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

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Informed Consent Form

(Version No.: V1.2, Version Date: Nov 29, 2025)

Dear Subject:

We would like to invite you to participate in a nationwide multi-center clinical study initiated by our hospital, titled "Perioperative Lidocaine Infusion for decreasing postoperative reoccurrence and metastasis risk in patients with Non-Small Cell Lung Cancer". Please read the following information as carefully as possible before you decide whether to participate in this study. It can help you understand the study, why it is being conducted, the procedures and duration of the study, as well as the potential benefits, risks, and inconveniences that may arise from participating in the study.

1. Research Background, Research Purpose, and Basic Research Content

Lung cancer is the leading cause of cancer-related deaths globally. According to the Chinese Center for Disease Control and Prevention, the five-year survival rate for lung cancer patients in China is 20%-30%. Surgery is one of the main treatment methods for lung cancer. Although the perioperative period is short, it can have a disproportionately significant impact on the long-term trajectory of cancer. Physiological changes caused by surgery can alter this dynamic. The wound healing response induced by surgery leads to stress, inflammation, and immunosuppression, promoting conditions for metastasis. Inflammatory

responses can promote tumor circulation, thereby increasing the chances of recurrence and metastasis. Therefore, using therapeutic agents to modulate the surgical response may avoid irreversible pro-metastatic processes. In this regard, lidocaine, as a mature and inexpensive drug, may provide a viable solution.

Lidocaine is a globally available and inexpensive drug traditionally used for anesthetizing specific body parts. Intravenous infusion of lidocaine has been proven to be an affordable and convenient method to alleviate extensive inflammatory responses during surgery, and animal experimental studies have shown that it can also inhibit the proliferation of lung cancer. In vitro studies have demonstrated that lidocaine can inhibit cancer cell proliferation and induce cancer cell death by reducing epidermal growth factor receptor (EGFR) response and inhibiting the activation of matrix metalloproteinase-9, an enzyme crucial for the degradation of the extracellular matrix by malignant cells. Lidocaine can also regulate gene expression by altering the DNA of malignant cells, thereby reducing cancer growth and metastasis. Additionally, studies have confirmed that sympathetic nerves have an impact on the survival microenvironment of lung cancer, which can weaken the efficacy of postoperative chemotherapy. However, lidocaine can inhibit the excitation of sympathetic nerves, indicating its potential value.

Surgical stress response leads to the release of pro-inflammatory

cytokines and inhibits immune cell function. Lidocaine has been shown to reduce inflammation in in vivo models by reducing cytokine release and subsequent migration. Clinical therapeutic doses of lidocaine can also enhance the function of NK cells, which are abundant in the lungs of lung cancer patients and play a crucial role in eliminating lung cancer and preventing metastasis formation. Furthermore, lidocaine can block Src activation, thereby reducing the invasiveness of cancer cells.

Lidocaine has an inhibitory effect on tumor cells, but most studies are based on animal research, often using toxic doses. There are few high-quality clinical studies. This study aims to investigate whether lidocaine infusion at clinically safe doses can provide value in prolonging survival for lung cancer patients after surgery, which is of great significance.

Overview of research content: Subjects who met the inclusion and exclusion criteria were randomly assigned to either the lidocaine infusion group or the placebo saline infusion group. Postoperative follow-up observations were conducted to assess indicators such as cancer recurrence time and disease-free survival

2. Specific procedures, processes, and methods

This study is expected to enroll 1400 subjects, with 500 subjects expected to be enrolled at our center. Suitable subjects will be selected based on the inclusion and exclusion criteria, and after signing the

informed consent form for the clinical trial, they will be randomly divided into two groups at a ratio of 1:1. The efficacy of intravenous (IV) lidocaine administration (an initial dose of 1.5 mg/kg infused for at least 10 minutes, followed by a maintenance dose of 1-1.5 mg/kg/h until return to the ward) compared to placebo (normal saline) in patients undergoing minimally invasive lung cancer surgery will be compared. Regular follow-ups will be conducted from the date of surgery until 36 months, observing the time of cancer recurrence or death, as well as the objective response rate or disease-free survival of the patients.

1. Inclusion and exclusion criteria

Inclusion Criteria

1). Age range: 18-80 years old,

2). Electively undergo minimally invasive (laparoscopic or robotic) surgery for the treatment of lung cancer with clinical pathological stages I and II.

3). Willing and capable of providing consent.

Exclusion criteria

1). Palliative surgery without the intention of cure.

2). ASAIV.

3). Patients with known or suspected allergies to lidocaine.

4). Patients who are currently pregnant or breastfeeding.

5).Patients who may experience adverse reactions due to accumulation of

lidocaine during intravenous infusion, according to the Summary of Product Characteristics (SmPC) for lidocaine.

6).Currently, there is abnormal liver function, with ALT or AST levels exceeding the laboratory reference range by a factor of 2.

7).Currently, there is severe renal insufficiency (serum creatinine ≥451umol/L or glomerular filtration rate (calculated using the MDRD formula) <30ml/min).

8). Epilepsy.

9). Patients with cardiac conduction abnormalities, including second-degree or third-degree heart block without a pacemaker, left bundle branch block, sick sinus syndrome, and pre-excitation syndrome (confirmed by medical history and electrocardiogram), as well as those with low cardiac output due to reduced left ventricular ejection fraction.

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

11). Patients who are using medications that may cause exclusion reasons, including Class I and Class III antiarrhythmic drugs (such as mexiletine and amiodarone), cimetidine, and antiviral drugs. Eligibility will be determined by local clinicians and verified by clinical trial doctors.

12). Patients with body weight less than 40kg

2. Observation indicators

2.1 Main outcome measure

Evaluate the recurrence of cancer in patients with lung cancer within 36 months from the date of surgery

2.2 Secondary outcome measure

1) Disease-free survival (DFS)

2) Objective response rate of patients

3) Health-related Quality of Life Questionnaire EQ-5D-5L

4) Cancer-specific quality of life measured using the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire.

2.3 Other observation indicators

1) Total hospitalization duration, including readmissions, up to 36 months.

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

3). Changes in reticular fiber lysis markers (matrix metalloproteinases MMP-9, MMP-2) from baseline on the 3rd day after the end of treatment and at discharge.

4). Perioperative nausea, vomiting, delirium, pain control, and the occurrence of cardiovascular accidents 6 and 12 months after the end of treatment.

3. Basic Information of Researchers and Qualifications of Research Institutions

The Anesthesiology Department of the First Affiliated Hospital of

Ningbo University has evolved into a clinical department integrating clinical anesthesia, emergency resuscitation, pain treatment, teaching, and scientific research. Currently, there are 140 medical staff and 67 faculty members in the discipline, including 13 chief physicians and 30 associate chief physicians. The department has one master's supervisor from Zhejiang University and 10 master's supervisors from Ningbo University. In 2022, we recruited 5 master's degree candidates with equivalent educational background from Ningbo University (previously graduated from our department's standardized training program and doctors from other hospitals) and 6 master's degree candidates from Ningbo University. We have formed a professional talent team with a reasonable structure and echelon, full of vitality and potential.

The department head, Huang Changshun, is a chief physician, a master's supervisor at Zhejiang University School of Medicine, and a master's supervisor at Ningbo University School of Medicine. He is also an adjunct professor, the head of the Special Disease Center for Regional Anesthesia in Eastern Zhejiang, the head of the anesthesia specialty at the National Clinical Trial (GCP) Base, the head of the key supported discipline (anesthesiology) in Ningbo, one of the first outstanding young and middle-aged health technology talents in Ningbo, a leading and top-notch talent in Ningbo, and an excellent academic leader in medical and health care in Ningbo. He holds positions in multiple academic

organizations at or above the municipal level, serving as a member of the Critical Care Medicine Group of the Anesthesiology Branch of the Chinese Medical Association, a member of the Shock and Sepsis Professional Committee of the Chinese Research Hospital Association, a national member of the Blood Management Branch of the Chinese Cardiovascular and Thoracic Anesthesiology Society, a member of the Anesthesia Pharmacology Professional Committee of the Chinese Pharmacological Society, a vice chairman of the Anesthesiology Professional Committee of the Zhejiang Neuroscience Society, a standing committee member of the Anesthesiology Branch of the Zhejiang Medical Doctor Association, a member of the Anesthesiology Branch of the Zhejiang Medical Association, and a member of the Anesthesia Quality Control Center of Zhejiang Province. He is also the executive deputy director of the Ningbo Clinical Anesthesia Quality Control Center, an executive director of the Ningbo Integrated Traditional Chinese and Western Medicine Society, the chairman of the Anesthesiology Professional Committee, and the chairman of the Anesthesiology Branch of the Ningbo Medical Association.

Main research directions: Research on perioperative blood conservation and major organ function protection. As the first contributor, I have won one third prize of Zhejiang Provincial Science and Technology Progress Award, one second prize and one third prize of

Zhejiang Provincial Medical and Health Science and Technology Innovation Award, one second prize and two third prizes of Ningbo Municipal Science and Technology Progress Award. I have edited two monographs related to blood conservation and co-edited five others. As the first (or corresponding) author, I have published nine SCI papers and more than 20 papers in first-tier domestic core journals such as Zhonghua.

4. What do you need to do if you participate in the study?

Please provide the truthful information regarding your medical history and current physical condition. Timely inform the researcher of any discomfort you experience during this study, so that the researcher can make judgments and provide appropriate medical treatment or advice to ensure your safety. Do not take restricted medications, foods, etc. Inform the researcher whether you have participated in other studies recently or are currently participating in other studies. Inform the researcher if you are in a special period such as pregnancy or lactation. Any other matters that may involve or affect this study should be promptly informed to the researcher.

5. Possible benefits of participating in this study

By participating in this study, your condition may improve, or it may not improve or you may not directly benefit from it. This is because the study is a randomized, double-blind study, and you may be randomly

assigned to the control group, which is the saline group. However, the information obtained from this study will provide assistance to other patients who are troubled by the same or similar diseases in the future, and will contribute to the updating of human medical knowledge. Thank you for your contribution.

6. Possible adverse reactions and risks associated with participation in the study, as well as protective measures for you

Lidocaine is a clinically classic medication that can inhibit cancer cell proliferation at doses that have minimal impact on normal cells. The infusion dose and duration selected in this study fall within the recommended range outlined in a recent international consensus statement on the safe use of intravenous lidocaine infusion [13]. In the event of local anesthetic toxicity, ready-to-use 20% intravenous lipid emulsion can be administered in the operating room and intensive care unit according to the guidelines of the British and Irish Association of Anaesthetists.

Blood sample collection: Blood sample collection may cause discomfort and bruising, and in rare cases, infection may occur due to needle puncture into the skin. During blood draw, you may also feel dizzy, nauseous, or faint. If you feel unwell during or after blood sample collection, please inform the study doctor or a member of the research team.

7. Explanation of relevant expenses

Regardless of which group you are enrolled in, you will need to bear the regular costs of surgical anesthesia and the regular charges for lidocaine or saline used during the procedure. However, there will be no charges for the follow-up visits to you by the research doctors after the surgery.

8. Compensation for participating in the study

Participating in this study will not impose any additional financial burden as it involves conventional medical medication, and therefore, there will be no extra compensation

9. Compensation for research-related injuries

If you experience any discomfort or encounter any unexpected situations during the study, regardless of whether they are related to the study or not, you should promptly notify the doctor in charge of the study, who will make a judgment and provide medical treatment. If your injury is confirmed to be caused by the research trial, the sponsor will bear the reasonable costs of treatment and provide corresponding economic compensation or reimbursement in accordance with relevant laws of the People's Republic of China.

10. Possible alternative treatments and their main benefits and risks

If you do not participate in this study, anesthesia will still be administered using conventional general anesthesia drugs, without

lidocaine infusion.

Similar to the saline placebo infusion in the control group, it is safe and feasible, but the long-term benefits are currently unknown.

11. Confidentiality of your personal information

Your medical records (study medical records/CRF, laboratory test reports, etc.) will be fully preserved at the hospital where you seek treatment. The doctor will record the results of laboratory tests in your medical records. Without violating confidentiality principles and relevant regulations, researchers, monitors, auditors, ethics committees, and drug supervision and management departments will be allowed to access your medical records. Any public report on the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical information within the scope permitted by law.

Handling of biological samples and information after the study: All the examinations required of you in this study are clinical routine laboratory tests, which will be submitted for clinical routine inspection without additional processing of biological samples. Any remaining or excess samples will be destroyed within the hospital according to standard procedures. The preservation and management of research information and materials will be conducted in accordance with relevant clinical research laws and regulations.

The data and personal information of research participants involved in this study are solely for the purpose of this study and will not be provided to external parties, nor will it be used for product development, sharing, or secondary utilization.

The results of this study will not be directly fed back to the study participants. The research findings may be published in medical journals, and your identity will not be disclosed during the process. All information that can identify you will be kept confidential.

12. You can voluntarily choose to participate in the study and withdraw from it halfway

Whether or not to participate in the study is entirely up to you. You may refuse to participate in this study or withdraw from it at any time during the research process, and this will not affect your relationship with your doctor, nor will it affect your medical treatment or cause any other losses.

Out of consideration for your best interests, the doctor, researcher, or ethics committee may terminate your participation in this study at any stage during the research process.

Disclosure of new information: If new information arises after you have participated in the study that may affect your decision to participate in this study, we will promptly inform you of this important new information, and you can reconsider whether to continue participating in

this study or withdraw from it.

13. If you have any questions, who should you contact?

If any research-related injury occurs, or if you have any questions about this study, please contact the study doctor: Huang changshun; contact number:12957882779; In addition, this study has been reviewed and approved by the Medical Ethics Committee of the First Affiliated Hospital of Ningbo University. For matters related to ethics and rights, please contact the staff of the Medical Ethics Committee Office of the First Affiliated Hospital of Ningbo University at 0574-87085233.

14. What should we do now?

Whether to participate in this study is up to you (and your guardian). Before making the decision to participate, please ask your doctor as many questions as possible. Thank you for reading the above materials. If you decide to participate in this study, please inform your doctor, and he/she will arrange all matters related to the study for you. Please keep this information.

I confirm that I have read and understood the informed consent form for this study. I had the opportunity to ask questions and all my questions have been answered. I am aware that participation in the study is voluntary, and choosing not to participate or withdrawing at any time will not affect or harm my rights and interests. I voluntarily participate in this study, including accepting the treatment methods in this study, and agree

to have my medical data used for the publication of this study. I have received a signed copy of the informed consent form.

Study participant's signature: _____

Contact information: _____ Date: ____ year ____ month ____ day ____ hour ____ minute

Guardian's signature: (if required) _____; relationship with the research participant _____

Contact information _____ Date: YYYY-MM-DD HH:MM;

When neither the research participant nor their guardian has reading ability, the witness declares: I confirm that the information in the informed consent form has been informed and explained to the research participant and/or their guardian, and that the research participant and/or their guardian understands and comprehends this information and voluntarily agrees to participate in this study.

Justice Witness: (if needed):

Contact Information: Date: [year] [month] [day] [hour] [minute]

I confirm that I have explained the details of this study to the patient, including their rights as well as potential benefits and risks, and provided them with a signed copy of the informed consent form.

Researcher's signature: _____ Date: ____ year ____ month ____ day ____ hour ____ minute

Contact information: (Mobile phone)