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Lidocaine Infusion Decreases Postoperative Lung Cancer Reoccurance and Metatasis Risk: a Multicenter Randomized Controlled Study

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Clinical research protocol

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Perioperative lidocaine infusion for decreasing postoperative reoccurrence and metastasis risk in patients with Non-Small Cell Lung Cancer: a multicenter randomized controlled study

Research background

Lung cancer is the leading cause of cancer-related deaths worldwide, with 2.21 million patients dying from lung cancer in 2020, ranking second. A study in the UK reported a 10-year survival rate of 7.6% for males and 11.3% for females with lung cancer. The Chinese Center for Disease Control and Prevention reports that the five-year survival rate for lung cancer patients in China is 20% -30%. [1] Therefore, lung cancer remains a major health issue of global concern. Surgery is one of the main treatment methods for lung cancer. Although the perioperative period is short, it may have a disproportionately significant impact on the long-term trajectory of cancer. The physiological changes caused by surgery can alter this dynamic. The wound healing response caused by surgery leads to stress, inflammation, and immune suppression, promoting metastatic conditions. Inflammatory response can promote tumor circulation, thereby increasing the chances of recurrence and metastasis. Therefore, using therapeutic agents to regulate surgical response may avoid irreversible pro metastatic processes [3]. From this

perspective, lidocaine, as a mature and inexpensive drug, may provide a feasible solution.

Lidocaine is a globally available and inexpensive medication traditionally used for anesthesia of specific body parts. Intravenous infusion of lidocaine has been proven to be an economical and convenient method that can alleviate widespread inflammatory reactions during surgery [4], and animal experiments have shown that it can also inhibit the proliferation of lung cancer [5]. In vitro studies have shown that lidocaine can inhibit cancer cell proliferation and induce cancer cell death by reducing the epidermal growth factor receptor (EGFR) response and inhibiting the activation of matrix metalloproteinase-9, which is crucial for extracellular matrix degradation in malignant cells. Lidocaine can also regulate gene expression by altering the DNA of malignant cells, thereby reducing cancer growth and metastasis [6]. In addition, studies have shown that the sympathetic nervous system has an impact on the survival microenvironment of lung cancer, which can weaken the effectiveness of postoperative chemotherapy [7]. However, lidocaine can inhibit the excitation of the sympathetic nervous system, indicating the potential value of lidocaine.

Surgical stress response leads to the release of pro-inflammatory cytokines and inhibition of immune cell function [3]. Lidocaine has been shown to alleviate inflammation in an in vivo model by reducing cytokine

release and subsequent metastasis. The clinical therapeutic dose of lidocaine can also enhance the function of NK cells [8]. There are a large number of NK cells in the lungs of lung cancer patients, which play a key role in eliminating lung cancer and preventing metastasis formation [9]. In addition, lidocaine can block Src activation, thereby reducing the invasiveness of cancer cells [10].

The consequences of cancer recurrence and metastasis highlight the necessity of intervention in terms of increasing incidence rate, mortality and financial burden [11]. A Cochrane review emphasized the necessity of well-designed randomized controlled trials to reduce cancer recurrence.

Cancer staging is indeed associated with recurrence, especially when cancer cells migrate from the primary site. Stage I ground glass nodules, even if the pathological type is invasive adenocarcinoma and larger than 3cm, still have a 5-year 100% survival rate. Stage III and IV lung cancer, due to the invasive spread of cancer, surgery is usually not for cure, but mainly for symptom relief, and lidocaine is unlikely to provide benefits. Stage I solid nodular lung cancer involves vascular and pleural invasion, while stage II involves vascular and lymphatic system invasion, requiring extensive surgical resection [12]. These patients may benefit the most from lidocaine and will be the main target of this study. We will recruit patients with all cancer stages to understand potential differences in

response to lidocaine treatment.

Lidocaine has an inhibitory effect on tumor cells, which is mostly based on animal studies, and toxic doses are often used in animal studies. There are few high-quality studies in clinical practice. This study aims to explore whether lidocaine infusion at a safe dose can bring the value of prolonging survival for lung cancer patients after surgery, which is of great significance.

Research objective

1. Main objective: To evaluate the effect of perioperative lidocaine infusion on postoperative reoccurrence and metastasis in patients with non-small cell lung cancer.

2. Secondary objective: To explore the value of perioperative lidocaine infusion in prolonging the survival of patients with non-small cell lung cancer

Research design types, principles, and experimental procedures

1. Research Design

This is a 1:1 parallel double-blind (patient and data collector blinded, prepared by anesthesia nurses and administered by anesthesiologists) randomized controlled trial comparing the efficacy of intravenous infusion of lidocaine versus placebo/saline during minimally invasive (thoracoscopic or robotic) surgery in lung cancer patients.

1.1 Sample size calculation

For the time to event outcome, use the median reoccurrence time of similar populations in the literature to estimate the hazard ratio (HR). The median reoccurrence time described in the literature is 18 months. If we do not want to miss the 6-month improvement in event time in the treatment group, then HR estimates the risk ratio of reoccurrence time at 18 months in the control group and 24 months in the treatment group.

Risk ratio=(risk rate of treatment group)/(risk rate of control group)

Risk rate=1/(median recurrence time)

Therefore, the risk ratio can be estimated as: Risk ratio=(1/24)/(1/18)=18/24=0.75

The estimated risk ratio is 0.75, which represents a 25% reduction in risk effect for the treatment group compared to the control group. The sample size is based on the parallel design of the superiority program, survival endpoint, 90% efficacy, 0.05 significance level, bilateral significance level, HR 0.75. Using PASS11 software, it is estimated that each group requires 635 cases, and an increase of 10% would result in 700 cases per group. Therefore, the planned total sample size is 1400 patients with lung cancer.

2、 Case selection

In this experiment, qualified participants will be recruited from each center, as the annual number of lung surgeries in each center reaches around 8000 cases.

Inclusion Criteria

1. Age range: 18-80 years old.

2. Electively undergo minimally invasive (thoracoscopic or robotic) surgery for clinical stage I and II lung cancer.

3. Willing and capable of providing consent.

Exclusion criteria

1. Palliative surgery without intention of cure.

2. ASA IV

3. Patients who are known or suspected to be allergic to lidocaine.

4. Patients who are currently pregnant or breastfeeding.

5. According to the Summary of Lidocaine Product Characteristics, patients who may experience adverse reactions due to accumulation of lidocaine intravenous infusion.

6. The current liver function is abnormal, with ALT or AST exceeding the laboratory reference range by 2 times.

7. Currently severe renal insufficiency (blood creatinine ≥ 451umol/L or glomerular filtration rate (calculated by MDRD formula)<30ml/min).

8. Epilepsy.

9. Cardiac conduction abnormalities, including second or third degree heart block without a pacemaker, left bundle branch block, sick sinus syndrome, and pre excitation syndrome (confirmed by

electrocardiogram based on medical history), as well as patients in a low cardiac output state with currently reduced left ventricular ejection fraction.

10. Concurrent use with continuous infusion of other local anesthetics (such as epidural).

11. Patients who use drugs that may cause exclusion reasons, including Class I and III antiarrhythmic drugs (such as metoprolol, amiodarone), cimetidine, and antiviral drugs. Qualifications will be determined by local clinical doctors and verified by clinical trial doctors.

12. Patients weighing less than 40kg

Termination criteria for the study (subjects experiencing conditions that make it inappropriate to continue the study, including worsening of the condition, serious adverse events, poor compliance, etc.)

Research methods

1. Intervention measures

Research drug (IMP)

2% lidocaine hydrochloride injection for infusion, prepared as a 50mL syringe and continuously pumped for administration.

Placebo

0.9% sodium chloride solution for infusion, prepared into a 50mL syringe and continuously pumped for administration.

2. Dose plan

Lidocaine is administered intravenously at an ideal body weight (IBW) of 1.5 mg/kg starting from anesthesia induction, for 10-20 minutes, and then continuously infused at 1-1.5 mg/kg/h until 12 hours after returning to the ward, with a maximum rate of 120 mg/h. Use ideal weight instead of actual weight to prevent toxicity in very overweight patients. In patients with a weight lower than the ideal weight, the actual weight should be used to calculate the dose. The patient needs to be admitted to a highly dependent ward or equivalent facility for continuous cardiac monitoring during lidocaine infusion. Patients in the placebo group had the same infusion rate as those in the treatment group.

Example

IBW (Kg) initial dose (1.5 mg/kg) infusion rate (1.5 mg/kg/h)

40 3ml（10-20min） 1-3ml/h

50 3.75ml（10-20min） 1.25-3.75 ml/h

60 4.5ml（10-20min） 1.5-4.5 ml/h

70 5.25ml（10-20min） 1.75-5.25 ml/h

80 and above 6 ml (20 minutes) 2-6 ml/h

Table 1: Dose Guidelines Based on IBW (Broca Index): Male: Height (cm) -100; Female: Height (cm) -105. Attention: For patients with a weight lower than the ideal weight, the actual weight should be used to calculate the dosage.

Therefore, for the placebo/saline group, if the IBW is 70kg, the patient will receive an initial infusion of 0.9% sodium chloride at 5.25ml over 10-20 minutes, followed by an infusion at 1.75-5.25ml/h.

3. Dose adjustment

Dose changes are not allowed in this study. If the supervising medical professional suspects acute systemic local anesthetic toxicity symptoms, the infusion must be stopped and not continued. In this case, supportive treatment and lipid rescue will be provided. The discussion on the possible adverse events caused by lidocaine toxicity is as follows. If the infusion is interrupted due to issues such as infusion pump failure, catheter failure, or accidental disconnection, the infusion can be restarted at the original rate and the event recorded.

4. Additional care and procedures

To reduce the possibility of confounding factors, general anesthesia should be maintained under a combination of intravenous and inhalation anesthesia. Postoperative care follows the unit's standard to enhance postoperative rehabilitation protocol. The pain control program will be consistent with the unit's standard procedure. However, during IMP infusion, simultaneous continuous infusion of other local anesthetic drugs (such as epidural or wound catheters) cannot be performed.

5. Postoperative analgesia management

To reduce the possibility of confounding factors, general

anesthesia should be maintained under a combination of intravenous and inhalation anesthesia. Postoperative care follows the unit's standard to enhance postoperative rehabilitation protocol. The pain control program will be consistent with the unit's standard procedure. However, during IMP infusion, simultaneous continuous infusion of other local anesthetic drugs (such as epidural or wound catheters) cannot be performed. After the surgery, all patients were uniformly treated with sufentanil 2ug/kg diluted to 100ml and pumped with 2ml/h for intravenous analgesia

6. Randomization

After obtaining consent, participants will be randomly assigned (1:1) to receive intravenous lidocaine or placebo using a minimization algorithm. The minimum criteria include age (<45 years, 45-65 years, 65-80 years), gender, trial center.

6. Observation project

Main outcome measure

Assess the reoccurrence time of lung cancer patients within 36 months from the date of surgery.

Secondary outcome measure

1. Disease free survival (DFS)
2. Objective remission rate of patients' diseases
3. Health related Quality of Life Questionnaire EQ-5D-5L
4. Cancer specific quality of life measured using the Functional

Assessment of Cancer Therapy (FACT-L) questionnaire.

Other observation indicators

1. The total length of hospital stay, including readmission, is 36 months.

2. Changes in pro-inflammatory cytokine levels (IL-6, TNG - α) from baseline on the third day after treatment and upon discharge.

On the 1st and 3rd day after treatment and at discharge, changes in reticular fiber dissolution markers (matrix metalloproteinases MMP-9, MMP-2) from baseline were observed.

3. Perioperative nausea, vomiting, delirium, pain control, and incidence of cardiovascular accidents 6 and 12 months after treatment completion.

7、 Efficacy evaluation criteria

Follow up chest CT scans at 6, 12, 18, 24, and 36 months after surgery were conducted to evaluate whether lung cancer patients had cancer reoccurrence and the time of reoccurrence within 36 months from the date of surgery. And evaluate the cancer specific quality of life using the lung cancer treatment function assessment questionnaire for patients. The shortened recurrence time and improved specific quality of life indicate therapeutic efficacy.

8. Observation of adverse events

Lidocaine can inhibit cancer cell proliferation at doses that have minimal impact on normal cells. The infusion dose and duration selected

in this study are within the recommended range of the latest international consensus statement on the safe use of intravenous lidocaine infusion. Lidocaine should be administered intravenously at an initial dose of no more than 1.5mg/kg of ideal body weight, with an initial infusion time of at least 10 minutes. During the maintenance period, the infusion rate of 1.5mg/kg/h should not exceed 24 hours, and the maximum infusion rate should not exceed 120mg/h. The above medication should be calculated based on ideal body weight. If the actual body weight is lower than the ideal body weight, it should be calculated based on the actual body weight. When toxicity occurs, according to the guidelines of the British and Irish Society of Anesthesiologists, lidocaine infusion can be temporarily suspended and treatment can be carried out using readily available 20% intravenous lipids in the operating room and intensive care unit.

9. Quality Control and Quality Assurance in Research

Strictly follow relevant SOPs during the clinical research process, conduct unified training before the implementation of the study, and monitor IMP/placebo infusion as part of the standard care for patients. Due to the infusion of IMP/placebo from the start of surgery until 12 hours after returning to the ward, all participants were hospitalized during the infusion period. The infusion rate table will be provided to the research team to minimize user errors during administration. The data

will be collected at the hospital during routine hospital appointments and postoperative recovery periods. We will strive to collect outcome data from all randomly assigned participants, regardless of whether they received IV lidocaine/placebo. Communicate with the surgeon and strictly follow the diagnosis and treatment plan according to the protocol. Strictly develop a follow-up plan form. The data is recorded using Redcap software.

10. Statistics process

Statistics will be recorded and managed using Redcap data, and analyzed using SPSS21 software. The analysis will be conducted according to the intention to treat principle. The statistical analysis plan for this study includes summarizing baseline data, conducting primary outcome analysis using time to event analysis, and conducting additional survival analysis. Baseline variables such as age group, gender, comorbidities, ASA classification, cancer stage, cancer TNM classification, pathological type, neoadjuvant targeted therapy, radiotherapy, and chemotherapy will be summarized using appropriate descriptive statistical methods, using mean and standard deviation or median and quartile range (depending on the applicability of continuous variables). The categorical variables will be summarized using the frequency and percentage of participants in each category. Researchers will use EDC to fill out CRF. The data will be stored on a secure server.

The source documents of CRF report information will be archived in the center and available for monitoring, IRB/IEC review, and regulatory inspection as needed. According to applicable regulations, researchers must retain all research records/documents.

The main outcome is defined as the time of cancer reoccurrence within 36 months after surgery in patients with stage I and II lung cancer. Multiple Cox regression models will be used to analyze the main results and adjust the truncated data. The truncated data includes participants who have not experienced recurrence or death within 36 months, as well as those who have been lost to follow-up or withdrawn from the study.

The risk ratio will be estimated by comparing the risk rates ofthe placebo group and the lidocaine group, taking into account the truncated data of the participants and adjusting for covariates. In addition, Kaplan Meier plots will be used to visualize and compare survival distributions, while Log rank tests will evaluate the differences between the two groups.

We will use the study drug allocation (x=0 placebo, x=1 lidocaine) as the independent variable, the time of cancer recurrence or death as the dependent variable, and age group (<45, 45-65, 65-80), gender, number of comorbidities, ASA classification, cancer staging, neoadjuvant radiotherapy, and chemotherapy as adjusted covariates.

Clean the experimental data and construct an analysis dataset suitable for statistical analysis. Data quality control is achieved through the accuracy

(numerical range), reasonableness (whether the category is reasonable), and handling of missing data (by checking and supplementing missing data). Then conduct statistical analysis. Missing data will be compensated through multiple imputation and pattern mixing methods to explore the robustness of treatment effect estimation. We will explore the reasons for missing data, such as loss to follow-up or withdrawal, and report them. We will seek clarification of missing data through routine data collection with the clinical team. Resolve data queries before analysis.

11、 Ethics in Clinical Research

Clinical research will follow relevant regulations such as the Helsinki Declaration of the World Medical Assembly. The clinical study will only be conducted after the ethics committee approves the trial protocol before the start of the research. Before each participant is enrolled in this study, the researcher is responsible for fully and comprehensively introducing the purpose, procedures, and potential risks ofthis study to the participant or their representative, and signing a written informed consent form. The participant should be informed of their right to withdraw from this study at any time, and the informed consent form should be kept as a clinical research document for future reference. During the research process, the personal privacy and data confidentiality of the subjects will be protected.

Research time

January 2026 December 2026: Project initiation, completion of data

collection for 400 patients

January 2027 December 2027: Complete data collection and mid-term analysis for 600 patients

January 2028 to October 2028: Complete data collection for 400 patients

October 2028 to December 2028: Data organization and statistical analysis. Complete the paper writing and submit the SCI paper as soon as possible.

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