

# Efficacy of Perioperative Continuous Intravenous Lidocaine Infusion for 72 Hours on Postoperative Pain and Recovery in Patients Undergoing Hepatectomy: Study Protocol for a Prospective Randomized Controlled Trial

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**Purpose:** Many patients develop severe and persistent pain after hepatectomy delaying postoperative rehabilitation. Studies have suggested that intravenous lidocaine infusion relieved postoperative pain and improved overall postoperative outcomes. However, its efficacy on hepatectomy is still masked, due to the postoperative metabolic change of lidocaine by the liver. We hypothesized that intravenous lidocaine infusion in the perioperative period would lead to postoperative pain reduction and improve the overall patient experience.

**Study Design and Methods:** In this prospective double-blind, randomized controlled design trial, 260 adults scheduled for hepatectomy will be allocated to the lidocaine and the placebo groups. The lidocaine group will be administered lidocaine intravenously during intraoperative period and 72 postoperative hours; the placebo group will be administered normal saline at the same volume, infusion rate, and timing. The primary outcome is the incidence of moderate-severe pain (numeric rating scale  $\geq 4$ ) during movement at 24 hours after surgery. The secondary outcomes include the incidence of moderate-severe pain at 24 hours after surgery at rest, the incidence of moderate-severe pain at 48 and 72 hours after surgery at rest and during movement, the cumulative morphine consumption at 24, 48 and 72 hours postoperatively, bowel function recovery, the incidence of postoperative nausea and vomiting, the incidence of postoperative pulmonary complications, the length of hospital stay, levels of inflammatory factors and patient satisfaction scores.

**Discussion:** This is the first prospective trial to shed light on the efficacy of intraoperative period and 72 postoperative hours intravenous lidocaine on postoperative pain and recovery after hepatectomy. The findings will provide a new strategy of perioperative pain management for hepatectomy.

**Keywords:** intravenous lidocaine, hepatectomy, postoperative pain, recovery

## Introduction

Liver cancer is the second leading cause of cancer-related death, which accounts for 8.2% of cancer worldwide.<sup>1,2</sup> Hepatic resection is widely accepted as the mainstay of curative therapy for liver cancer. Miserably, patients after hepatectomy always suffer from acute postoperative pain. Studies showed that nearly 60% of patients experience moderate or even severe pain within the first 24–72 hours postoperatively.<sup>3</sup> Postoperative pain management remains a formidable challenge

after hepatectomy. Inadequate pain management impacts on numerous aspects of patient health, resulting in the extension of hospital stay, and the reduction of postoperative quality of life.<sup>4</sup> Moreover, poorly controlled pain after upper abdominal surgery not only causes shallow breathing but inhibits effective coughing, giving rise to secretion retention and increasing the incidence of pulmonary complications.<sup>5</sup> Thus, pain management after hepatectomy is an urgent problem to be solved.

Epidural analgesia is advocated as first-line therapy for postoperative analgesia after major abdominal surgery by current guidelines.<sup>6,7</sup> However, epidural analgesia is not suitable for all patients and still has significant risks (eg, epidural hematoma).<sup>8,9</sup> This risk will increase with coagulopathy, whose peak occurs around 2–5 days after hepatectomy.<sup>10</sup> Other regional analgesia techniques (eg, transversus abdominis plane block, thoracic paravertebral block) remain far from satisfactory as well because they are hard to achieve an effective continuous analgesic block. The strategy that patient-controlled intravenous analgesia (PCIA) combined with local subcutaneous wound infiltration is still the mainstay for postoperative pain control currently. While PCIA can reduce the complications relevance to epidural puncture, its opioids consumption probably leads to adverse effects such as postoperative nausea and vomiting (PONV), intestinal paralysis, itching, et al, impacting on postoperative recovery severely.<sup>11</sup> Hence, it is urgent to find a non-opioid analgesic as alternative which can relieve postoperative pain built around the premise of a rapid recovery.

Besides local anesthesia, lidocaine is capable for general anesthesia, intrathecal anesthesia, and antiarrhythmic as well.<sup>12,13</sup> In 1961, Bartlett and Hutaserani had firstly shown the efficacy of systemic lidocaine for the relief of postoperative pain.<sup>14</sup> Recent studies have given credit for the strategy that bolus infusion of lidocaine 1~1.5 mg/kg during anesthesia induction followed by a continuous infusion of lidocaine 1.5~2 mg/kg/h until the end of surgery. This strategy is supposed to reduce the postoperative pain, opioid consumption, inflammatory response, and PONV remarkably. Not only that, but it accelerates the recovery of gastrointestinal motility and reduces the hospital length of stay.<sup>15,16</sup> Even so, studies of general anesthesia with intravenous lidocaine infusion are confined to urogenital,<sup>17,18</sup> digestive,<sup>19–21</sup> breast,<sup>22</sup> thoracic and cardiovascular surgery.<sup>23</sup> To date, there is no published clinical trial on intravenous lidocaine for hepatectomy and its efficacy is still unrevealed. It is accepted that liver takes

leading role to metabolize lidocaine and the alteration of liver function takes place after hepatectomy. This shows that monitoring the plasma concentration and the adverse effects of lidocaine are of the utmost importance. In addition, previous studies concentrated mainly on the efficacy of continuous intravenous lidocaine within the first 24 hours while the most severe postoperative pain usually occurs in the first 24–72 hours after abdominal surgery. As a short-acting local anesthetic, lidocaine has a half-life of only 100 minutes.<sup>24</sup> Whether prolonging the lidocaine infusion may offer a more satisfactory relief to patients with severe postoperative pain after hepatectomy? Is lidocaine equally safe in such surgery?

To answer the above questions, we designed a prospective double-blind, randomized controlled trial to evaluate the analgesic efficacy of intravenous lidocaine during intraoperative period and 72 postoperative hours for hepatectomy, and verify its safety in liver surgery by monitoring the plasma concentration and the adverse effects of lidocaine.

## Methods

### Study Design, Approval, and Registration

The present study is a single-center, prospective double-blind, randomized controlled trial. This protocol is in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement.<sup>25</sup> We followed the SPIRIT checklist to address the recommended items in our clinical trial protocol and documents (see Reporting Checklist in [Additional file 1](#)). And all procedures in the trial will be conducted in accordance with the World Medical Association's "Helsinki Declaration (version 19 October 2013)". Ethics approval has been received from West China Hospital, Sichuan University. Approved No. of Ethics Committee: 2019–093. The trial has been registered at [clinicaltrials.gov](http://clinicaltrials.gov) on 16 February 2020 (NCT04295330) and illustrated in [Figures 1](#) and [2](#). The first participant was recruited on 27 February 2020, and the anticipated completion date will be May 2022.

### Study Aim

The aim of our study is to evaluate the efficacy of intravenous lidocaine during intraoperative period and 72 postoperative hours on postoperative pain and recovery in patients undergoing hepatectomy.

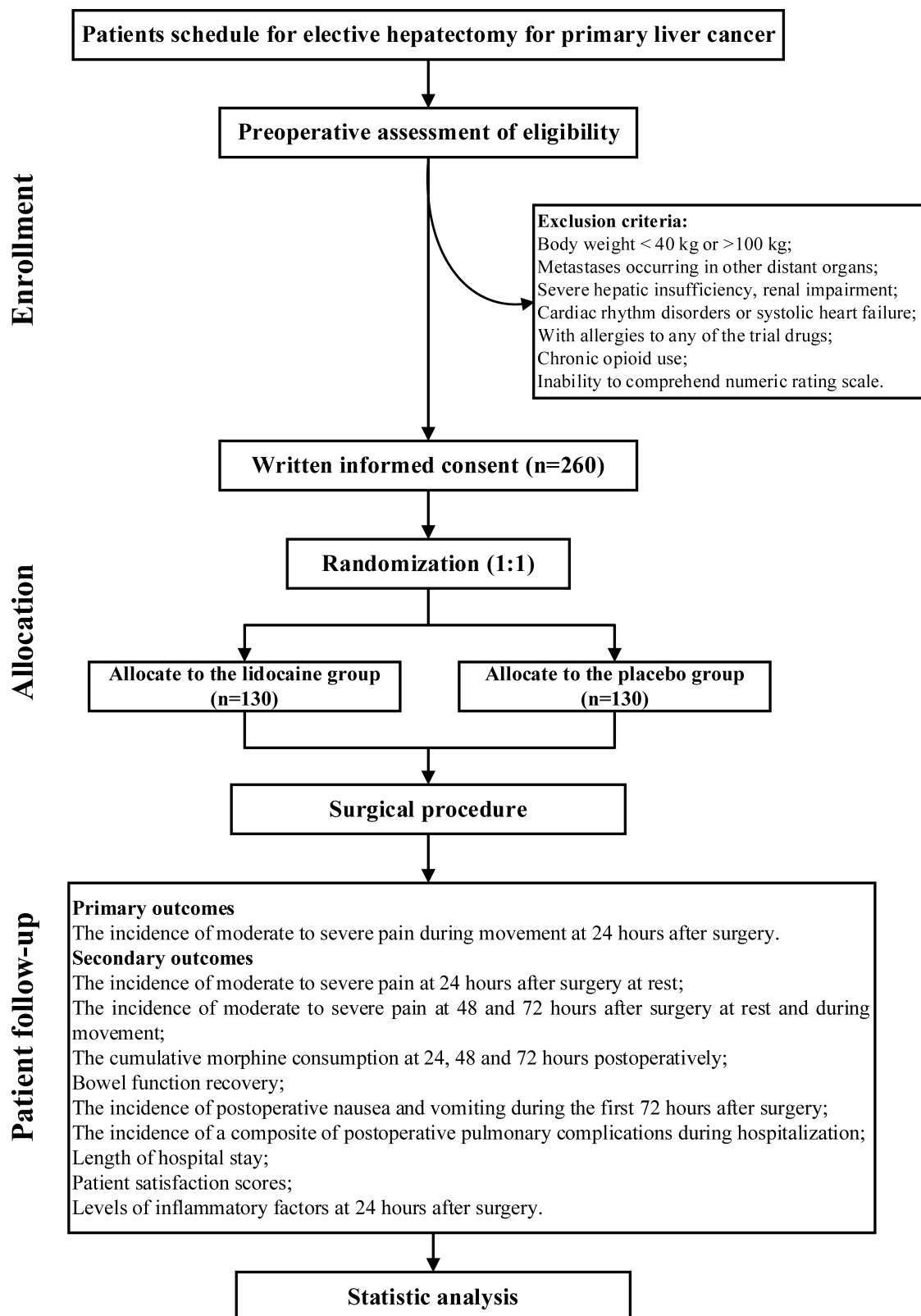


Figure 1 Flow chart of the present study.

| STUDY PERIOD                                      |                     |                 |                |                                   |                                   |                                   |                             |                |
|---|---------------------|-----------------|----------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------|----------------|
|   | Enrollment          | Allocation      |                |                                   | Post-Allocation                   |                                   |                             |                |
| TIMEPOINT   | -t <sub>1</sub>     | 0               | t <sub>1</sub> | t <sub>2</sub>                    | t <sub>3</sub>                    | t <sub>4</sub>                    | t <sub>5</sub>              | t <sub>6</sub> |
|   | Preanesthetic visit | Operating award | PACU           | 1 <sup>st</sup> postoperative day | 2 <sup>nd</sup> postoperative day | 3 <sup>rd</sup> postoperative day | discharge from the hospital |                |
| <b>ENROLMENT:</b>                                 |                     |                 |                |                                   |                                   |                                   |                             |                |
| Eligibility screen                                | X                   |                 |                |                                   |                                   |                                   |                             |                |
| Informed consent                                  | X                   |                 |                |                                   |                                   |                                   |                             |                |
| Exclusion criteria                                | X                   |                 |                |                                   |                                   |                                   |                             |                |
| Allocation  |                     | X               |                |                                   |                                   |                                   |                             |                |
| <b>INTERVENTIONS:</b>                             |                     |                 |                |                                   |                                   |                                   |                             |                |
| Lidocaine or placebo                              |                     |                 | X              |                                   |                                   |                                   |                             |                |
| Bolus 1.5 mg·kg <sup>-1</sup> ·h <sup>-1</sup>    |                     |                 | X              |                                   |                                   |                                   |                             |                |
| Infusion 1.5 mg·kg <sup>-1</sup> ·h <sup>-1</sup> |                     |                 | X              |                                   |                                   |                                   |                             |                |
| PCIA(Lidocaine 30mg/kg)                           |                     |                 |                | ←—————→                           |                                   |                                   |                             |                |
| <b>ASSESSMENTS:</b>                               |                     |                 |                |                                   |                                   |                                   |                             |                |
| Moderate to severe pain                           |                     |                 |                |                                   | X                                 | X                                 | X                           |                |
| Cumulative morphine consumption                   |                     |                 |                |                                   | X                                 | X                                 | X                           |                |
| Bowel function recovery                           |                     |                 |                |                                   | X                                 | X                                 | X                           | X              |
| PONV  |                     |                 |                | X                                 | X                                 | X                                 | X                           |                |
| Pulmonary complications                           |                     |                 |                | X                                 | X                                 | X                                 | X                           | X              |
| Length of hospital stay                           |                     |                 |                |                                   |                                   |                                   |                             | X              |
| Satisfaction scores                               |                     |                 |                |                                   |                                   |                                   | X                           |                |
| Inflammatory factors                              |                     |                 |                |                                   | X                                 |                                   |                             |                |

**Figure 2** SPIRIT figure for the schedule of enrollment, interventions and assessments. **Abbreviations:** PCIA, patient controlled intravenous analgesia; PACU, post-anesthesia care unit; PONV, postoperative nausea and vomiting.

## Participants

All patients scheduled for elective hepatectomy for primary liver cancer at the West China Hospital (Sichuan, China) will be screened.

## Informed Consent

All participants in the study will sign informed consent documents. Moreover, all participants will be given sufficient time to decide whether to participate in this study. Patients who participate in the study will have the right to obtain all relevant information, and they will be allowed to withdraw their consent or discontinue participation at any time during the study.

## Inclusion Criteria

Inclusion criteria will be as follows: patients scheduled for elective hepatectomy for primary liver cancer, aged 18 to 80 years, American Society of Anesthesiologists (ASA) physical status I–III.

## Exclusion Criteria

Participants meeting one or more of the following criteria will be excluded: body weight <40 kg or >100 kg; metastases occurring in other distant organs; severe hepatic insufficiency (aspartate aminotransferase or alanine transaminase or bilirubin >2.5 times the upper limit of normal), renal impairment (creatinine clearance <60 mL/min); cardiac rhythm disorders or systolic heart failure (second- and third-degree heart block, ejection fraction <50%); with

allergies to any of the trial drugs; chronic opioid use; inability to comprehend numeric rating scale.

## Randomization, Allocation and Concealment

Once informed consent has been received and patients will be randomized to the lidocaine and placebo groups at a 1:1 ratio. Randomization will be performed with a random number list generated by a computer. Opaque sealed envelopes containing the participant’s order on the outside and the participant’s group on the inside will be used to ensure that the group allocation is not disclosed. Before surgery, the opaque sealed envelope with the patient’s distribution information will be opened by the research investigator. There was no difference in color between the lidocaine and normal saline. A 50-mL syringe labeled “research solution” consisting of lidocaine or normal saline and a PCIA device will be prepared by a research investigator according to the group allocation. The participants, the anesthesiologist, data collectors, the physicians performing the follow-up, and data analysts will be blinded to the group allocation. Blinding will be maintained until completion of the final analyses.

## Interventions

Patients who meet the enrollment criteria will be randomized 1:1 to either the lidocaine or the placebo group. Three investigators (Y Xu, M Ye, X Xiao) will explain the

treatment intervention in detail and supervise the compliance of the intervention throughout the entire procedure.

## The Lidocaine Group

In the lidocaine group, at the end of the induction of general anesthesia, a bolus injection of lidocaine 1.5 mg/kg, calculated using the patient's ideal body weight and given as an infusion over 10 minutes, followed by a continuous infusion of lidocaine at 1.5 mg/kg per hour for the whole surgical procedure and will be discontinued at the end of surgery. Postoperative pain management during the first 72 postoperative hours will involve the use of a PCIA device, which will contain lidocaine 30mg/kg, sufentanil 2 µg/kg, granisetron 12 mg diluted to 200 mL in 0.9% normal saline.

## The Placebo Group

In the placebo group, the same volume of normal saline will be administered during anesthesia. The postoperative PCIA device will contain sufentanil 2 µg/kg, granisetron 12 mg diluted to 200 mL in 0.9% normal saline solution with a total volume of 200 mL.

All the background infusion of PCIA will be set at 2 mL/h, the bolus volume of each PCIA press is 2 mL and the lockout interval is 15 minutes.

## Perioperative Management

### Preoperative Visit and Evaluation

The day before the operation, all patients will receive an explanation of how to use the PCIA device and rate pain intensity on a pain numeric rating scale (NRS), identifying 0 as "no pain" and 10 as "worst imaginable pain".

### Induction and Maintenance of Anesthesia

All anesthetic procedures will be performed in a standardized fashion. For premedication, all patients will receive 50 mg flurbiprofen axetil intravenously 30 minutes before the surgical incision. In all patients, upper limb intravenous access will be secured and standard monitoring will be applied, including electrocardiogram, pulse oximetry, blood pressure, and the bispectral index (BIS). After preoxygenation, anesthesia will be induced by a bolus injection of Propofol 1.5–2 mg/kg and midazolam 2 mg, sufentanil 0.2–0.3 µg/kg. Tracheal intubation will be facilitated with cis-atracurium 0.2 mg/kg. Anesthesia will be maintained with remifentanil 0.1–0.2 µg/kg/min and desflurane or sevoflurane in a mixture of air 40% and O<sub>2</sub> 60% to maintain BIS within 40 to 60. Systolic arterial

blood pressure will be maintained within 20% of baseline values, and hypotension (MAP <55 mm Hg) will be treated with intravenous phenylephrine. At the end of the surgery, local subcutaneous wound infiltration of 0.25% ropivacaine 20 mL will be administered. Patients will be extubated in the operating room after completion of the surgical procedure and admitted to the post-anesthesia care unit (PACU).

## Postoperative Management

Patients will be transferred to the PACU for continuous monitoring of vital signs. The Aldrete score will be recorded before leaving the PACU. The level of pain will be assessed by using a NRS (NRS, 0 = no pain, 1–3 = mild pain, 4–6 = moderate pain, 7–10 = severe pain). As soon as the NRS score exceeds 3, patients will receive a 0.1 µg/kg intravenous bolus dose of sufentanil. Patients will be discharged from the PACU only once the Aldrete score is 9, and once there is no evidence of pain and/or PONV.

Patients will receive intravenous analgesia with PCIA during the first 72 hours after surgery. If a patient feels pain, he or she can push the PCIA button repeatedly until feeling relief. If a participant's NRS score is >3 after the maximum dosage of 10 mL/hour, he or she will be administered dezocine 5 mg intravenously. The fluid balance, enteral nutrition, antibiotic use will be at the clinicians' decision.

## Collection of Blood Samples

Blood samples will be drawn immediately after the bolus infusion of lidocaine, at the end of surgery, and 24 hours after surgery to measure plasma lidocaine concentrations. Blood samples will also be collected at 24 hours after surgery for subsequent measurement of IL-6, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). The obtained samples will be labelled, centrifuged, frozen, and stored locally at -80° for subsequent testing.

## Follow-Up Visits

All participants will be visited from the day before the surgery to 3 days after surgery. The follow-up will include the cumulative consumption of morphine, NRS scores, the PONV, indicators of bowel function recovery, the use of additional rescue medication (type and dosage) and adverse events. The follow-up will be completed by trained interviewers who are blinded to the group allocation. A patient will be excluded from the study if any of the following situations occur: the patient has an allergic reaction, severe



cardiovascular events that cannot be addressed with symptomatic treatment occur, the test cannot be completed due to the patient is unwilling to continue the study.

## Data Collection

### Baseline Characteristics and Intraoperative Data of Patients

The preoperative data collected will be as follows: age (years), sex (male or female), height, weight, coexisting medical conditions, comorbidities, smoking history, pre-existing pain, preoperative laboratory data (such as hemoglobin, white blood cell, platelet count, prothrombin time, activated partial thromboplastin time, international normalized ratio, alanine transaminase, total bilirubin and albumin), the tumor size and location. The intraoperative data collected will be as follows: surgery type (open or laparoscopic), duration of surgery and anesthesia, the volume of packed red blood cells transfused, the volume of crystalloids and colloids given, blood loss, the dose of lidocaine (intraoperative), total doses of remifentanyl, cumulative sufentanyl dose. The amount of opioid analgesics consumed will be converted to an equivalent dose of intravenous morphine.

### Postoperative Data of Patients

Patients will be visited and evaluated over the first 72 hours after surgery. Pain is assessed using an 11-point NRS scale (0 = no pain, 10 = worst pain imaginable) at 24, 48, and 72 hours after surgery. Patient satisfaction will be obtained at 72 hours after surgery. PONV will be recorded for all patients up to 72 hours after surgery. Postoperative pulmonary complications will be recorded for all patients up to discharge from the hospital after surgery. Lidocaine-related adverse effects and the dose of lidocaine infusion (postoperative) will be recorded up to 72 hours after surgery. The time to first defecation and time to first flatus also will be recorded. Further, the length of hospital stay will be collected from each patient.

## Outcomes

### Primary Outcomes

The primary outcome is the incidence of moderate to severe pain (NRS  $\geq 4$ ) during movement (ie, deep breathing) at 24 hours after surgery.

### Secondary Outcomes

The secondary outcomes are: (1) The incidence of moderate to severe pain at 24 hours after surgery at rest; (2) The

incidence of moderate to severe pain at 48 and 72 hours after surgery at rest and during movement; (3) The cumulative morphine consumption at 24, 48 and 72 hours postoperatively (postoperative opioid use is reported as morphine milligram equivalents, calculated using the Practical Pain Management calculator); (4) Bowel function recovery (defined as the time to first defecation or time to first flatus); (5) The incidence of PONV during the first 72 hours after surgery (we considered it PONV if patients felt any nausea or had any vomiting); (6) The incidence of a composite of postoperative pulmonary complications during hospitalization, defined as positive if any component developed before discharge after surgery; These complications included respiratory infection, respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm, or aspiration pneumonitis (see [Table S1](#) in Additional file 2 for definitions);<sup>26</sup> The diagnoses of pleural effusion, atelectasis, and pneumothorax were based on chest x-rays and were adjudicated by assessors blinded to study group allocation; (7) Length of hospital stay (determined by the number of days from admittance to discharge); (8) Patient satisfaction scores (satisfaction scores regarding pain control and the overall recovery process were obtained at 72 hours after surgery, using a 11-point Likert scale, with 0 indicating “very dissatisfied” and 10 indicating “very satisfied”); (9) Levels of inflammatory factors (IL-6, TNF- $\alpha$ ) at 24 hours after surgery.

## Assessment of Safety

The interventional treatment will be administered to patients with standard hemodynamic monitoring in the setting of a fully equipped operating room. This enables immediate detection and treatment of adverse events. Administration of lidocaine will be immediately stopped in cases when the patients exhibit any adverse events associated with the lidocaine, such as ECG irregularities, drowsiness, light-headedness, metallic taste, peri-oral numbness and tinnitus. Also, after leaving the operation room, all patients will be intensively monitored for the occurrence of severe adverse events, first in the PACU and later in the ward. Moreover, we will monitor the plasma lidocaine concentration immediately after the bolus infusion, at the end of the surgery and 24 hours after surgery. All study-related adverse event details such as the nature, severity, and treatment will be recorded on the case report forms until they are resolved and the patient is stable. Whenever an adverse event occurs, it will be reported to

the principal investigator immediately, and the severity, cause and consequences will be determined. The principal investigator will report suspected unexpected serious adverse reactions to the national health authorities.

## Statistics

### Sample Size Estimate

Based on our pilot study, the incidence of moderate to severe pain during movement at 24 hours after surgery in the lidocaine group was lower than those in the placebo group. The sample size was calculated with the model of Test for Two Independent Proportions [Differences] in PASS V.15 software (NCSS, Kaysville, Utah, USA) based on the incidence of moderate to severe pain during movement at 24 hours (49% in the lidocaine group, 67% in the placebo group) as the primary outcome and the different test as the study design. Given an alpha level of 0.05 (two-sided), a beta level of 0.2, and an additional dropout rate of 10%, the total sample size required is 130 in each group. Therefore, 260 patients (130 in each group) will be enrolled in this study.

### Statistical Analyses

The data will be presented as counts and percentages for qualitative data, as means and standard deviation for normally distributed quantitative data, or as medians and interquartile range for non-normally distributed quantitative data. Baseline characteristics will be compared using Chi-square test or Fisher's exact test, a Student's *t* test, or a nonparametric test as appropriate. The analysis of the primary outcome will be performed using the Chi-square test or Fisher's exact test. The incidence of moderate to severe pain at 48 and 72 hours after surgery will be compared between the two groups using the Chi-square test or Fisher's exact test. The cumulative morphine consumption after surgery will be compared between the two groups using Student's *T*-test or Mann–Whitney *U*-test (after the normality test). The recovery time of bowel function will be compared between the two groups using Student's *T*-test or Mann–Whitney *U*-test (after the normality test). The length of hospital stay will be compared between the two groups using Student's *T*-test or Mann–Whitney *U*-test (after the normality test). The satisfaction scores will be compared between the two groups using Student's *T*-test or Mann–Whitney *U*-test (after the normality test). The incidence of PONV and pulmonary complications will be compared between the two groups by using the Chi-square test or Fisher's exact test. The levels

of inflammatory factors at 24 hours after surgery will be compared between the two groups by using Student's *T*-test or Mann–Whitney *U*-test (after the normality test). Subgroup analysis will be performed to compare patients with open or laparoscopic hepatectomy.

The statistical analyses will be carried out under the responsibility of the methodologist of the clinical research center of the West China Hospital. Results are considered statistically significant if  $P < 0.05$ . All data will be analyzed using SPSS software version 22.0 (IBM Corp, Armonk, NY, USA).

### Data Management and Monitoring

All original data will be recorded in case report forms. The study supervisor (Chunling Jiang) will supervise the conduct of the trial conduction and perform monthly audits of the trial.

### Discussion

Perioperative lidocaine infusion has shown promise for perioperative pain management in many procedures. Yet, there are no published data regarding systemic lidocaine application in liver surgery. Here, we conduct the first prospective randomized controlled trial to investigate the efficacy of intravenous lidocaine during intraoperative period and 72 postoperative hours for postoperative pain and recovery of patients undergoing hepatectomy.

Patients undergoing hepatectomy always suffer extreme pain sustaining for 48–72 hours generally. To ease the pain, postoperative pain control is essential for promoting the recovery of patients after liver surgery. It is revealed by a series of published studies that perioperative lidocaine infusion reduces postoperative pain and accelerate postsurgical recovery prominently. However, evidence for liver surgery remains masked. Beyond that, previous studies restricted the intravenous infusion of lidocaine to the intraoperative period and 24 postoperative hours while lidocaine has a half-life of only 100 minutes. Hereby, we speculate that extended intravenous lidocaine infusion helps to relieve postoperative pain and accelerate recovery. To prove this point, patients will be administered with bolus infusion of lidocaine 1.5 mg/kg during anesthesia induction, a continuous infusion of lidocaine 1.5 mg/kg/h during anesthesia maintenance, and PCIA with lidocaine delivered via an infusion pump device during the first 72 hours postoperatively.

Up to now, the mechanisms lying below the intravenous lidocaine for perioperative analgesia are still elusive.

Current evidence indicates that it seems not to be a sodium channel blockade, because only a very small proportion of neuronal sodium channels will be blocked with its typical perioperative blood levels.<sup>27</sup> Instead, it tends to associate with anti-nociception, anti-hyperalgesia, and interferes with other molecular targets especially those involved in inflammatory signaling pathway. The efficacy of intravenous lidocaine on inflammatory response is under heated debate. Li and his team found that lidocaine could alleviate the inflammatory response induced by gastrectomy. Their results showed that the concentrations of IL-6, TNF- $\alpha$  in plasma of lidocaine group were significantly lower than those in placebo group after surgery.<sup>28</sup> However, de Oliveira et al draws the opposite conclusion that intravenous lidocaine failed to interfere with the production of IL-6 after hysterectomy.<sup>29</sup> The differences in surgery types may be responsible for the conflicted results above. In this study, we intend to uncover the efficacy of intravenous lidocaine on inflammatory response by monitoring the plasma concentrations of TNF-A, IL-6 at 24 hours after hepatectomy.

What cannot be ignored is that liver plays a major role in lidocaine metabolism. Liver resection not merely reduces liver size, also results in its transient ischemia state closely followed by reperfusion owing to hepatic inflow occlusion. As a result of the above, the dysfunction of liver is inevitable especially in drug metabolism. Thus, the safety and adverse effects of intravenous lidocaine in liver surgery deserve our concern. Few adverse effects of continuous intraoperative infusion of lidocaine 1.5–3 mg/kg/h were reported previously.<sup>30,31</sup> Mild adverse effect, including dizziness and visual disturbances, is the most common type,<sup>32</sup> meanwhile serious adverse effect, including neurologic changes and cardiac toxicity, is rarely reported. The accessible evidence suggested that the toxic reactions of lidocaine seem to take off when its plasma concentration reaches 5  $\mu\text{g}/\text{mL}$ .<sup>33</sup> For safety's sake, we will measure the plasma concentration of lidocaine immediately after the bolus injection, at the end of the surgery and 24 hours after surgery. In addition, to identify and manage potential adverse events promptly, all participants will be closely monitored after drug administration. If the patients present any adverse events associated with lidocaine, such as ECG irregularities, drowsiness, light-headedness, metallic taste, peri-oral numbness and tinnitus, the drug will be out of use immediately. Moreover, we will prepare 20% lipid emulsion in the operating room to cope with severe local anesthetic toxicity.

In conclusion, this prospective, randomized, placebo-controlled, double-blinded study is designed to evaluate the analgesic efficacy of intravenous lidocaine infusion during intraoperative period and 72h postoperative hours on postoperative pain and recovery in patients undergoing hepatectomy. If our hypothesis is proven, this pattern of administration may serve in subsequent multimodal analgesia acting as a cost-effective and appropriate method to improve postoperative pain management and promote recovery.

## Abbreviations

PCIA, patient controlled intravenous analgesia; PONV, postoperative nausea and vomiting; SPIRIT, Standard Protocol Items Recommendations for Interventional Trials; ASA, American Society of Anesthesiologists; NRS, numeric rating scale; BIS, bispectral index; PACU, post-anesthesia care unit; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

## Trial Status

The trial was registered at ClinicalTrials.gov on 16 February 2020 (NCT04295330). The study was approved by the ethics committee of the West China Hospital, Sichuan University (approval No. 2019-093). The first participant was recruited on 27 February 2020, and the anticipated completion date will be May 2022.

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## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *Ca-Cancer J Clin*. 2017;67(1):7–30. doi:10.3322/caac.21387



2. Chen J, Zhang Y, Lu L, et al. Liver cancer screening in China: practices and its extended questions. *Hepatoma Res.* 2019;5(4):16–32. doi:10.20517/2394-5079.2019.03
3. Behman R, Cleary S, McHardy P, et al. Predictors of post-operative pain and opioid consumption in patients undergoing liver surgery. *World J Surg.* 2019;43(10):2579–2586. doi:10.1007/s00268-019-05050-7
4. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. *J Pain Res.* 2017;10:2287–2298. doi:10.2147/JPR.S144066
5. Shea RA, Brooks JA, Dayhoff NE, et al. Pain intensity and post-operative pulmonary complications among the elderly after abdominal surgery. *Heart Lung.* 2002;31(6):440–449. doi:10.1067/mhl.2002.129449
6. Wheatley RG, Schug SA, Watson D. Safety and efficacy of post-operative epidural analgesia. *Brit J Anaesth.* 2001;87(1):47–61. doi:10.1093/bja/87.1.47
7. Chou R, Gordon DB, de Leon-casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain.* 2016;17(2):131–157. doi:10.1016/j.jpain.2015.12.008
8. Cook TM, Counsell D, Wildsmith JA, et al. Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. *Brit J Anaesth.* 2009;102(2):179–190. doi:10.1093/bja/aen360
9. Pitkanen MT, Aromaa U, Cozantitis DA, et al. Serious complications associated with spinal and epidural anaesthesia in Finland from 2000 to 2009. *Acta Anaesth Scand.* 2013;57(5):553–664. doi:10.1111/aas.12064
10. Wrighton LJ, O'Bosky KR, Namm JP, et al. Postoperative management after hepatic resection. *J Gastrointest Oncol.* 2012;3(1):41–47. doi:10.3978/j.issn.2078-6891.2012.003
11. Myles PS, Power I. Clinical update: postoperative analgesia. *Lancet.* 2007;369(9564):810–812. doi:10.1016/s0140-6736(07)60388-2
12. Eipe N, Gupta S, Penning J. Intravenous lidocaine for acute pain: an evidence-based clinical update. *BJA Educ.* 2016;16(9):292–298. doi:10.1093/bjaed/mkw008
13. Berk T, Silberstein SD. The use and method of action of intravenous lidocaine and its metabolite in headache disorders. *Headache: J Head Face Pain.* 2018;58(5):783–789. doi:10.1111/head.13298
14. Bartlett EE, Hutaserani O. Xylocaine for the relief of postoperative pain. *Anesth Analg.* 1961;40(3):296–304. doi:10.1213/0000539-196105000-00011
15. Li J, Wang G, Xu W, et al. Efficacy of intravenous lidocaine on pain relief in patients undergoing laparoscopic cholecystectomy: a meta-analysis from randomized controlled trials. *Int J Surg.* 2018;50:137–145. doi:10.1016/j.ijssu.2018.01.001
16. Reeves DJ, Foster AE. Continuous intravenous lidocaine infusion for the management of pain uncontrolled by opioid medications. *J Pain Palliat Care Pharmacother.* 2017;31(3–4):198–203. doi:10.1080/15360288.2017.1313356
17. Grady MV, Mascha E, Sessler DI, et al. The effect of perioperative intravenous lidocaine and ketamine on recovery after abdominal hysterectomy. *Anesth Analg.* 2012;115(5):1078–1084. doi:10.1213/ANE.0b013e3182662e01
18. Wuethrich PY, Romero J, Burkhard FC, et al. No benefit from perioperative intravenous lidocaine in laparoscopic renal surgery. *Eur J Anaesth.* 2012;29(11):537–543. doi:10.1097/EJA.0b013e31828356bad6
19. Weibel S, Jokinen J, Pace NL, et al. Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis. *Brit J Anaesth.* 2016;116(6):770–783. doi:10.1093/bja/aew101
20. Terkawi AS, Tsang S, Kazemi A, et al. A clinical comparison of intravenous and epidural local anesthetic for major abdominal surgery. *Reg Anesth Pain Med.* 2016;41(1):28–36. doi:10.1097/AAP.0000000000000332
21. Song X, Sun Y, Zhang X, et al. Effect of perioperative intravenous lidocaine infusion on postoperative recovery following laparoscopic Cholecystectomy – a randomized controlled trial. *Intl J Surg.* 2017;45:8–13. doi:10.1016/j.ijssu.2017.07.042
22. Chang YC, Liu CL, Liu TP, et al. Effect of perioperative intravenous lidocaine infusion on acute and chronic pain after breast surgery: a meta-analysis of randomized controlled trials. *Pain Pract.* 2017;17(3):336–343. doi:10.1111/papr.12442
23. Cui WH, Li YP, Li SR, et al. Systemic administration of lidocaine reduces morphine requirements and postoperative pain of patients undergoing thoracic surgery after propofol-remifentanyl-based anaesthesia. *Eur J Anaesth.* 2010;27(1):41–46. doi:10.1097/EJA.0b013e3182832d5426
24. Svensson I, Sjostrom B, Haljamae H. Assessment of pain experiences after elective surgery. *J Pain Symptom Manage.* 2000;20(3):193–201. doi:10.1016/s0885-3924(00)00174-3
25. Chan AW, Tetzlaff JM, Gotsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ.* 2013;346:e7586. doi:10.1136/bmj.e7586
26. Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology.* 2010;113(6):1338–1350. doi:10.1097/ALN.0b013e3181fc6e0a
27. Krause KH, Demareux N, Jaconi M, et al. Ion channels and receptor-mediated Ca<sup>2+</sup> influx in neutrophil granulocytes. *Blood Cells.* 1993;19(1):165–173. doi:10.1007/BF01737691
28. Lv X, Li X, Guo K, et al. Effects of systemic lidocaine on post-operative recovery quality and immune function in patients undergoing laparoscopic radical gastrectomy. *Drug Des Devel Ther.* 2021;15:1861–1872. doi:10.2147/DDDT.S299486
29. de Oliveira CMB, Coelho LMG, Valadão JA, et al. Assessment of the effect of perioperative venous lidocaine on the intensity of pain and IL-6 concentration after laparoscopic gastroplasty. *Obes Surg.* 2020;30(10):3912–3918. doi:10.1007/s11695-020-04748-1
30. Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response: a new therapeutic indication? *Anesthesiology.* 2000;93(3):858–875. doi:10.1097/0000542-200009000-00038
31. Sun Y, Li T, Wang N, et al. Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials. *Dis Colon Rectum.* 2012;55(11):1183–1194. doi:10.1097/DCR.0b013e318259bcd8
32. Lauwick S, Kim DJ, Mistraretti G, et al. Functional walking capacity as an outcome measure of laparoscopic prostatectomy: the effect of lidocaine infusion. *Brit J Anaesth.* 2009;103(2):213–219. doi:10.1093/bja/aep103
33. Foo I, Macfarlane AJR, Srivastava D, et al. The use of intravenous lidocaine for postoperative pain and recovery: international consensus statement on efficacy and safety. *Anaesthesia.* 2020;76(2):238–250. doi:10.1111/anae.15270

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