**Protocol title: Nitroglycerin Versus Milrinone for Low Central Venous Pressure in patients undergoing laparoscopic hepatectomy: А** **double-blinded randomized controlled trial**

### Project summary

The rationale: Conventional anaesthetic methods used to reduce central venous pressure (CVP) during hepatectomy include fluid restriction and vasodilator drugs, which may cause decrease in blood perfusion of relevant organs and may offset the benefits of low blood loss. In our previous research, hypotension was a frequent occurrence in patients undergoing laparoscopic hepatectomy under low central venous pressure (LCVP). We have observed the MAP decreased by more than 20% in 84.7% of the patients. A recent study also showed that milirone was better choice to reduce CVP with better hemodynamic manifestation and enhanced postoperative recovery compared with nitroglycerin during hepatectomy. The effect of milirone on patients undergoing laparoscopic hepatectomy (LH) is not yet established as the study only assessed open hepatectomy. In addition, milrinone is less commonly used clinically to reduce CVP, and its benefit in reducing CVP and bleeding in the surgical field during LH remains unclear. Therefore, further study of this important issue is necessary.

The objectives: To compare the effects of milrinone and nitroglycerin in controlling LCVP undergoing LH. We attempt to test the hypothesis that maintaining a LCVP with milrinone during LH would improve the surgical field and provide hemodynamic stability with less effort in a double-blinded randomized controlled trial.

Methods: We are going to enroll 68 patients undergoing laparoscopic hepatectomy under LCVP, and randomly divide into the milrinone group (n = 34) and the nitroglycerin group (n = 34). Milrinone was infused with a loading dose of 10 μg/kg followed by a maintenance dose 0.2–0.5 μg/kg/min and nitroglycerin was given at the rate of 0.2–0.5 μg/kg/min until the liver lesions were removed. Patient and surgical characteristics, intraoperative vital signs, blood loss, the condition of the surgical field, the dosage of norepinephrine, perioperative laboratory data and postoperative c[omplication](javascript:;)s were compared between groups. The primary outcome was blood loss during LH.

Populations: 68 participants will be randomised to either a milrinone group or nitroglycerin group (34 to each).

Time frame: Patients are recruited from June 2022 to september 2023, postoperative follow-up lasted until 1 month later.

Expected outcomes: We hypothesize that milrinone is feasibily and effective in controlling low CVP(LCVP) during laparoscopic hepatectomy(LH), and has benefit on intraoperative blood loss, surgical environment, hemodynamic stability and patients’ recovery, comparing with the conventional anaesthetic method by nitroglycerin. Therefore, maybe milrinone could reduce the incidence of postoperative complications, and improve the outcome of laparoscopic hepatectomy patients.

Name and address of the sponsor/funder: Science and Technology Bureau of Jinhua Municipal.

The main investigator: Huayan Lv, Xiaofeng Jiang, Jun Guo and Shian Yu design the study. Na Yang is responsible for conducting the research.

### Rationale & background information

Laparoscopic hepatectomy (LH) was previously considered unfeasible due to the complex vascular anatomy and the unique risk of bleeding associated with the liver. However, advancements in surgical laparoscopic techniques, equipment, and anesthesia over the past two decades have revealed LH as a safe, minimally invasive, and effective surgical procedure; therefore, it is a widely performed technique1. Laparoscopic hepatic hemostasis techniques are more challenging compared with open liver resection. Intraoperative blood loss is a major challenge faced by hepatic surgeons and also a key factor influencing the success of laparoscopic surgery. Blood loss during liver transection can be reduced through various strategies such as temporary vessel occlusion (including inflow occlusion and outflow occlusion); the use of different hemostatic instruments, equipment, and hemostatic topical agents; and the implementation of appropriate anesthesia methods. These anesthesia methods include low central venous pressure (LCVP), hypoventilation, the reverse Trendelenburg’s posture, epidural anesthesia, normovolemic hemodilution, and different pharmacological interventions2,3. LCVP is recommended during hepatic transection by Enhanced Recovery After Surgery (ERAS) Society to minimize the risk of bleeding during surgery (evidence level: high; grade of recommendation: strong)4. LCVP is associated with reduced blood loss, length of hospital stay, and surgical time3,5.

No standard protocols are currently available on the details of LCVP management, and the best technique to achieve LCVP during liver resection has not been established4,6,7. Conventional anesthesia used to minimize CVP includes intravenous (IV) fluid restriction during surgery, proper patient positioning, and the use of different drugs such as glyceryl trinitrate and diuretics6,7. Nevertheless, fluid restriction along with intraoperative blood loss and glyceryl trinitrate can lead to hemodynamic instability5. In our previous study, we found that hypotension occurs frequently in patients undergoing LH under LCVP. We found that the mean arterial pressure (MAP) decreased by more than 20% in 84.7% of the patients8. Ryu et al. reported that milrinone can provide a superior surgical environment and hemodynamic stability during living donor hepatectomy9. A recent study also reported that milirone is a better choice to reduce CVP with better hemodynamic manifestation and improved postoperative recovery compared with nitroglycerin during hepatectomy10. The results are favorable although the study only assessed open hepatectomy; therefore, its effect on patients undergoing LH is not yet established. Additionally, milrinone is clinically less commonly used to reduce CVP. Furthermore, its benefit in reducing CVP and bleeding in the surgical field during LH remains unclear11, which warrants further investigation.

Theoretically, a vasodilator agent that possesses a positive inotropic effect could potentially provide a more rational approach for controlled LCVP and clinical outcomes during LH compared with a pure vasodilator. We hypothesized that milrinone can be effective in minimizing intraoperative blood loss during LH while also effectively controlling LCVP compared with nitroglycerin. Therefore, in this study, we aimed to compare the efficacy and safety of milrinone and nitroglycerin in controlling LCVP during LH and to assess their effect on clinical outcomes. We established a simple, standardized, and safe approach for LCVP anesthesia during LH.

**References (of literature cited in preceding sections)**

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### Study goals and objectives

The goal of our study is to verify the effect of milrinone on controlled low central venous pressure during laparoscopic hepatectomy, comparing with nitroglycerin. The blood loss, surgical field (assessed using a four-point scale), the intraoperative hemodynamics signs were compared between groups. The postoperative recovery quality, pre- and post-operative haematological markers of vital organs, length of stay were also collected and compared.

### Study design

Our study design: prospective, double blinded, randomized controlled trial.

Inclusion criteria:

1. The patients who plan to undergo laparoscopic liver resection with low central venous pressure，surgery of greater than 2hours expected duration.

2. The patients age range from 18 to 70 years.

3. ASA grades is I~II.

Exclusion criteria:

1. Body mass index (BMI) > 35 kg/m2
2. History of cranial cerebral trauma surgery; history of stroke, or other CNS Diseases and Psychiatric diseases.
3. Primary hypertension > 180mmHg, uncontrolled hypertension or [postural](C:/Users/Administrator/AppData/Local/youdao/dict/Application/8.9.9.0/resultui/html/index.html#/javascript:;) [hypotension](C:/Users/Administrator/AppData/Local/youdao/dict/Application/8.9.9.0/resultui/html/index.html#/javascript:;);
4. Severe heart diseases: [hypertrophic](javascript:;) [Cardiomyopathy](javascript:;)，myocardial infarction，cardiac function grades III~IV, echocardiographic indicates LEVF < 50% or patients with moderate and severe valve regurgitation and preoperative arrhythmia;
5. Dyspnea, respiratory failure;
6. Abnormal liver and kidney function.
7. recently (within 2 weeks) using heparin antithrombin or warfarin anticoagulant factor or aspirin antiplatelet aggregation and other anticoagulant drugs.
8. known allergy to any drug used in the study;

### Methodology

This study protocol will be submitted to the Ethics Committee of Jinhua Hospital Affiliated to Zhejiang University for approval. Then this trial will be registered at the Chinese Clinical Trial Registry. After the study is approved for clinical registration, the trial will be performed from June 2022 to september 2023.

All patients who met the inclusion criteria are documented consecutively. Light abnormal liver function with Child–A liver function is not an exclusion criterion. Randomization is performed after the patients are deemed eligible and have agreed to participate in the study. The computer-generated random numbers will be sealed in opaque envelopes and kept by a nurse. The n[urse anesthetist](javascript:;)s open the envelopes and dispense the experimental drug after the patients have entered the operating room.

The patients are randomly divided into the milrinone group and the nitroglycerin group, 34 patients each. The patients, the surgeons, the attending anesthetist, and the researcher who collects the follow-up survey data and performs the statistical analysis are blinded to the group allocation.

Anesthetic procedures

All patients will receive standardized anesthetic protocol without premedication. In the preoperative preparation room, a peripheral intravenous line is established for all patients by the nurse. Then, internal jugular double-lumen catheterization will be performed by the anesthetist in the preparation room under local anesthesia. The fluid administration is restricted at an infusion rate of 2–3 ml/kg/h before a[nesthesia induction](javascript:;). After entering the operating room, under standard monitoring and CVP monitoring (the central venous catheter line is also connected to [transducer](javascript:;)), anesthesia is induced with atropine 0.2 mg, sufentanil (0.8 μg/kg), etomidate (0.2–0.3 mg/kg), and cis-atracurium (0.3 mg/kg). After anesthesia induction and stabilization, radial arterial puncture and subcostal transversal fascia block are performed by the attending anesthetist. The arterial line is connected to the Vigileo/FloTrac monitor (Edwards Lifesciences, Irvine, CA, US) for realtime hemodynamic monitoring (arterial pressure, cardiac index(CI), cardiac output(CO) and systemic vascular resistanve index(SVRI)). Anesthesia is maintained with propofol, remifentanil, cis-atracurium, and sevoflurane (0.5%–1%). Mechanical ventilation is initiated using a fraction of inspired oxygen (FiO2) of 50% and a tidal volume of 8 mL/kg with a frequency 12 /min. The minute ventilation is adjusted to maintain the end–tidal carbon dioxide partial pressure (PetCO2) concentration between 35 and 50 mmHg. During surgery, the anesthesiologist should regulate the anesthetics to maintain the bispectral index score (BIS) of anesthetic depth between 40 and 60.

In both groups, after induction of anaesthesia, fluid administration is restricted with an infusion rate of 2–3 ml/kg/h before liver parenchymal transection. Either milrinone or nitroglycerin is administered once pneumoperitoneum establishment. In the milrinone group, 10 μg/kg of milrinone is administered over 10 min as a loading dose, and then, milrinone is infused with the rate of 0.2–0.5 μg/kg/min until the liver lesions are removed. In the nitroglycerin group, nitroglycerin is given at the rate of 0.2–0.5 μg/kg/min. Either milrinone or nitroglycerin infusion should be stopped after completion of parenchymal transection. In both groups, the intermittent Pringle manoeuvre is applied or not at the discretion of the surgeon in order to reduce bleeding. Intermittent Pringle manoeuvre will be performed in cycles of 15/5 min for clamping/unclamping with a laparoscopic appropriately prepared Foley’s catheter of the hepatic pedicle in our unit. During liver parenchymal transection phase, the fluid infusion rate is adjusted by the attending anesthesiologist according to the CVP and the condition of the surgical field. The condition of the surgical field during liver resection is evaluated using a four–point grading scale (table 1). After completion of parenchymal transection, the rate of intravenous fluid administration should increase to maintain the CVP be close to the baseline level before induction. Fluid administered intra-operatively is lactate Ringer solution routinely. Colloid solution should be administered only when blood loss more than 500 mL for volume replacement. Packed concentrated red blood cells should be transfused if the intraoperative red blood cell volume detected by blood gas analysis was lower than 25%. The amount of intraoperative blood loss is the sum of the volumes of blood contained in suction systems and the amount on the gauzes.

Table 1 : Grading criteria for evaluating the surgical field

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| Grade | Description |
| I | very lax hepatic veins, minimal bleeding at resection plane, very easy to operate; |
| II | lax hepatic veins, a little bleeding at resection plane, easy to operate; |
| III | tense hepatic veins, appreciable bleeding at resection plane, somewhat difficult to operate |
| IV | very tense hepatic veins, profuse bleeding at resection plane, very difficult to operate |

We plan to use an infusion pump for the fluid administration before liver parenchymal transection; after completion of parenchymal transection, we use a normal infusion set for fluid resuscitation. The amount of intraoperative blood loss is the sum of the volumes of blood contained in suction systems and the amount on the gauzes. Estimated blood amount on the gauzes (mL)=(Weight of gauzes after surgery – weight of gauzes before surgery) / 1.054(average blood density g/mL). The volume of blood loss and the volume of fluids administration are rounded to an integer. The value is accurate to the tens place, the ones place is omitted.

During the surgery, the case report form was manually recorded by an anesthetic assistant according to the device data. The hemodynamic data (heart rate [HR], pulse oximetry (SpO2), invasive MAP, CVP, BIS, PetCO2, CI, SVRI, and CO) were recorded at the following predefined time points: before (T0) and after induction (T1), before milrinone/nitroglycerin administration (T2), 10 min after milrinone/nitroglycerin administration (T3), right before the initiation of liver parenchymal transection (T4), midway through liver parenchymal transection (T5), right after the completion of parenchymal transection (T6), and at the end of the surgery (T7). Noradrenaline was administered to the patients in the two groups to maintain an MAP of more than 65 mmHg. In both groups, perioperative hypotension was defined as a 30% reduction of MAP from baseline.

Blood samples were collected to identify end-organ perfusion markers (lactate concentration) and examine routine blood factors at the beginning and end of the surgery. After the surgery, the patients woke up, were extubated in the operating room, and then were transferred to the post-anesthesia care unit with an intravenous patient-controlled analgesia device. The blood samples were taken for liver and renal function tests preoperatively, immediately after the surgery, and on postoperative days 1, 3, and 7. Additionally, we monitored postoperative recovery and complications. Postoperative complications were classified according to the Clavien–Dindo classification. Postoperative mortality was defined as any death within 30 days after the surgery.

Surgical procedures

After pneumoperitoneum is established, patients are placed in the reverse Trendelenburg position. The operator stands between the legs with one assistant on each side. The carbon dioxide pneumoperitoneum during surgery is usually maintained at 8-12mmHg. In both groups, the intermittent Pringle manoeuvre is applied or not at the discretion of the surgeon in order to reduce bleeding. Intermittent Pringle manoeuvre will be performed in cycles of 15/5 min for clamping/unclamping with a laparoscopic appropriately prepared Foley’s catheter of the hepatic pedicle in our unit. The surgeons usually use an ultrasonic surgical aspirator and the clamp–crush method for liver parenchymal transection. The major Glissonian pedicle or the hepatic vein was divided by a laparoscopic linear stapler and the main bile duct was controlled by a stapler or a Hemolock clip. The extent of hepatic resection is divided into major liver resection and minor liver resection. The extent of liver resection is assessed by the operator. Three liver segments or more resected is defined as major liver resection, while wedge resection and left lateral sectionectomy are defined as minor liver resection.

LCVP management and CVP measurement

The method to lower the CVP during laparoscopic hepatectomy has been used widely, and includes fluid restriction, patient positioning with the upward head tilt, and use of vasodilators or diuretics to achieve a CVP of < 5 cmH2O at the beginning of liver parenchymal transection. If the CVP did not reach the target value, the patient remained in the study according to the intention-to-treat principle.

Ventilation management and PetCO2 measurement

After anesthetic induction and tracheal intubation, mechanical ventilation is performed with a fraction of inspired oxygen (FiO2) of 50% and a tidal volume at 8 mL/kg. The minute ventilation is adjusted to maintain the end–tidal carbon dioxide partial pressure (PetCO2) concentration between 35 and 50 mmHg. The PetCO2 is monitored continuously during surgery and recorded automatically using a computer. In addition, blood samples are collected from the radial artery for arterial BGA (blood gas analyzer: GEM Premier 3500, Instrumentation Laboratory, Lexington, MA, US) at beginning and end of surgery, and the PaCO2 was maintained at < 60 mmHg throughout the intraoperative period. In general, the PetCO2 can be lower than the PaCO2 by approximately 5 mmHg, as observed in our clinical practice. If the PetCO2 is beyond the target value (35 to 50 mmHg) during surgery, the patient remained in the study according to the intention-to-treat principle.

Postoperative complications

We will observe the postoperative recovery and record the postoperative complications. Intra-abdominal infection was confirmed by elevation of white blood cell, imaging or drainage fluid culture and usually treated with broad-spectrum or sensitive antibiotic. Abdominal hemorrhage would be considered by a drop of hemoglobin more than 30 g/L, compared with postoperative baseline; transfusion of blood products and/or invasive reintervention would be necessary for haemostasis. Biliary fistula was defined as bilirubin concentration of drainage fluid was at least three times of the serum concentration for more than 3 postoperative days and would receive conservative treatment unless severe peritonitis occur. Ileus manifesting as nausea, vomiting, and no passage anus gas for more than 5 days after surgery would be included as postoperative complication. Seroperitoneum was diagnosed as the abdominal ultrasonography found more than 200 ml liquid in abdomen and would require paracentesis. The diagnostic criteria of postoperative liver failure included persistent hyperbilirubinemia (>50 mmol/L), ascites, coagulatory disorder (INR>1.7) and emergence of hepatic encephalopathy. Once transthoracic ultrasonic cardiogram verified ejection fraction <50% with clinical manifestation of dyspnea or edema, cardiac insufficiency would be diagnosed. If the two aforementioned complications occurred, patients would be transferred to intensive care unit. The postoperative complications were classified according to the Clavien–Dindo classification, table 2.

Table 2: The Clavien–Dindo Classification of Surgical Complications

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| --- | --- |
|  | Classification of Surgical Complications |
| Grades | Definition |
| Grade I: | Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and  radiological interventions.  Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy.  This grade also includes wound infections opened at the bedside. |
| Grade II: | Requiring pharmacological treatment with drugs other than such allowed for grade I complications.  Blood transfusions and total parenteral nutrition are also included. |
| Grade III: | Requiring surgical, endoscopic or radiological intervention |
| Grade III-a: | intervention not under general anesthesia |
| Grade III-b: | intervention under general anesthesia |
| Grade IV: | Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management |
| Grade IV-a: | single organ dysfunction (including dialysis) |
| Grade IV-b: | multi organ dysfunction |
| Grade V: | Death of a patient |
| Suffix ’d’: | If the patient suffers from a complication at the time of discharge (see examples in Appendix B, http://Links.Lww-.com/SLA/A3),  the suffix “d” (for ‘disability’) is added to the respective grade of complication. This label indicates the need for a follow-up to  fully evaluate the complication |

**Safety considerations**

There are about 200 patients undergoing laparoscopic hepatectomy every year in our center. The surgeons of our research team have a lot of experience in laparoscopic hepatectomy to ensure patients safety. Intraoperative blood loss is challenging for hepatic surgeons due to the complicated anatomical structure and double blood supply system of the liver. In our hospital, the intermittent Pringle manoeuvre was used in most cases. Intraoperative ultrasonography was routinely performed to confirm the location and size of the tumor and check for intrahepatic vessels. Hemorrhage during hepatectomy is mainly due to damage of the hepatic vein inside the liver parenchyma. The surgeons usually use hemolok clip, diathermy and suture for haemostasis. When hemorrhage from hepatic vein laceration is large, the surgeons will use gauze compression or suture to cope with hepatic venous laceration.

Previous studies have reported that low CVP can lead to hemodynamic instability. We will monitor the invasive arterial pressure at all times during the operation, Noradrenaline was administered to the patients in the two groups to maintain an MAP of more than 65 mmHg. The colloid solution was administered for volume replacement when blood loss was more than 500 mL. Moreover, packed concentrated red blood cells were transfused if the intraoperative red blood cell volume detected by a blood gas analysis was lower than 25%.

Maintaining LCVP at a certain value helps obtain a good surgical field. Surgeons prefer even lower CVP, which would help obtain a better surgical field. However, extremely low CVP may be related to complications, especially in elderly individuals and people with heart or cerebral diseases. In our center, the target value of intraoperative CVP is dynamic and individualized. During surgery, LCVP management should not be conventional but should be based on a patient’s basic condition, intraoperative bleeding risk, and surgical field grading. The anesthesiologists should provide a good surgical field and communicate promptly with surgeons, as well as achieve optimal CVP and ensure tissue perfusion.

During liver parenchymal transection stage, the risk of air embolism may increase in patients undergoing laparoscopic hepatectomy under LCVP. PetCO2 monitoring is an important method for early detection of air embolism. The PetCO2 was monitored continuously during surgery. we also can use intraoperative color Doppler ultrasound to [make a definite diagnosis](javascript:;) of air embolism in real-time. Carbon dioxide embolism can cause transient hemodynamic instability. When carbon dioxide embolism occur, positive pressure ventilation, low carbon dioxide pneumoperitoneum pressure and compression of the heart might be the effective measure. Besides, the surgeons of our research team are proficient in hemostasis of hepatic venous bleeding which usually due to damage of the hepatic vein inside the liver parenchyma.

Even though well tolerated, milrinone has a few of reported adverse effects. A high intravenous loading dose frequently results in transient hypotension, and unsustained ventricular tachyarrhythmia was also reported in early clinical studies in congestive heart failure patients. Milrinone loading with 50ug/kg given over 10 min in the intensive care unit (ICU) may cause severe hypotensive episodes in open heart surgery patients and thus require vasopressors. To avoid hypotension caused by rapid milrinone administration, milrinone was administered at a low loading dose of 10 µg/kg over 10 min at the beginning of the surgery, followed by infusion at a rate of 0.2–0.5 μg/kg/min until the removal of the liver lesions. The safety of this dose has been confirmed by Ryu et al. Moreover, in the operating room environment where vital signs are under close observation, patient safety can be guaranteed to the greatest extent.

### Follow-up

The researcher who collects the follow-up survey data is blinded to the group allocation. The researcher will observe the postoperative recovery and record the postoperative complications. The postoperative complications are defined as above, and complications are diagnosed and treated by a professional hepatobiliary surgeon.

Postoperative complications are classified according to the Clavien–Dindo classification. The classification of complication classification is determined by our group. The postoperative follow-up lasted until one month after the operation. Postoperative mortality is defined as any death within 30 days after the surgery.

### Data management and statistical analysis

During the surgery, the case report form is manually recorded by an anesthetic assistant according to the device data. The hemodynamic data (heart rate [HR], pulse oximetry (SpO2), invasive MAP, CVP, BIS, PetCO2, CI, SVRI, and CO) are recorded at the following predefined time points: before (T0) and after induction (T1), before milrinone/nitroglycerin administration (T2), 10 min after milrinone/nitroglycerin administration (T3), right before the initiation of liver parenchymal transection (T4), midway through liver parenchymal transection (T5), right after the completion of parenchymal transection (T6), and at the end of the surgery (T7). Noradrenaline is administered to the patients in the two groups to maintain an MAP of more than 65 mmHg. In both groups, perioperative hypotension is defined as a 30% reduction of MAP from baseline.

Blood samples are collected to identify end-organ perfusion markers (lactate concentration) and examine routine blood factors at the beginning and end of the surgery. After the surgery, the patients wake up, are extubated in the operating room, and then are transferred to the post-anesthesia care unit with an intravenous patient-controlled analgesia device. The blood samples are taken for liver and renal function tests preoperatively, immediately after the surgery, and on postoperative days 1, 3, and 7. Additionally, we monitore postoperative recovery and complications. Postoperative complications are classified according to the Clavien–Dindo classification. Postoperative mortality is defined as any death within 30 days after the surgery.

The predefined primary endpoint was the difference in blood loss between the milrinone group and the nitroglycerin group during the surgery. Compared with the blood loss in patients in the milrinone and nitroglycerin groups undergoing hepatectomy surgery in a previous study, the mean (standard deviation [SD]) blood loss during liver resection was 240.83 (341.50) in the milrinone group and 499.23 (623.86) in the nitroglycerin group. Assuming a type I error of 0.05 and a type II error β of 0.80, calculations showed that 34 patients should be included in each group in order to determine a clinically relevant difference (G-power program, two-tailed). Therefore, the total sample size is 68 patients.

Data will be analyzed using IBM SPSS statistical software, version 20 (IBM, Chicago, IL, US). Categorical data are presented as numbers (percentages) and compared using the chi-square test or Fisher’s exact tests, as appropriate. Continuous data are presented as the mean (SD) and compared using Student’s *t*-test in the case of homogeneity of variance or presented as the median (interquartile range) and compared using the Mann–Whitney U test in the case of heterogeneity of variance. Repeated-measures analysis of variance is used for intragroup comparisons at different time points. The Kappa test is used to evaluate the consistency of surgical field grading between the surgeon and the first assistant. The Mann–Whitney rank sum test is used to evaluate the difference in surgical visual field grading between the two groups. A *P*-value of <0.05 is considered statistically significant for all analyses.

### Quality assurance

These variables (heart rate, SpO2, MAP, CVP, BIS, and PetCO2) are all automatically recorded by the computer and the FORE-SIGHT device every 5 minutes throughout surgery. The Case Report Form is manually completed by an anesthetic assistant according to the device data, and the anesthetic assistant is blinded to the group allocation. Zhijian Lan and Na Yang are responsible for quality control and review the data for the study.

### Expected outcomes of the study

Theoretically, a vasodilator agent that possesses a positive inotropic effect could potentially provide a more rational approach for controlled LCVP and clinical outcomes during LH compared with a pure vasodilator. The results of the present study will demonstrate that milrinone can be effective in minimizing intraoperative blood loss during LH while also effectively controlling LCVP compared with nitroglycerin. Conventional anaesthetic methods used to reduce CVP may result in decrease in insufficient blood perfusion of relevant organs, which may offset the benefits of low blood loss. In this study, we tried different pharmacological interventions in order to establish simple, standardized and safe approach of LCVP anesthesia during LH.

### Dissemination of results and publication policy

Huayan Lv, Na Yang and Shian Yu design the study. Na Yang is responsible for conducting the research. Wei Wang and Xiaoxia Huang will perform the study and obtain data. Huayan Lv and Xiaofeng Jiang perform the statistical analysis and write the manuscript. Bo Wu and Shian Yu cooperated with our research and completed the operation. Zhijian Lan and Jun Guo investigated, supervised the study, reviewed the data. Na Yang are responsible for quality control and review the data. Lei Zhang and Yuwen Lao helped carrying out the randomization and administered the experimental drug. The study will implement in Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, Zhejiang Province, People's Republic of China. The Science and Technology Bureau of Jinhua Municipalis will support our project financially (No. 2021-3-053; 2022-4-109).

### Duration of the project

From December 2021 to May 2022, [preparatory phase](javascript:;), [project startup](javascript:;).

From June 2022 to September 2023, complete all cases collection.

From October 2023 to October 2024, data collation, summary, and publication.

### Problems anticipated

The difficulty of the operation is uncertain, for example, abdominal organ adhesion and u[npredictable](javascript:;) intra-operative sustained hemorrhage, which may lead to the failure of laparoscopic surgery, and the operation method changes during the procedure. We should perform preoperative assessment and communication adequately about the difficulty to reduce such probability.

The CVP value is affected by a number of factors and may fluctuate during operation. However, our pilot study showed that the CVP value are fairly constantly intraoperative.

**Project management**

Huayan Lv, Na Yang and Shian Yu design the study. Na Yang is responsible for conducting the research. Wei Wang and Xiaoxia Huang will perform the study and obtain data. Huayan Lv and Xiaofeng Jiang perform the statistical analysis and write the manuscript. Bo Wu and Shian Yu cooperated with our research and completed the operation. Zhijian Lan and Jun Guo investigated, supervised the study, reviewed the data. Na Yang are responsible for quality control and review the data. Lei Zhang and Yuwen Lao helped carrying out the randomization and administered the experimental drug. The study will implement in Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, Zhejiang Province, People's Republic of China.

### Ethics

The protocol will be submitted to the Medical Ethics Committee of Jinhua Hospital Affiliated to Zhejiang University for review. The day before the operation, the investigators visit the patient, evaluate the inclusion criteria and exclusion criteria. The investigators explain the research trial to the patients and written informed consent was obtained from all patients.

### Informed consent forms

The informed consent forms (ICF) and the protocol (in Chinese) will be submitted to ethics committee for review in our hospital. The study will begin after the approval of ethics committee.

**Research protocol: part 2**

### Budget

This project applies for fund of Science and Technology Bureau of Jinhua Municipal, 50,000 yuan. The fund are used for:

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| --- | --- | --- |
| Item | Amount（yuan） | Explaination |
| anesthesia consumable materials | 10，000 | Central venous pressure monitoring |
| Publishing/literature/information dissemination / | 30，000 | Layout fee, retouching fee, etc |
| a[dministrative fee](javascript:;) | 5000 | management fees of the study |
| i[ncentive fee](javascript:;) | 5000 | i[ncentive](javascript:;) payment |

### Curriculum Vitae of investigators

The Principal investigator, Huayan Lv, Master of Medicine, graduated from Chongqing Medical University in the year of 2009 and has been engaged in clinical anesthesia since graduation. She has participated in two protocols of Science and Technology Bureau of Jinhua Municipal as the project principal. As the first participant, she participated in two provincial projects, and the completed key project of Jinhua Science and Technology Bureau (2017-3-005) won the third prize of the Golden Life Supplement Science and Technology Progress Award of Affiliated Jinhua Hospital, Zhejiang University School of Medicine. Since 2009, she has published 10 professional and technical articles as the first author in domestic first-class magazines.

The co-investigator, Xiaofeng Jiang, Master of Medicine, graduated from Wenzhou Medical University in the year of 2019. He has participated in two protocols of Science and Technology Bureau of Jinhua Municipal as the project leader, and has published 5 professional and technical articles.

The co-investigator, Bo Wu, Master of Medicine, hepatobiliary surgeon. He has participated in one protocols of Science and Technology Bureau of Jinhua Municipal as the project leader, and has published 8 professional and technical articles as the first author in domestic first-class magazines.

The co-investigators, Zhijian Lan, Wei Wang, Xiaoxia Huang, Lei Zhang, Yuwen Lao, Na Yang, and Jun Guo, are anesthesiologists in department of Anesthesiology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, Zhejiang Province. The team has rich experience in clinical anesthesia for all kinds of surgeries and has mastered the anesthesia key points of laparoscopic hepatectomy.

The co-investigator, Shian Yu, chief of department of Hepatological Surgery, he has completed more than 150 cases of laparoscopic hepatectomy every year.

### Other research activities of the investigators

Our previous research found that hypotension was a frequent occurrence in patients undergoing laparoscopic hepatectomy under LCVP. We have observed the MAP decreased by more than 20% in 84.7% of the patients. (reference to: Effects of targeted mild hypercapnia versus normocapnia on cerebral oxygen saturation in patients undergoing laparoscopic hepatectomy under low central venous pressure: a prospective, randomized controlled study)

The published essays of the investigators are as follow:

[1] Jianbo Xu, Yanhong Zhu 2, Shuai Zhen, Xiaofeng Jiang. Association between postoperative thrombocytopenia and outcomes after traumatic brain injury surgery: A cohort study. Acta Anaesthesiol Scand. 2023, 67(7):918-924.

[2] Xiong, C; Han, C; Lv, H; Lan, Z; Comparison of adjuvant pharmaceuticals for caudal block in pediatric lower abdominal and urological surgeries: A network meta-analysis. J Clin Anesth. 2022, 81,110907.

### Financing and insurance

Not applicable