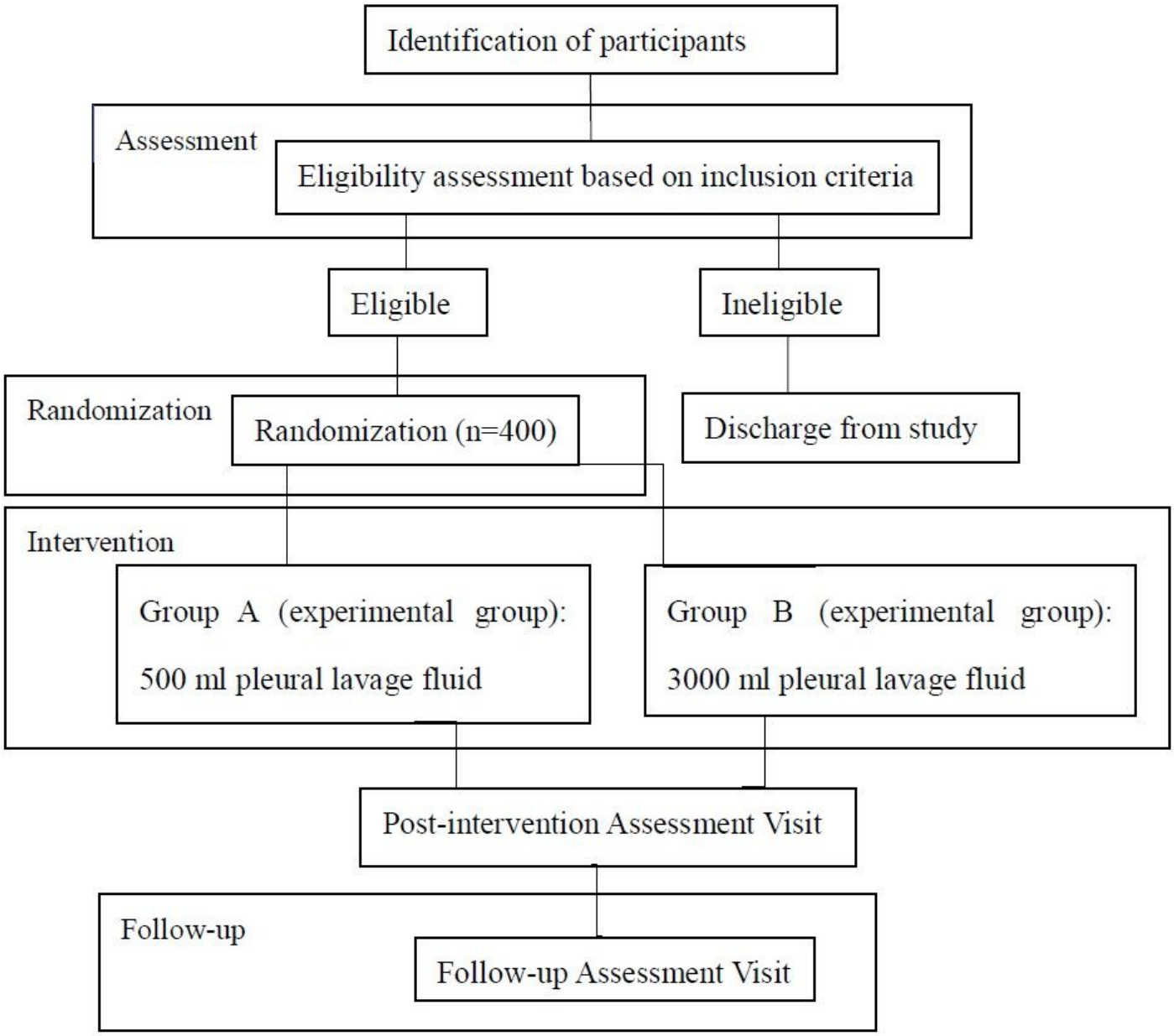

Figure 1

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

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

Figure 2

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

Supplementary Files

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