

Clinical Trial Protocol

TITLE: Prospective, Multicenter, Randomized, Single-blind, Parallel-controlled Clinical Trial Protocol for the Safety and Efficacy of Clinical Applications of the Endoscopic Instrument Control System

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Study protocol

1. Study purpose

To evaluate the safety and efficacy of the MicroHand S endoscopic instrument control system by using it in clinical treatment for the participants. Statistical analysis is conducted to determine whether the efficacy of the test product is non-inferior to that of the control product and to observe the incidence of organ and vascular injury related to the test product. Thus, to verify the safety and efficacy of the MicroHand S endoscopic instrument control system developed by WEGO Surgical Robot Co., Ltd in clinical application.

2. Content

This clinical trial is a prospective, multicenter, randomized, single-blind, parallel-controlled study. The instrument used in the experimental group is the endoscopic surgical robotic system developed by WEGO Surgical Robot Co., Ltd., and the instrument used in the control group is the endoscopic surgical robotic system developed by Intuitive Surgical.

Before patients are enrolled in this clinical study, the researchers will do a detailed screening of the subjects based on the inclusion and exclusion criteria to determine if the patients are appropriate for the clinical study. Patients who meet the conditions of the study will be required to sign an informed consent form. Then they will be randomly assigned to the test group or the control group. The surgical robot system will be used for treatment in both groups to evaluate the primary and secondary outcome measures and to observe the incidence of organ and vascular injury.

Finally, we evaluate the safety and efficacy of the test product through the comparison of the data obtained from the test group and the control group during the treatment.

3. Background

The development direction of medical treatment in the 21st century is to preserve the physiological structure and function of patients as much as possible. Compared with conventional laparotomy, minimally invasive surgery has obvious advantages in terms of treatment effect, pain relief, recovery, and medical cost. The endoscopic instrument control system, also known as the surgical robot, is a breakthrough in the field of surgery, which greatly expands the indications of minimally invasive surgery.

The endoscopic instrument control system has the characteristics of minimally invasive surgery and more technical advantages:

- (1). It can accurately simulate the movements of human hands, wrists and fingers with multi-degree of freedom.
- (2). It can proportionally reduce the surgeon's range of motion and improve the accuracy of surgical procedures.
- (3).The tremor filtering system filters the hand vibration of the surgeon and improves the

stability of the operation.

(4).The imaging system provides the surgeons with a three-dimensional magnifying view (5 to 10 times) of the field image to enhance the surgeon's visual perception.

(5). Using a surgical robot, the surgeon can sit in a comfortable chair so that they can relieve the operator's fatigue, reduce the probability of making mistakes due to tiredness, and improve the safety of the operation.

(6). The surgeons can use the "high-speed broadband" technology to interface with other digital devices and to control the surgical robot for a surgery.

From 2000 to the present, the "Da Vinci" robotic system has become the most commonly used robotic surgical system because of its superior design and performance. Since its inception, the system has been used in a variety of operations including cardiac surgery, general surgery, gynecology, head and neck surgery, thoracic surgery and urology.

As of October 2018, more than 4,000 systems were in use worldwide, with more than 5 million patients benefiting from the advanced minimally invasive techniques of da Vinci surgical robot. But its high cost, expensive annual maintenance cost, and accessory instruments limit the use of da Vinci's surgical systems in developing countries like China.

The endoscopic surgical robotic system developed by WEGO Surgical Robot Co., Ltd. is a minimally invasive surgical robotic system independently developed by China which is the first successful minimally invasive surgical robotic system in China with property rights. It can complete complex suture and knotting, replace the traditional planar imaging system with a three-dimensional stereo vision system to make the surgical field clearer. The adjustable mapping ratio and more practical energy device are its unique specialty. It can also greatly reduce the cost of robotic surgery.

The test product has passed the test of Beijing Medical Device Quality Supervision and Inspection Center of the China Food and Drug Administration. All met the standard requirements and issued qualified registration inspection. The clinical verification will be performed by the Third Xiangya Hospital of Central South University and the affiliated hospital of Qingdao University, to prove the safety and efficacy of this product.

4. Precautions of the test product

1. Please read the user manual and instructions carefully before using the console.
2. Operators are required to have certain qualifications. They are required for more than 5 years of experience in laparoscopic surgery, more than 1 year of experience in robotic surgery, and having been trained to operate the test product skillfully.
3. Before each operation, you must check whether the console is damaged, whether the control panel displays normal, and whether the connecting wires and interfaces are integrated.
4. After turning on the power, you shouldn't operate until the console completely starts and the operative arms and other surgical preparations are prepared.
5. The operation should be meticulous and gentle, avoiding excessive and violent movements to cause damage to subjects or instruments.
6. Emergency preparation for accidents must be done before surgery.
7. Disconnection is prohibited during the operation.
8. Do not embed any foreign components. Any foreign components embedded can cause

permanent damage to the product. If it does, immediately turn off the power and contact a qualified service person for repairing.

9. Do not attempt to disassemble or modify the product.

10. The console should be placed in a clean, dry, suitable temperature and humidity environment, having regular inspection and maintenance.

11. If the console has any malfunction, stop the procedure and report it to the manufacturer in time.

5. Study Methods

- (1) This study uses a multicenter, randomized, single-blind, parallel-controlled method to observe the efficacy and safety of the MicroHand S endoscopic instrument control system in clinical application.
- (2) The subjects' vital signs are recorded before the start of this study, which include blood routine, liver and kidney function, electrolytes, coagulation function, electrocardiogram, urine/blood pregnancy test (female) and related imaging examination. Preoperative combined medications are also recorded.
- (3) Qualified subjects are divided into the experimental group and the control group by randomized number given in an envelope. Both the endoscopic instrument control systems in two groups are examined before the test. After anesthesia, the endoscopic instrument control system is placed in an appropriate position. Then we connect the wires and power up the system. According to the requirements of the surgery, the operative arms are placed and slowly pushed through the Trocars of the abdominal wall. The surgeons start to perform the operation.
- (4) Surgical success rate, intraoperative blood loss, operative time, and installation time are recorded, as well as whether adjacent organs and blood vessels are injured due to the malfunction of the test system. The breakage rate of gallbladders is calculated. Surgeons need to fill the satisfaction questionnaire after the surgery.
- (5) Subjects take a test in 24 ± 2 hours after surgery using visual analogue scale (VAS) to evaluate the pain score. Postoperative blood routine examination, liver and kidney function, and electrolyte examination are performed. Time to first flatus, postoperative complications and hospital stay are recorded. Postoperative combined medications are also recorded. Adverse events and severe adverse events are assessed separately in 30 ± 5 days after surgery.
- (6) After the follow-ups of all subjects, the data will be arranged for statistical analysis. Ultimately the data of the two groups will be compared, so as to prove whether the experimental product developed by WEGO Surgical Robot Co., Ltd is non-inferior to the control group.

6. Arms and Interventions

- (1) Experimental group: MicroHand S endoscopic instrument control system
Using the MicroHand S endoscopic instrument control system to treat gallstone or cholecystitis in minimal invasive surgery.

(2) Control group: da Vinci endoscopic instrument control system
Using the da Vinci endoscopic instrument control system to treat gallstone or cholecystitis in minimal invasive surgery.

7. Subject recruitment

7.1 Inclusion criteria

- (1) 18-65 years old, male or female
- (2) American Society of Anesthesiologists (ASA) Level 1, Level 2 or Level 3
- (3) BMI 18-30Kg/m²
- (4) Benign gallbladder diseases such as acute or chronic cholecystitis, gallstones and polypoid lesions of gallbladder
- (5) Subjects or their legal representatives/guardians voluntarily participate in clinical trials and have signed informed consent

7.2 Exclusion criteria

- (1) Participating in any other clinical trial within 30 days before signing the informed consent form
- (2) Pregnancy or lactation
- (3) With a history of epilepsy or psychosis
- (4) With a history of previous operations at related sites
- (5) Severe cardiovascular and cerebrovascular diseases with New York grade III-IV cardiac function or pulmonary insufficiency that can't tolerate the operation
- (6) Severe liver and kidney insufficiency such as cirrhosis and renal failure
- (7) Acute cholecystitis lasting for more than 72 hours, acute cholecystitis with severe complications such as cholecystitis, gangrene, perforation, etc., and gallbladder thickness thicker than 10 mm
- (8) Acute cholangitis, gallstone with acute pancreatitis, primary common bile duct stones, intrahepatic bile duct stones and obstructive jaundice
- (9) Gallbladder cancer or protuberant lesions are suspected to be cancerous
- (10) Severe allergic constitution and suspected or identified addicts to alcohol or drugs
- (11) Abdominal infection, peritonitis, diaphragmatic hernia, severe systemic infection or metastatic diseases
- (12) Other situations that researchers consider it inappropriate to participate in this clinical trial

7.3 Inclusion time

After signing the informed consent, subjects who meet the inclusion criteria and do not meet the exclusion criteria can be enrolled within 14 days. It is expected to take 12 months from the first case to the last case.

7.4 The expected duration of the study

The expected duration time of each subject is 33 days. Considering that the robotic

surgery has not been widely carried out in China, as well as the poor subject compliance, the overall duration of this clinical trial is expected to be 13 months.

7.5 The expected duration time of each subject

Each subject is observed up to 30 days after surgery, and efficacy and safety are evaluated at the end of the follow-up. So the expected duration of each subjects is 33 days. The additional 3 days are used for preoperative examination.

7.6 Number of subjects required

In this clinical trial, 168 patients are enrolled, including 84 in the experimental group and 84 in the control group.

7.7 Drop-outs and removal of the subjects

All subjects who sign the informed consent form and participate in the study, whenever they withdraw from the study for any reason, as long as they do not complete the observation period specified in the protocol, they are shedding cases. Usually in these situations:

- (1) The subject or his/her legal guardian requests to withdraw from the clinical trial.
- (2) Adverse events (AE), severe adverse events (SAE), or any device defects that prevent subjects from continuing to participate in the study.
- (3) The researchers consider it medically necessary for the subjects to terminate the study.
- (4) Other reasons for subjects to suspend the study.

When the subject drops out, the researcher should take various methods, such as paying a visit, making a follow-up appointment, phone call, letter, etc., to contact the subject as far as possible and ask the reason. Any drop-out due to adverse events should be recorded in the CRF form and notified to the sponsor, regardless of whether there is a causal relationship with the test product or not. All subjects enrolled in the study should retain various original data and documents, both for retention and for intentional analysis (ITT Analysis).

All subjects meeting the following criteria should be removed:

- (1) Those found to violate the inclusion criteria or meet the exclusion criteria during the trial.
- (2) Withdrawing the informed consent.
- (3) The informed consent form is not signed or there is no informed consent process.
- (4) Failing to obtain observation data.

Case removal is one of the key indicators to determine the endpoint data set of clinical trials. If there is a condition that affects the treatment or safety evaluation of the case, such as unavailable observational data, the case should be considered as not included in the analysis set. It must be decided after discussion between the principal investigator, the data manager, the statistical analyst and the sponsor.

8. Efficacy evaluation

8.1 Primary outcome measure: surgical success rate

The surgical success rate is defined as the proportion of successfully operative subjects in the experimental group or the control group.

Surgery conversion in this study means a robotic surgery has to be converted to a

laparoscopic surgery. Usually there are 3 kinds of reasons: active conversion, passive conversion and malfunction of the endoscopic instrument control system.

(1) Active conversion:

During the surgery, surgeons may encounter some situations that make them impossible to keep the operation going such as severe adhesion, anatomical variation or failing to expose the surgical site. Or when surgeons are dissociating the tissue, they have difficulties to find certain important vascular structure and to make a normal anatomy of the clearance. At this point, surgeons initiatively decide to convert to a laparoscopic surgery.

(2) Passive conversion:

During the surgery, some unexpected accidents happen and surgeons have to convert to laparoscopic surgery. Usually these accidents include injury of tissues and organs, unstoppable bleeding, and difficult suture using the surgical robot. Passive conversion is related to surgical techniques of the surgeons. With the experience accumulating and the operative skill improving of surgeons, the passive conversion rate will decrease significantly.

(3) Malfunction of the endoscopic instrument control system:

Serious malfunction of the test product may occur during the surgery (such as strong interference between the console and the operative part, the operative arm dysfunction and can't be repaired by resetting, surgical instrument can't loosen the tissue, etc.) The operation is unable to continue, so surgeons have to convert to laparoscopic surgery. Usually the malfunction is caused by unreasonable design, unqualified instruments or inappropriate operation of the product arms. It indicates the deficiency of the test product.

Notes:

1) Surgical success is defined as the successful completion of all surgical operations through the experimental products or the control products.

2) Surgical failure is defined as the unaccomplishable surgical operations using the experimental or control products as planned. The reason includes passive conversion and malfunction of the products. Noticeably, active conversion does not mean a surgical failure.

8.2 Secondary outcome measures:

(1) The breakage rate of gallbladder:

The breakage rate of gallbladder is defined as the proportion of the subjects in the experimental group or the control group with specimen breakage.

(2) Comprehensive Complication Index (CCI)

CCI is calculated using online tools provided by <http://cci.assessurgery.com>. Based on the Clavien-Dindo complications grade system (appendix.1), all complications and adverse events after surgical intervention are taken into consideration. The overall incidence is measured on a scale ranging from 0 (no complication) to 100 (death).

(3) Operative time (min)

The length of time from the beginning of the operation after the robot installation to the end of the suture of the incision.

(4) Intraoperative bleeding (L)

The total bleeding volume from the beginning of the operation to the end of the suture of the incision. It can be calculated by measuring the blood volume in the vacuum suction device and weighing the gauze after using them to wipe the bleeding.

(5) Postoperative pain

Postoperative pain is assessed by visual analogue scale (VAS) 24-26 hours after the operation, ranging from 0 (no pain) to 10 (maximum pain).

(6) Time to first flatus (h)

The time from the end of the operation to the subject's first flatus after surgery.

(7) Surgeon's satisfaction

After the operation, surgeons fill a questionnaire to score the flexibility, intuition and stability of the products, as well as their sense of delay and fatigue when using the products. Each question in the score ranges from 1 to 5 points and the total score is 100.

(8) Installation time (min)

The time from the power-on of the products to the end of the connection between trocars and the operative arms.

(9) Hospital stay (days)

The total hospital days of subjects from admission to discharge.

8.3 Selection criteria of surgeons

In order to strictly guarantee the homogeneity of the surgeons, they need to meet a certain standard. Generally, they are required to have more than 5 years of endoscopic surgery experience and more than 1 year of robotic surgery experience, and have passed the test product training and obtained the operation training certification.

9. Safety evaluation

9.1 Safety evaluation indicators:

- (1) The incidence of organ and vascular injury events which include the following:
 - 1) Any damage to the adjacent organs (liver, spleen and intestine) due to the malfunction of the products.
 - 2) The blood vessel injury caused by the malfunction of the products during the operation resulting in massive bleeding.
- (2) The incidence of adverse events from the end of the operation to discharge.
- (3) The incidence of the malfunction of the products which includes the following:
 - 1) The connection between the console and the operative arms receives strong interference, which cannot be solved by resetting.
 - 2) The tissue cannot be loosened when the surgical instrument is clamped.
 - 3) Device installation false alarm.
 - 4) Failure or damage of the surgical instruments during an operation.
- (4) Vital signs: temperature, heart rate, respiration, and mean arterial pressure.
- (5) Laboratory examinations: blood routine, liver and kidney function, and electrolytes.

9.2 Indicators measurement methods

- (1) Vital signs: Twice a day before surgery, twice at the beginning and end of the operation, and twice at 3-5 days after the operation. Six times in total.
- (2) Laboratory examination: once before the operation and once within 3~5 days after the operation. At least twice in total.

10. Procedures

10.1 Records needed before starting

- (1) Basic information of subjects: the gender, height, weight and vital signs, etc.
- (2) Medical history: course of disease, severity of illness, medication, and previous surgical history.
- (3) Informed consent form.
- (4) Electrocardiogram.
- (5) The imaging examination: color ultrasound of liver, bile, pancreas and spleen and electronic gastroscopy. For subjects who are more than 50 years old, heart ultrasound and neck vascular ultrasound are needed.
- (6) Laboratory examinations: blood routine, liver and kidney function, coagulation function and electrolytes.

10.2 Standard operating procedures

- (1) Examining the console: appearance inspection, instrument performance, screen display and technical index.
- (2) Examining the operative arms: appearance inspection, movements, instrument performance, and technical index.
- (3) Connecting the endoscopic instrument control system and preparing the initialization of the system for a few seconds.
- (4) Starting the operation: anesthesia, position adjustment, pneumoperitoneum, setting trocars, and 3D laparoscopic light source.
- (5) Brief procedures of the operation:
 - 1) The surgeons control the operative arms to grab the neck of the gallbladder or Hartmann's fossa with the bipolar electric knife and pull it to the upper right.
 - 2) The surgeons use the electric hook to dissociate the serosal membrane of gallbladder tube, make blunt dissection of gallbladder tube and gallbladder artery, and pay attention to distinguish common bile duct and common hepatic duct.
 - 3) The surgeons use hemo-lok clips to clamp the tube as close as possible to the neck of the gallbladder, and cut with surgical scissor between two hemo-lok clips.
 - 4) The surgeons clamp the neck of the gallbladder and pull upward. Simultaneously, we use ultrasonic knife to carefully detach along the gallbladder wall. The assistant should pull gently to hold the tension between the gallbladder and liver, which makes it easier to detach.
 - 5) After fully dissociation of the gallbladder, the surgeons take it out of the abdominal cavity through the 12mm trocar. Then we check if there is any bleeding or leakage before withdrawing orderly.
 - 6) The surgeons suture the surface wounds and turn down the products.