Comparison of perioperative outcomes between bipolar sealing device and ultrasonic shears during laparoscopic gastrectomy for early gastric cancer

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Study Institution: Seoul National University General Surgery
Study in charge: Seong-Ho Kong

Study Summary

Study title	(Korean) **위암 환자의 복강경 위절제술에서 에너지 기반 절단기구 간의 비교 연구**
	(English) **Comparison of perioperative outcomes between bipolar sealing device and ultrasonic shears during laparoscopic gastrectomy for early gastric cancer**
Study in charge	Seong-Ho KONG, associate professor, Seoul National University Hospital
Fund support	Medtronic, Inc

Study purpose	The purpose of this study was to compare the perioperative outcomes for patients including inflammatory response of energy-based shears devices used in laparoscopic gastrectomy for early gastric cancer.
Study design	A randomized comparison between three groups by single blind method.
Study period	IRB approval date ~ 4 years
Study Subject (Clinical trial drug etc)	Preoperative gastric cancer in the middle or lower part of stomach, which is expected to be 1 stage.
Number of subjects	189 people (3 groups x 63 people)
Vulnerable subjects	No applicable
Study Method	Three energy-based devices were randomly assigned to the group of patients with early gastric cancer in the lower or middle part of stomach, followed by laparoscopic distal gastrectomy by single blind method. Main analysis group Group A: Ultrasonic shears Group B: Bipolar electrocautery Explorative analysis group Group C: Hybrid devices
Validity evaluation	Primary evaluation index: Serum CRP after 2 days of post-operation Secondary evaluation index: Serum IL-6, IL-10, Amount of Indocyanine green in the peritoneal cavity after surgery, which is injected submucosally before dissection

Safety evaluation	Second Evaluation Index: 1. Blood loss during surgery 2. Complications within 30 days after surgery
Possible effects and outcomes	The purpose of this study was to investigate the perioperative outcomes of different types of energy-based devices which are considered as the most important factor for laparoscopic gastric cancer and to provide scientific basis for selecting safe and effective surgical devices for gastric cancer.

Study Plan

1. Study title

Comparison of perioperative outcomes between bipolar sealing device and ultrasonic shears during laparoscopic gastrectomy for early gastric cancer.

2. Study institution and address

Study Institution	Address
Seoul National University Hospital Stomach, GS, Cancer Research Center	Seoul National University Hospital, 101 Daehak-ro, Jongro-gu, Seoul
Seoul National University Bundang Hospital GS	Seoul National University Bundang Hospital, 82 Gumi-ro 173 beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do

3. Names & Title of study in charge & co-researchers

1) Study in charge : Seong-Ho, Kong, Seoul National University Hospital, Stomach, GS, Clinical Associate Professor

2) Co-researchers :

	Hospital	Specialty	Title	Name
Co-researcher	Seoul National University Hospital	Surgery	Professor	Han-Kwang Yang
Co-researcher	Seoul National University Hospital	Surgery	Professor	Hyuk-Joon Lee
Co-researcher	Seoul National University Hospital	Surgery	Professor	Do Joong Park
Co-researcher	Seoul National University Hospital	Surgery	Fellow	Ji-Hyeon Park
Co-researcher	Seoul National University Hospital	Tumor biology	Researcher	Eunhee Koo
Co-researcher	Seoul National University Hospital	Tumor biology	Researcher	Hyun Myong Kim

Clinical trial manager	Seoul National University Hospital	Surgery	Research coordinator	Dan Bi Lee
Clinical trial medical device manager	Seoul National University Hospital	Department of Nurse	Nurse	Yu Hee Shin
Co-researcher	Seoul National University Bundang Hospital	Surgery	Professor	Hyung-Ho Kim
Co-researcher	Seoul National University Bundang Hospital	Surgery	Professor	Sang-Hoon Ahn
Co-researcher	Seoul National University Bundang Hospital	Surgery	Professor	Young-Seok Park
Co-researcher	Seoul National University Bundang Hospital	Surgery	Professor	Yun-Suhk Suh
Clinical trial manager	Seoul National University Hospital	Surgery	Research nurse	Mi-Sook Chang
Clinical trial manager	Seoul National University Hospital	Surgery	Research nurse	Ga-Yeong Shin

3) Study in charge :

- **Seong-Ho Kong, Clinical Associate Professor, Department of Surgery, Seoul National University Hospital**
- **Sang-Hoon Ahn, Clinical Assistant Professor, Department of Surgery, Seoul National University Bundang Hospital**

4) Clinical trial drug management pharmacist / Clinical trial medical device manager

Hospital	Department	Title	Name
Seoul National University Hospital	Department of Nurse, Operating Room D4	Nurse	Yu Hee Shin
Seoul National University Bundang Hospital	Department of Nurse, Operating Room	Nurse	Eun Hye Gil

4. Research request institution : Not applicable

5. Fund support

Medtronic, Inc.

6. Predicted study period

IRB approval date ~ 5 years

7. Target disease

Gastric Cancer

8. Study background and aim

1) Study background

(1) Background of diseases and standard treatment

Gastric cancer is one of the highest incidence and mortality cancer worldwide. The primary treatment for gastric cancer is surgical resection, and surgical resection for gastric cancer without distant metastasis is recommended by the Korean Gastric Cancer Society, the Japan Gastric Cancer Society, and the NCCN.

In gastric cancer, primary standard treatment or surgical bleeding, leakage, obstruction, perforation, surgical site infection and general anesthesia are still considered as negative factors for surgery. Also, open surgery increases the risk of bleeding compared to minimally invasive procedures including laparoscopic surgery. In addition, in some studies, D2 lymphadenectomy has been reported to be more risky in surgical complications than D1 lymphadenectomy. The gastric resection which is considered as one and only cure for gastric cancer as well as the surgical methods for minimizing surgical complications, mortality rate and hospital stay have been continuously studied and developed, and the development of surgical devices which can be used more safely and effectively help the surgeons at the same time.

(2) The use of energy-based shear devices in GS surgery

Harvey Williams Cushing firstly used electrosurgery for NS surgery and electrocautery has been widely used in the operating room due to the effectiveness of simultaneous dissection and hemostasis. Monopolar is a type of electrocautery which has a pencil or needle-shaped active electrode and attaches a grounding electrode to the patient's body so that the current from the active electrode can escape from the patient's body. If unipolar is used, current from the active electrode can irritate or unintentionally damage surrounding muscles and nerves, and electrical systems such as cardiac pacemakers and cochlear implants.

Ultrasonically activated shears (UAS) are devices which use ultrasound energy instead of electrical energy to destroy hydrogen bonds in proteins and modify tissue proteins at the time of dissection or hemostasis of tissue. Modified proteins produce sticky clot. The heat generated by the UAS is approximately 80 °C, which is lower than the heat generated by the general electrocautery 150~400 °C. It decreased the range of thermal injury to surrounding tissue. However, the temperature of occurrence may be increased and it can damage to surrounding tissues if you use the device more than 10 seconds at one time. Advantages of USA are shortened operative time, reduced bleeding during surgery, and relatively low normal tissue damage.

An advanced bipolar sealing device is used to coagulate proteins by passing bipolar electrical energy through the blades of the operative site and to dissect the center of the

solidified tissue with a blade at one time. In previous laboratory studies, there was report, saying that no significant difference in the extent of heat spread to the surrounding tissue between the ultrasonic shears and the bipolar sealing device, but the bipolar sealing device is generally able to dissect longer tissue at one time, so that the degree of heat spread to the surrounding tissue may be less than the ultrasonic shears.

(3) The results of the research team

I. According to a study of 56 patients in 2011-2012 named "energy-based device in open gastrectomy for gastric cancer" (IRB No. H-1004-004-068), the amount of hemorrhage with the use of ultrasound shears was reduced compared to the group of using unipolar electrocautery. There was no significant difference in the inflammatory response.

II. A study of 17 patients in 2014-2015 named "single-group clinical study to evaluate the efficacy and safety of articulating bipolar vessel sealer system in robotic gastrectomy for early stage of gastric cancer" (IRB No. 1404-129-574)" results postoperative inflammatory reaction and albumin loss were significantly less in the group of advanced bipolar electrocautery than the group of ultrasonic shears.

2) Research hypothesis and purpose

According to our preliminary results, advanced bipolar electrocautery in laparoscopic gastrectomy is expected to lower the peritoneal and systemic inflammatory response, which is reflected in serum CRP 2 days after the surgery, compared to the ultrasonic shears or the hybrid device. Hybrid device are expected to produce results similar to USA when considering the operating feature and heat generated; however, there is no previous study with hybrid device. We intend to conduct exploratory data collection and comparison with hybrid device.

The aim of this study was to evaluate the effects of energy-based shear devices used in gastric surgery on patients including postoperative inflammation.

9. Code name of the test drug, general name of the main ingredient, drug substance and its amount, dosage form, etc.

Authorization Number (Rate)	A35025.01 (2)
Product	HARMONIC® HD 1000i Shears, HARHD20 & HARHD36
Feature	curved shears, 36cm shaft length

Effect	A device used for the incision or coagulation of soft tissue in the surgery of general surgery, plastic surgery, pediatric surgery, obstetrics, urology, thoracic surgery, orthopedic surgery (spine and joint operation), etc.
Manufacturer	Ethicon Endo-Surgery, Inc (America)

Authorization Number (Rate)	A350525.01
Product Name	Ligasure Maryland
Feature	curved shears, 23 cm shaft length
Effects	Electrodes used for dissection and coagulation of human tissue and blood vessels during operation, which is connected to electric energy source
Manufacturer	Medtronic, Inc (USA)

Authorization Number (Rate)	A35010.01
Product Name	Thunderbeat
Feature	curved shears, 23 cm shaft length
Effects	A device that can suture and incise tissue and blood vessels during surgery by using high frequency electrical output and ultrasonic vibration at the same time.
Manufacturer	Aomori Olympus Co.,Ltd Olympus Winter & Ibe GmBH

1) Subject for trial mediation (surgical method, diagnosis method, etc.)

(1) Mediation subject and diagnosis method:

A case of primary gastric cancer diagnosed as pathologically adenocarcinoma through endoscopic biopsy,

(2) Mediation procedure:

i. Under general anesthesia, insert 1 to 5 trocars around the navel and epigastrium and make a space with carbon dioxide. Laparoscopic distal gastrectomy and lymphadenectomy are performed using a randomly assigned energy-based shears.

ii. Omentectomy: Partial resection

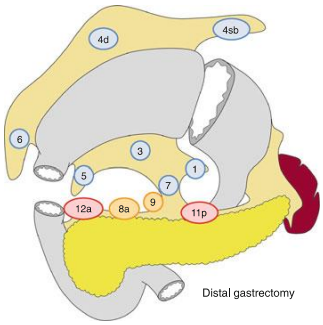
iii. Gastric resection range: Perform a conventional distal gastrectomy to resect approximately 1/2 - 2/3 of the upper stomach.

iv. Lymph node dissection: D1 + lymph node dissection is performed according to the

Japanese Gastric Cancer Treatment Guideline 3rd edition. (Lymph node dissection zones # 1, # 3, # 4d, # 4sb, # 5, # 6, # 7, # 8a, #9) (image1)

2.3.1.2 Distal gastrectomy

D0: Lymphadenectomy less than D1
D1: Nos. 1, 3, 4sb, 4d, 5, 6, 7
D1+: D1 + Nos. 8a, 9
D2: D1 + Nos. 8a, 9, 11p, 12a.



(image 1). Distal Gastrectomy and Lymph Node Resection Range

v. The following ae the resection procedures using medical devices
   ① Omentectomy
   ② Dissection and ligation of blood vessels and lymph nodes supplied to the lesser curvature and the greater curvature
   ③ Approach and dissection of the right gastroepiploic artery (mesocolon seperation)
   ④ mobilization between duodenum and pancreas
   ⑤ Pylorus and hepatic artery dissection
   ⑥ Lymph node dissection along the pancreatic duct
   ⑦ Lymph node dissection along the diaphragm's crus

vi. The following blood vessels are ligated by clip in common to the three groups.
   ① Superior artery, left artery
   ② superior mesenteric artery, left superior mesenteric artery

vii. anastomosis: Perform intracorporeal or extracorporeal in gastroduodenostomy, gastroenteroanastomosis or Roux-en-Y

viii. Proof of operative range: Based on photographic records of the scope of lymph node resection and the pathology records of the number of resected lymph nodes in each lymph node group after gastrectomy.

ix. Drainage tube: JP (x1). Locate in the lower left lobe of the liver along the right abdominal wall.

x. Nasogastric tube: Can be used if needed. If there is no evidence of bleeding after

surgery, remove it within 1 day after surgery.

10. Selection Criteria, Exclusion Criteria, Number of Targeted Subjects, and Basis for Calculations

1) Selecting Criteria

(1) Patients with pathologically proven primary adenocarcinoma.

(2) Patients who are expected to R0 resection for the purpose of cure by distal gastrectomy.

(3) Patients with the 1st stage of the preoperative clinical stage; the 7th edition of AJCC / UICC TNM staging system (T1N0, T1 & borderline lymphadenopathy, T2N0 in preoperative gastroscopy, gastroscopy and abdominal computed tomography) Patient scheduled for gastrectomy in Seoul National University Hospital

(4) 20~80 years old

(5) Outpatient follow-up should be possible for 30 days after surgery, and there should be no problem in communication with the patient.

(6) Patients who agreed to participate in the trial in paper.

(7) Patients with the CRP ≤ 1.0mg/dl before surgery.

2) Exclusion Criteria

(1) Patients with a history of upper abdominal surgery.

(2) Patients with prior therapy for gastric cancer (chemotherapy, radiotherapy). (except ESD)

(3) Patients who should undergo other long-term merger resection during distal gastrectomy. (except cholecystectomy)

(4) Patients with significant ascites by CT.

(5) Patients with cirrhosis in CT brfore surgery

(6) Patients with heart disease (history of uncontrolled hypertension, angina or coronary artery disease, history of cardiac muscle disease, Ejection Fraction <50%)

(7) Patients with inappropriate renal function (serum creatinine > 1.4 mg/dL or BUN > 26 mg/dL)

(8) Patients with abnormal coagulation (PT INR > 1.2 or aPTT > 45 sec)

(9) Uncontrolled diabetic patients

(10) Inflammatory bowel disease patients including Crohn's disease, ulcerative colitis, tuberculous enteritis

(11) Patients taking aspirin or platelet inhibitors within 5 days before surgery

(12) Patients taking anticoagulants

(13) Patients with the history of steroid use which needs stress dose inoculation

(14) Pregnancy

(15) Other patients who are deemed unable to participate in the clinical trial by the tester

(16) History of sensitivity to iodine, in case the test using indocyanine green is applied

(17) Previous history of gout

3) Target number of subjects and basis of calculation

Total target number : 189, competitive enrollment at SNUH and SNUBH

Calculation methods of the subjects

Primary evaluation variable: Cerum CRP value on Post-op 2nd day

Subjects of the study

Main analysis group

A. Ultrasonic shears

B. Bipolar sealing device

Explorative analysis group

C. Hybride device

Study hypothesis:

- Null hypothesis: No difference in CRP value on post-op 2nd day between two groups.
- Alternative hypothesis: Difference in CRP value on post-op 2nd day between two groups.

Hypothesis for calculation of number of subjects:

(1) Level of significance, $\alpha = 0.05$

(2) Ratio between groups, group A: group B = 1:1

(3) Type 2 error (β) is 0.20, retaining power of the test at 80%

(4) Ultrasound dissector and Bipolar's post-op's CRP average and standard deviation was 11.5 ± 6.6 and 8.0 ± 2.8 from preceding research of "Research of availability and safety in using Articulating bipolar vessel sealer system in early Robotic gastrectomy in early stage gastric cancer". Subjected patients were 17, small in numbers and it was for Robotic LAP surgery, not conventional LAP surgery. Therefore, to avoid chances for reflecting not enough subjected patients, we have calculated subjected patient numbers from conservative standard deviation.

Program used for calculation: PASS (Power Analysis and sample size software; http://www.ncss.com)

Calculation result of study subject number:

Group Comparison	Group 1		Group 2		Subject number of each group	Total subject number with 10% omission rate
	Mean	Standard deviation	Mean	Standard deviation		
A vs B	**11.5**	**6.6**	**8.0**	**6.6**	**57**	**189**

** Total subject number with 10% omission rate = subject number of each group / 0.9 * 3*

The primary concern of this study is to compare ultrasonic shears (A) and advanced bipolar Sealing device (B). Hybrid instrument (C) is expected to have similar temperature from its operating features even though there is no previous trustworthy research. We have decided total of 189 target patients, same numbers in A and B in order to contrast balance weigh in equal condition.

4) Study subjects invitation plan

Invitation will be made to patients, satisfying selection/exemption criteria among those who are gastric cancer patient visiting Gastric Cancer Center in Seoul National University Hospital or hospitalized gastric cancer patient who requested gastric cancer treatment to the study research team. Invitation will be explained verbally, with a consent form.

11. Research method

1) Research method in detail

Under general anesthesia of the patient, satisfying selection/exemption criteria, the subject will be appointed to the each study group of 1:1:1 ratio and the surgery will only use an energy-based device of each selected group. The patients will be randomized using web-based program, which will be generated by medical research collaboration center (MRCC), Seoul National University Hospital. Institutes and the presence of incision during anastomosis (intracorporeal or extracorporeal anastomosis) will be the stratification factors during randomization. Blood loss, blood transfusion volume, operation time, cytokines and others will be measured during the operation and amount of drainage, laboratory test and adverse reaction will be post-operatively observed and accessed. Unless follow-up or extension of admission is needed due to the adverse reaction, patients will be discharged during the post-op 5-10 days. Follow-up will be made until the first out-patient visit after 2-3 weeks of discharge.

(1) Evaluation criteria during operation

① Blood loss during operation: Output-input.

The blood loss will be measured with sum of absorbed blood in gauzes and absorbed amount using inhalator.

Absorbed blood in gauze: measure weight of the gauze before the operation then calculate the difference after the operation.

Absorbed amount of blood using inhalator: blood collected in the inhalator bottle will be moved to the 50cc syringe then the amount of blood will be measured. If saline is used for wash out operation region during the operation, that amount will be omitted.

② Operation time

③ Transfusion volume

(2) Pre- and Post- operation management

i. Within a month from the date of operation: A laboratory test (CBC, admission panel, CRP, triglyceride, amylase, PT, aPTT), age, medical history, ASA classification, weight, height.

ii. 1 day before operation: bowel preparation (empty stomach and enema): use of a laxative before operation (Mg. citrate powder intake, suppository bisacodyl 10mg) and suppository glycerin enema and bisacodyl 10mg on the day of operation.

iii. low molecular weight heparin (LMWH): to prevent DVT, hypodermic medication of 20mg 1 time/ 1day may possible after 2 ~3 days post operatively.

(3) Post-operative evaluation

① PCA (patient controlled analgesia): includes Morphin and fentanyl. When need additional pain control, Nalbuphin (IM) or Fentanyl patch will be used

② From POD 1 to 4, VAS pain score will be measured daily.

③ Gas out, day of starting liquid diet will be recorded

④ Complications: Within the follow-up period, from the end of operation to 2-3 weeks after discharge, patients will be monitored to check for complications and mortality before POD 30. Complications will be measured by Clavien-Dindo classification. Any reasons for re-admission through an out-patient clinic or emergency during the follow-up period will separately be recorded.

(4) Laboratory test

i. POD 2, 4: Blood test (CBC, admission panel, CRP, triglyceride, amylase)

ii. POD 2: Amylase and triglyceride test in the drain. Measurement of drainage by 1-3 days after surgery

iii. Cytokines Test:

- Serum IL-6, IL-10: Obtain peripheral blood in 5ml bottle of EDTA bottle : just after the induction of the anesthetia, 2-3 hours after the end of the operation, the 2nd post-operative day, and the 4th post-operative day.

- EDTA bottle is centrifuged at 3000 rpm for 15 minutes as soon as possible after collection. It is divided into 200ul each, and then cytokine assay is asked to clinical research laboratory. On holidays when it is difficult to conduct the test, it is centrifuged, stored at -80 °C and analyzed at the day available.

(5) Evaluation of the sealing potency of each instrument using indocyanince green (ICG)

i. Limited to the patients enrolled in Seoul National University Hospital

ii. ICG (2.5 mg/ml, 1ml at each point) will be injected to the submucosal layer of 2 parts of the lesser curvature (antrum, angle) and 2 parts of the greater curvature (antrum, lower body) of the stomach, at the beginning of the operation under general anesthetia. Presence of leakage will be checked by the laparoscopic view.

iii. Irrigation during the operation is discouraged as much as possible. Used gauze pieces are preserved in the dark container. The gauze used before LN#1 dissection is collected separately with the gauze used in LN#1 dissection.

iv. The gauze used before gastrectomy is opened and taken with a SPY® near-infrared camera. Especially, the gauze used in LN#1 dissection is checked separately.

v. The gauze used after the photographing is put into 200 ml of 70% alcohol and stored for 10 minutes in a shade state to extract ICG from the gauze. Then shoot with a near infrared camera.

vi. The brightness of the fluorescence in the photographed image is calculated with the image analysis program.

2) Comparison group setting and random assignment method

- This clinical trial was designed to prevent bias that could be involved in assigning registered clinical trial subjects to each group and to identify characteristics of known or unknown subjects that could act as a confounder in evaluating their treatment effects (Eg, demographic characteristics and baseline characteristics) to increase the likelihood of a balanced

distribution between the two groups, thereby increasing the comparability of the three groups and randomizing to select the three groups from the same group.

- At the time of the clinical trial registration, the subjects who signed the consent form can only be identified by the initial name, and the subject will be given a consecutive subject screening number by the researcher.
- After the screening number was assigned, the subjects who satisfied all the inclusion criteria and were not eligible for any exclusion criterion were judged to be suitable for the study. After the insertion of the laparoscopic trocar under general anesthesia, (Eg, after a confirmation of unexpected intraperitoneal or severe adherence do not exist), randomization should be performed. A randomization number (patient ID) will be awarded in a strictly sequential manner in accordance with the randomization table generated by the medical statisticians in advance.
- The randomized method uses a centralized stratified block randomization method to ensure a balanced distribution among the three groups. Institutes and the presence of incision during anastomosis (intracorporeal or extracorporeal anastomosis) will be the stratification factors.
- If a clinical trial subject discontinues clinical trials, the random assignment number assigned to the subject will not be re-used and the subject will not be able to participate in the trial again.
- The trial will be conducted with a single blind spot. Therefore, the practitioner knows the contents of the randomization, but does not disclose the contents of the clinical trial subjects for about 4 weeks after the end of the clinical study.

3) How to use test medical device, combination therapy, reasons for selection when using treatments

Energy-based devices are used in accordance with the manufacturer's manual and the commonly used principles of laparoscopic surgery, and the sites of use during surgery are as described in above 9-1)-(2).

4) Observation items, clinical examination items and observational examination methods

(1) Primary endpoint: Serum C-reactive protein (CRP) at POD 2

(2) Secondary endpoint:

- Blood loss during operation, amount of blood transfusion

- IL-6, IL-10 in serum and ascites at 2-3 hours after surgery and POD 2, 4
- Complication within 30 days after surgery, mortality rate
- At 4 days postoperatively, serum CRP
- Postoperative visual pain score (VAS score)
- The timing of gas release after surgery, start time of liquid diet
- Length of stay, re-admission, emergency room visit and reasons
- Amount of drainage after surgery
- Concentration of triglyceride and amylase in drain
- Amount of Indocyanine green in the peritoneal cavity after surgery, which is injected submucosally before dissection (only in Seoul National University Hospital)
- Number of resected lymph nodes

item	Pre-Op (Baseline)	Immediately after opening abdomen	Intra-Op	POD (Post Operative Day)						1st outpatient visit after discharge	End of study/ Early termination
				2-3hr	#1	#2	#3	#4	Discharge		
Informed consent[1]	✓										
Selection/exclusion criteria	✓										
Demographic information	✓										
History, ASA	✓										✓
Physical examination, weight	✓										✓
Random assignment		✓									
Lab (cbc, admission panel, amylase, CRP[2], triglyceride[3])	✓					✓		✓		(✓)	
Blood cytokine[4]		✓		✓		✓		✓			
JP drain amount					✓	✓	✓				
JP drain TG, amylase						✓					
ICG concentration[5]			✓								
Operation[6]											
Blood volume			✓								✓
Operation time			✓								✓
Amount of blood transfusion			✓								✓
Surgical information			✓								✓
Analgesic medication (excluding PCA)					✓	✓	✓	✓			
VAS pain score	✓				✓	✓	✓	✓			
Gas out day									✓		
Soft diet starting date									✓		
EGD, EUS,CT	✓										
Hospital stay count									✓		✓
Pathologic result confirmation	✓								✓	✓	
Adverse events[7]			✓	✓	✓	✓	✓	✓	✓	✓	✓
Follow-up visit										✓	

[1] All procedures, including selection / exclusion criteria, may be initiated after voluntary written consent has been obtained from the subject. If surgery is not performed within thirty days after obtaining the consent form, the procedures for rehabilitation shall be carried out.
[2] CRP was further examined within 2 days before surgery
[3] Triglyceride is examined by the researcher's option on the first outpatient visit after discharge
[4] After patient anesthesia in the surgical field, blood is drawn through the A-line.
[5] Only for Seoul National University Hospital
[6] Surgery is performed according to standard surgical guidelines.
[7] Adverse events are evaluated up to POD # 30.

4-1) Baseline before surgery

1) Subject consent form
2) Demographic information
3) Detailed medical history
4) Significant medication or operation history
5) Physical examincation
6) Laboratory test : CBC, PT, aPTT, BUN, Triglyceride, Albumin, Total bilirubin, Creatinine, CRP, Amylase, – use the test results within 30 days before surgery
7) Concomitant medication (including drugs within the past week)
8) EGD, EUS, CT use test results within 2 months from the scheduled date of surgery.
9) Measure VAS score on the day before surgery.

4-2) operation day

1) Randomization: prior to surgery.
2) Operation method: Lymph node dissection range (D1+) and removed lymph node area, mating method, etc. are recorded; and the ablation range is left as a photograph.
3) Volume of blood loss
4) Operation time
5) Volume of blood transfusion
6) Cytokine test : as described in 11-1)-(4)
7) ICG measure : as described in 11-1)-(5)
8) Adverse reaction

4-3) POD 1 ~ discharge date

1) Amount of drainage: measured in 24 hour unit
2) Number of lymph nodes removed
3) Amount of blood transfusion
4) Adverse reaction
5) Laboratory test (POD 2, 4): serum CBC, admission panel, CRP, triglyceride, amylase, IL-6 and IL-10
6) Triglyceride and amylase from JP drain (POD 2)
7) Date of gas out and initiation of soft diet
8) Complications

4-4) Follow-up: first outpatient visit after discharge (3-4 weeks after surgery)

1) Adverse reaction
2) Complications
3) Re-admission or emergency visit record and reason

4-5) unscheduled evaluation and early termination:

- If an evaluation of the subject is performed at an unscheduled point of time, record the evaluation items such as adverse reactions, dropouts, clinical measurement results, and medical treatment.
- For those patients who have dropped out, the evaluation items should be measured at the time of withdrawal.

5) Differentiation from existing treatments and research

Many of the existing studies comparing energy-based devices have been performed in laboratories; so there has been a limit to assessing the effects of surgery on patients. The purpose of this study was to evaluate the effect of each surgical instrument on the patients in stomach cancer surgery, especially for lymphadenectomy and hemostasis.

6) Benefits and risks of the subject

The energy-based devices used in this study are the devices commonly used in stomach cancer surgery with the approval of the Ministry of Food and Drug Safety. The side effects and risks that may occur in this study are expected not to go beyond the range of complications that are expected to occur in stomach cancer operation, not due to the malfunction of the energy-based resection mechanism. Thus, the additional risk of participating in the study by the study participants does not outweigh the risks in general gastric cancer surgery. On the other hand, if energy-based resection devices have different effects on the subjects of clinical studies, it can provide a basis for surgeons to select surgical instruments used for gastric surgery.

7) Stop/drop criteria

If known to have violated the plan during the course of the trial, the tester should determine whether the subject should continue or discontinue the trial. In addition, the case record should contain details of the violation of the plan and its reasons.

7-1) Clinical trial stop

If the situation observed during the clinical trial is judged to be unacceptable to proceed with the clinical trial, the person responsible for the clinical trial should ask the clinical trial screening committee to suspend the clinical trial. In accordance with the decision of the clinical trial committee, it can stop. If the clinical trial is discontinued, the person responsible for the trial should notify the clinical trial committee about suspension as well as in written form

7-2) Dropout criteria

Details of reasons for suspension and withdrawal due to non-conformity are recorded in the case record.

Subjects who have been randomly assigned but have not completed this trial for any reason are classified as 'withdrawal'. If the tester decides that the subject is required or should be dropped, the subject may be withdrawn at any time.

The reasons for the dropout are as follows

1) If the subject or legal representative requests to stop participating in the clinical trial.
2) Surgery, drugs, or other medical equipment used in combination, which may affect safety and efficacy.
3) If non-resection operation is performed
4) If the subject does not comply with the instructions of the tester or does not comply with the items indicated in the consent, it affects the evaluation of the effectiveness rate.
5) If the subject dies due to a cause not related to the clinical trial.
6) In case of violation of the selection exclusion criterion, however, in case of merging and resection surgery other than distal gastrectomy is performed, it is not categorized as withdrawal and analyzed as ITT group not the PPT group.
7) If the examiner finds that it is difficult to continue the examination.

7-3) Treatment of dropouts

If the subject is withdrawn, record the reason for the withdrawal and records related to the clinical trial conducted before the withdrawal. The final evaluation should also be done for the dropout subjects. Data on dropouts are included in the safety and efficacy assessment statistics unless there are good reasons or justification.

The missing subjects cannot be re-enrolled.

8) Standards, evaluation methods and reporting methods for safety including side effects

In this study, we will evaluate the following postoperative complication, this is not different from the complications that usually occur in stomach cancer surgery. Evaluation of complications and confirmation will be performed according to the following items and will be graded according to

the Clavien-Dindo classification. The incidence of complications among the groups will be compared through crossover analysis.

1) Wound infection: It refers to the case where additional wounding treatment is required to wound site due to seroma, hematoma, wound infection, wound dehiscence and wound evisceration.
2) Fluid collection / abscess: A case of abdominal abscess confirmed by abdominal ultrasonography or computed tomography of the abdomen.
3) Intra-abdominal bleeding
4) Intraluminal bleeding
5) Intestinal obstruction: Refers to a case where there is a suspicion of mechanical intestinal obstruction or a suspicion of intestinal obstruction in the absence of gas passage.
6) Ileus: Refers to the cases of vomiting during the course of the operation after the operation or difficulty in the progress of the meal, and the presence of paralytic obstruction in the abdominal plain radiograph.
7) Stenosis: Upper endoscopy or upper gastrointestinal stenosis refers to the case with anastomotic stenosis.
8) Leakage: Case where the intestinal contents are discharged into the drain tube or leaked on examination of the upper gastrointestinal tract.
9) Fistula: Refers to the case identified on the fistulogram.
10) Pancreatitis: A case in which the serum amylase level was significantly (150 or more) elevated due to symptoms indicating pancreatitis.
11) Pulmonary complications: refers to atelectasis, pleural effusion, empyema, pneumonia, pneumothorax
12) Urinary tract infection: refers to cases in which symptoms such as frequency of urination, nocturia, urination difficulty, or urinalysis show a significant increase in WBC
13) Renal dysfunction: Serum Creatinine > 1.4 mg/dL (EMR reference value)
14) Hepatic dysfunction: GOT, GPT > 100 IU/L
15) Cardiac: Clinically diagnosed as heart failure or myocardiac infarction based on symptoms and signs such as pleural effusion, hypotension, chest pain, elevated cardiac enzyme, and echocardiography
16) Endocrine: Diabetic ketoacidosis, hyperglycemic hyperosmolar state, Addison's disease, hypothyroidism, etc. Clinically diagnosed
17) Stasis: Refers to the case where food is obstructed to pass through the anastomosis, even though there is no evidence of intestinal obstruction, stenosis, leakage, or peritonitis.

18) Pancreatic leakage: A case when the amylase level of the drain tube 3 days or more after surgery exceeds 540 U/L, which is three times the normal maximum value of 180 U/L of the normal blood test (1, 3, Check on day 5).

19) Chylous ascites: Suspected when the color of a clear white fluid is found with the naked eye, and JP diagnoses that triglyceride is 110 mg/dL.

20) Deep Vein Thrombosis

21) Central venous infections

9) Evaluation standards, evaluation methods and analysis methods (statistical analysis methods, etc.)

(1) Primary endpoint: Two days after surgery, serum CRP

; Student's t test or ANOVA test was performed by using the mean of CRP value on the second day between the three groups.

(2) Secondary endpoint:

- Blood loss during operation (ml), amount of blood transfusion (pint); Output-input (ml). Gauze measures the total weight of gauze used during surgery and calculates the difference from the gauze weight measured before surgery. Inhalation volume is calculated by subtracting the amount of 0.9% physiological saline solution applied to the surgical site from the total inhalation volume.

- Serum IL-6, IL-10

Serum IL-6 and IL-10 levels were measured at baseline immediately after general anesthesia and insertion of the trocar. The mean value of serum IL-6 and IL-10 levels 2-3 hours after the operation, the 2^{nd} postoperative day, and the 4^{th} postoperative day are compared by Student's t test or ANOVA test.

- Amount of remaining ICG : Total amount of the remaining ICG will be calculated by the mean value of concentration of the ICG measuring 3 sets for each patient multiplied by 500 (ml) (600 or 700 ml for corresponding cases), and the mean value of the amount of ICG will be compared between each group using t test.

- Complications and mortality rate within 30 days after surgery: Clavien-Dindo classification is used to grade the complications of the three groups and the $\chi 2$ test is performed using the Cross Table for the frequency of complications and Grade IIIa complications. For the total complications, the Student's t test or the ANOVA test was performed using the Comprehensive Comorbidity Index between the three groups.

- After 4 days postoperatively, serum CRP, amylase, serum/ascites triglyceride: The preoperative mean value was used as the baseline and the Student's t test or the ANOVA test was performed on the mean value of the three groups at the 4th postoperative day

- Post-operative pain medication frequency: Student's t test or ANOVA test is performed on the average daily frequency of use among the three groups of non-PCA narcotic analgesics.

- Postoperative visual pain score (VAS score): The mean postoperative VAS score between the three groups is verified by Student's t test or ANOVA test.

- Post-operative transfusion, gas evacuation, liquid diet initiation: If the postoperative Hb < 8, transfusion can be performed under the judgment of the tester and record transfusion. The mean number of days from the day of surgery was verified by Student's t test or ANOVA test among the three groups.

- Length of hospital stay: The average number of days between surgery and discharge is assessed by Student's t test or ANOVA test among the three groups.

- Re-admission, emergency room visit: Within 30 days from the date of surgery, record admission / visit and evaluate complications if you are re-admitted to the hospital or visited the emergency room.

- A new version of the harmonic scalpel was introduced during the research and the target of the ultrasonic group is being studied with a new product. (Since IRB approval in July 2018)

- We will compare the results of the patients who underwent surgery in the ultrasonic group regarding to old instrument versus new instrument. In the comparison between the groups, it will be analyzed whether there is a difference between the inclusion and the non-inclusion of the subject who underwent surgery with the old apparatus. In these ways, it will be notated in the final report whether there is any influence on the results of the study by the change of the device.

9-1) General principles of statistical analysis.

A Statistical Analysis Plan (SAP) will be created before the database locks. A blinding review of the data will focus primarily on issues related to the exclusion of patient or patient data from missing and analyzed data.

The subjects to be validated for the data obtained from the subjects of the clinical trial are

classified into the ITT (intention-to-treat) analysis group and the PP (per protocol) analysis target group.

- ITT analysis group consisted of all randomized subjects after satisfying the selection / exclusion criteria.
- The subjects who underwent the PP analysis were those who completed the clinical trials of the ITT target group, and observed the primary efficacy variables as planned without violating the critical clinical trial plan. Completion of the clinical trial is defined as discharge following normal procedure without further hospitalization after surgery. Critical clinical trial protocol violations include:
  - Violation of selection / exclusion criteria
  - Random assignment violations
  - Take medication for concomitant medication
  - In case of any other serious clinical trial protocol violation
- The analysis of the basic characteristics of the patients, including demographic data and clinical history data, is evaluated using the ITT analysis group. All of the validation variables were analyzed for the ITT group and the PP group. The results of the study on serum CRP at day 2 postoperatively were used as the main evaluation group.

Safe Safety evaluation variables such as adverse events and adverse reactions are analyzed using the safety analysis target group.

- The safety analysis group consisted of all subjects who underwent randomized placement.
- Statistical tests for all efficacy / safety parameters should be performed at the 5% significance level. If the data do not meet the assumptions needed to perform a parametric test, a non-parametric test such as the Wilcoson rank-sum test is performed.

A multivariable analysis of primary and primary secondary efficacy variables is performed. Multivariate analysis uses multiple linear regression models or multiple logistic regression models depending on the type of outcome variable. The main independent variable is the test, we will include the gender and stage of the stratified variables used in randomization in the model and the perturbed variables identified in the demographic and clinical history data analyzes to control the effect. For repeated measurement data, perform a multivariate analysis using the generalized estimation equation (GEE). If a significant interaction effect is found between the treatment group and the participating laboratories and / or the treatment group and the confounding variables, the effect is controlled by including the interaction term in the multivariate model.

- The content of the pre-planned subgroup analysis to be performed in this trial is as follows:

- Gender Male Female)
- BMI (<25 / ≥25)
- Cancer stage (TNM stage)
- Operator
- In vitro / Internal Anastomosis

◆ The differences between the groups were assessed using the Student's t-test (or the corresponding nonparametric Wilcoxon rank-sum test) or the $\chi 2$ test (or Fisher's exact test, the corresponding nonparametric method) Analysis. If control of disturbance variables is required, multivariate analysis is performed.

9-2) Treatment of missing values.

In general, the missing value will be treated as a missing state, and no alternative missing statistic is used. Therefore, only observations will be used for data analysis. Discrepancies data are replaced by missing values at the responsibility of the clinical trial manager.

10) Clinical trial and treatment standard

The same type of treatment and treatment will be given to patients with general gastric cancer who are being treated at Seoul National University Hospital.

11) Study Schedule

42 months after IRB approval: registration of clinical trial subjects and clinical trials
42 months ~ 48 months: Data analysis and presentation

12. Data and Safety Monitoring Plan

1) The person in charge of monitoring

* Monitoring supervisor: Seong-Ho Kong, Associate Professor, Surgery, Seoul National University Hospital

* Person in charge of monitoring: Hwinyeong Choe, Department of Nurse, Seoul National University Hospital

2) Data and safety information monitoring items

* Study accruals item: all items in the case record of the clinical trial subject being monitored

* Safety items: adverse reactions (complications)

3) Data and safety monitoring method and cycle

Designated monitoring personnel shall be monitored to ensure the safety and data availability

of those who comply with the Clinical Trial Management Standards for Medicines (KGCP) and participate in clinical studies. The monitoring person will randomly select one person at the time of registration for the first clinical trial and every 20 people at the time of registration, confirm the completeness of the case record, clarity, check with the data base. Food and Drug Administration, Clinical Trials Review Committee, may be required to see evidence documents, case records, and other test documentation for inspection or surveillance by the implementing agency, the examiner accepts this and should always cooperate in this process.

4) Abnormal drug response report, non-compliance of study, report of unexpected problem

The researcher and the person in charge should ensure the safety of the subject. If the unexpected serious adverse reaction, serious research failure or unexpected problem occurs, the doctor or researcher who confirms it should report it immediately to the research director. The investigator reports to the IRB a report on serious adverse reactions within 15 working days of the researcher. Significant adverse events are the following adverse reactions that occur due to clinical trial medical devices:

- to cause death or life-threatening
- If you need to extend the period of hospitalization or hospitalization
- causing persistent or meaningful impairment or impairment
- If it causes birth defects or abnormalities
- Other important medical events

The tester shall record in the case record information on the date of occurrence, disappearance date, extent, treatment, progress, and the causal relationship with the clinical trial device. Whether or not there is a relation with the medical device for clinical trial is evaluated based on the following, and the opinion of the tester is described.

① Clear Relevance

- If the timing of the use of the medical device for clinical testing and the appearance of the adverse reaction is reasonable
- If the adverse event is most likely explained by the medical device for clinical use for any other reason
- Disappearing due to discontinuation of medical devices for clinical trials
- Reuse (only if reusable) Results are positive
- If the adverse event is consistent with information already known to the clinical trial

medical device or the same series of medical devices

② Multi-related Relevance

- If there is evidence that a medical device for clinical trials has been used
- If the timing of the use of the medical device for clinical testing and the appearance of the adverse reaction is reasonable
- Adverse events are more likely to be explained by the use of medical devices for clinical use than for other reasons
- Disappearing due to discontinuation of medical devices for clinical trials

③ Suspected Relevance

- If there is evidence that a medical device for clinical trials has been used
- If the timing of the use of the medical device for clinical testing and the appearance of the adverse reaction is reasonable
- If the adverse events are judged to be due to the use of medical devices intended for clinical use at the same level as other possible causes
- Disappearance of medical devices for clinical trials (if implemented).

④ Low related Relevance

- If there is evidence that a medical device for clinical trials has been used
- There are other possible causes of the adverse reaction
- If the result of discontinuing use of the medical device for clinical trials (if implemented) is negative or ambiguous
- Reuse of medical devices for clinical trials (if possible only) Results are voiceless or ambiguous

⑤ None Relevance

- If the subject does not use the medical device
- If the timing of the use of medical devices for clinical trials and the occurrence of adverse events is not feasible
- There are other obvious causes for adverse events

⑥ Unknown

- If information cannot be judged as insufficient or conflicting and cannot be supplemented

or verified

5) Study Abortion Criteria

Discontinuation of research or change of plans may be considered in the following cases.

- If the achievement of the target number of study subjects is expected to be delayed by more than one year from the original plan

- If a large number of unexpected serious adverse events occur in relation to a particular organization, determine whether to exclude studies from the study group or to the remaining groups

13. Measures to protect the safety of the subjects

1) Basic plan for securing ethics of research

This study will comply with the most recent Helsinki Declaration (revised in 2013) and the ICH-GCP, and implementation will begin after IRB approval. The types of surgical instruments used are not blindfolded. Researchers strive to minimize the effects of bias on the results of the research and strive to do their best to ensure the safety of the study subjects.

2) Consent process of the subject

In this study, the doctors included in the collaborators will explain the subject in detail of pre-screening research in a language that can be understood by the general public. The description of the study will be performed at the ward at the time of admission to the outpatient clinic or surgery, and the explanatory text and the consent form will be provided to the subject so that they can decide whether to consent for a sufficient time. During the explanation and agreement acquisition process, the research will be voluntary and will attempt to minimize the likelihood of compulsory or unjustified impact by explaining that withdrawal is possible at any time and ensuring standard best practice, whether or not the research is agreed. Consent will be obtained by voluntarily signing the consent form with the subject of the clinical study, and a copy of the statement and agreement will be provided to the subject.

3) Compensation plan of subject

This study was conducted according to standard surgical methods using medical devices that are already widely used and approved, and there are no additional outpatient visits. Therefore, there is no financial compensation for participants participating in research.

As the Cytokine test is not included in routine medical care, the research cost will be charged.

In the present study, the postoperative complications were predicted not to exceed the range of

complications after general gastric cancer surgery. However, if unanticipated adverse events are considered to be directly related to participation in the study, the reimbursement will be made as prescribed in the insurance under the Clinical Study Subject Compensation Code.

4) Personal information protection plan of research subject

- All researchers who participated in the study in the course of this study try to do their best to protect the personal information of the research subjects. Clinical research subjects should be given a separate study number that cannot be linked to personal information, and should be handled only by those responsible for recording case records and responsible researchers. The data for matching between the research number and the medical record number should be written in an encrypted Excel file and kept on the responsible researcher's computer. Only limited researchers authorized by the responsible researcher or responsible researcher Approach. All research related records, including case records, will be kept for three years from the end of the research. Of the documents that are past the retention period, personal information will be destroyed in accordance with Article 16 of the Enforcement Decree of the Personal Information Protection Act.

5) Additional protective measures if they include vulnerable subjects: Not applicable

14. Storage and Disposal considerations: Not applicable

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