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A prospective randomized study comparing electrosurgical bipolar systems versus conventional electrocautery after sentinel lymph node biopsy in obese or preoperative chemotherapy treated breast cancer patients

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Affiliation: Breast Surgery
PI: Jong-Ho, Cheun

Study protocol

1. Study name

A prospective randomized study comparing electrosurgical bipolar systems versus conventional electrocautery after sentinel lymph node biopsy in obese or preoperative chemotherapy treated breast cancer patients

2. Study sites

SMG-SNU Boramae medical center, 20, Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, South Korea

3. Principal investigator

Jong-Ho, Cheun (Clinical pf.)

4. Sponsor

None

5. Participated study period

~ 2027-04-07

6. Study disease

Breast Cancer

7. Background and Purpose

1) Background

The most common complications of breast cancer surgery are lymphorrhea and seroma. Seroma increases the length of hospital stay, the duration of outpatient treatment, and patient discomfort. Persistent seroma can lead to re-hospitalization due to wound infection caused by repeated aspirations. Seroma generally occurs in 10% to 85% of cases after breast cancer surgery. Risk factors associated with seroma or lymphorrhea identified in previous studies include age over 60, high BMI, tumor size, preoperative chemotherapy, extent of breast tissue resection, number of lymph nodes removed, and number of lymph node metastases.

Efforts to reduce seroma after breast cancer surgery include meticulous techniques such as sharp dissection, the use of monopolar energy devices, and ligation of blood vessels and lymphatics. Recently, the bipolar energy sealing system has been increasingly used. LigaSure, which uses electric energy and

pressure to denature collagen and elastin in tissue, has been shown to reduce surgical time and medical costs compared to traditional clamp-and-tie methods and advanced sealing systems in various surgeries, including breast cancer.

In breast cancer surgery, using a electrosurgical bipolar systems for ligating blood vessels and lymph nodes has several potential advantages. Traditional ligation using sutures or monopolar energy devices can be influenced by surgical technique and has drawbacks such as thermal injury to surrounding tissue. In contrast, the bipolar energy sealer applies both electric energy and pressure simultaneously, minimizing thermal injury to surrounding tissue while ensuring permanent vessel and lymphatic ligation.

A 2008 prospective study showed that using bipolar energy sealers in axillary dissection allowed for earlier removal of drains compared to conventional methods. Other studies have shown less blood loss, lower drainage output, and shorter hospital stays during surgery. Recent research has also reported new applications of bipolar energy sealers in skin-sparing mastectomy, indicating active use in breast surgery overseas. A study conducted at Severance Hospital in South Korea found that using bipolar energy sealers reduced drainage.

However, most of these studies were conducted abroad with a small number of reported cases, and the results mainly concern axillary lymph node dissection (ALND), which is where seroma is most often formed. With the decreasing trend of ALND due to advances in preoperative chemotherapy and radiotherapy, there is a lack of studies on whether using electrosurgical bipolar systems helps reduce seroma formation after sentinel lymph node biopsy.

2) Hypothesis and purpose

This study aims to determine whether the use of electrosurgical bipolar systems helps reduce seroma formation in high-risk patients undergoing sentinel lymph node biopsy (SLNB) for breast cancer surgery. The study will focus on patients who have undergone SLNB and exhibit high drainage output, particularly those who are obese or have undergone preoperative chemotherapy

8. Information and Management of Clinical Trial Drugs

Experimental Medical Devices, Interventions (Surgical Methods, Diagnostic Methods, etc.)

This study will use LigaSure™ Maryland Jaw type (LGS) (Medtronic [formerly Covidien], Minneapolis, USA) and Bovie, which are already FDA-approved and commonly used in surgeries for various cancers, including breast cancer. (LigaSure group vs. Bovie group)

9. Inclusion / Exclusion criteria

1) Inclusion criteria

- Women aged 20-80
- Candidates for breast-conserving surgery and axillary sentinel lymph node biopsy

- BMI over 25 or those who have received preoperative chemotherapy
- Overall performance status of Eastern Cooperative Oncology Group (ECOG) 0-2
- Participants who understand the study contents and can provide written consent
- Participants without evidence of distant metastasis

2) Exclusion criteria

- Those with suspected axillary lymph node enlargement or metastasis on preoperative imaging (breast MRI, chest CT, breast ultrasound)
- Among patients who had confirmed lymph node metastasis before neoadjuvant chemotherapy, whose preopreative image showed residual disease at axillary lymph node
- Those planning for mastectomy
- Those planning for axillary lymph node dissection without SLNBx
- Male breast cancer patients
- Patients with bilateral breast cancer
- Illiterate individuals, foreigners, or others who cannot read or understand the consent form
- Individuals who voluntarily decide not to participate in the study or do not sign the consent form
- Those judged by the researcher to be inappropriate for participation in this study
- Study participants who did not have a drain inserted in the surgical area
- If the randomized device is not used due to surgical room conditions (e.g., unavailability due to other emergency surgeries, device malfunction) and another device is substituted

3) Target Number of Subjects and Basis for Calculation

- 40 Participants (1:1 Random Assignment)
- Since there are no previous studies focusing exclusively on patients who have undergone sentinel lymph node biopsy, this study will initially be conducted as a pilot study. Subsequently, the amount of drainage in the participants will be calculated, and a second study will be conducted after statistically determining the sample size

4) Plan for Recruiting Study Participants

Among those diagnosed with breast cancer and operated on at the research institution, individuals who meet the selection criteria will be included. They will be informed about the study and included as participants if they voluntarily agree to participate. No recruitment notice will be used

10. Study methods

1) Specific methods

① Enrollment and screening

- The research team will explain the study to eligible participants during their consultation, and the

study will proceed only with participants who agree to participate.

② **Operation methods**

- The day before surgery, surgical instruments will be prepared according to random assignment.
- For study group participants, during surgery, electrosurgical bipolar systems will be used as much as possible for tissue dissection and vessel ligation.
- For control group participants, electrosurgical bipolar systems will not be used at all, and traditional electrocautery will be used instead.
- Participants who undergo axillary lymph node dissection (ALND) during surgery due to sentinel lymph node positivity in intraoperative frozen section analysis will be excluded from the study. Participants will also be excluded if a positive resection margin necessitates a mastectomy.
- Drains (JP) will be placed in the axillary region, and drains in the breast surgery site will be placed at the surgeon's discretion.
- Hemostatic agents like Surgicel, fibrin glue, and Hemostop will not be allowed during surgery, and anti-adhesion agents will be used for all patients.

③ **Measurements of drainage and follow-up**

- Drain removal will occur once daily drainage output falls below 30cc.
- Discharge will be determined by the attending physician, and if there are no issues with the drain, the patient will visit the clinic 7-14 days after surgery to check the drainage output.
- If the drainage output does not drop below 30cc within 7 days after surgery, the patient may be discharged with the drain and will have it removed at the clinic after a week. In this case, the patient will be instructed to record the drainage output before discharge.
- The drainage output should be recorded once or twice daily, and the daily and total outputs should be noted in the clinical records.
- Any surgery-related complications within one month after surgery will be recorded.

2) Randomization

- Randomization will be requested from Dr. Kang Eunhye, a clinical professor at Seoul National University Hospital who is not involved in this study. This researcher will pre-prepare and store the random allocation table using a stratified random number table based on obesity or preoperative chemotherapy. The research participants will be assigned to the control or test group according to the sequence in this allocation table, and the seed number required to reproduce the random number table will be recorded and stored. The researcher, being independent from the study, will not see the participants before they are enrolled in the study, and will maintain allocation concealment from the research team.

The randomization results will not be available to researchers participating in the study and will be confirmed via phone call the day before surgery.

- Even if participants are excluded because they undergo ALND through frozen section analysis during surgery, the study institution will write a screening case report form (CRF) for all participants who are enrolled and randomized. If the participant does not receive the appropriate treatment or is excluded, the reason must be clearly recorded in the CRF.

3) Plan for intervention

- Experimental: LigaSure used
- Control: Conventional Bovie used

4) Endpoint

- **Primary endpoint**

  : Total Drainage Output After Surgery (mL): The output is calculated by combining the measured amount until the drain is removed and the amount aspirated during outpatient aspiration, if performed.

- **Secondary endpoint**

  : Inpatient Drainage Output (mL): The total amount measured before the drain is removed.

  : Time Until Drain Removal (days)

  : Axillary Lymph Node Surgery Time (min): Time taken from axilla skin incision to the end of SLNB

  : Postoperative Complication Rates:

  i. Lymphorrhea: Serous drainage of more than 50mL per day.
  ii. Seroma: Aspiration drainage of more than 10mL after drain removal.
  iii. Wound Infection: Redness and pain at the surgical site accompanied by discharge or abscess.
  iv. Wound Dehiscence: Wound opening of more than 2cm.
  v. Bleeding: Bleeding requiring transfusion or reoperation.
  vi. Nerve Injury: Motor impairment of the ipsilateral shoulder/scapula and arm confirmed on electromyography.

5) Distinction from Existing Treatments and Research

Previously, Bovie was primarily used for SLNB. Existing research has focused on patients undergoing axillary lymph node dissection (ALND), but no studies have used electrosurgical bipolar systems on those undergoing SLNB.

6) Benefits and Risks to Participants

This study is a clinical trial using hemostatic devices for breast cancer surgery, which have already been approved by the FDA. There are no specific side effects or complications associated with this device. Therefore, this study is expected to pose minimal risk with no anticipated side effects

7) Criteria for Study Discontinuation or Withdrawal:

Participants will be discontinued or withdrawn from the study in cases where they do not consent to the study or if sufficient data cannot be obtained. The following cases will lead to participant discontinuation or withdrawal, with the date and reason documented in the case report form:

1. Violation of inclusion criteria or meeting exclusion criteria (including cases where the surgery plan changes to mastectomy or axillary lymph node dissection during the surgery)
2. Inability to follow up with the participant
3. Violation of the study plan by either the researcher or the participant
4. Withdrawal of consent by the participant
5. Intake of medication that may affect study outcomes
6. Other situations where the responsible party deems it inappropriate to proceed with the study

8) Safety Assessment Criteria, Assessment Method, and Reporting Method, including Adverse Events

The electrosurgical bipolar systems are medical devices registered with the FDA, and there are no specific safety concerns. In the event of any unforeseen adverse effects, we will follow the safety assessment criteria, assessment methods, and reporting procedures established by the hospital's IRB, which include adverse effects

9) Statistical Analysis Plan

- The statistical significance level will be defined as a p-value less than 0.05.
- Analyses of demographic and other baseline characteristics for continuous data will include the number of participants, mean, standard deviation, median, minimum, and maximum values. The statistical significance of differences between groups will be tested using the t-test or Mann-Whitney U test. For categorical data, frequencies and percentages will be presented, and statistical significance between groups will be tested using the chi-squared test or Fisher's exact test. Drain removal (event) and time to removal will be analyzed using the Kaplan-Meier and log-rank methods, as well as the Cox proportional hazards model.

10) Data management plan

- The data collected in this clinical trial will be stored using the screening number and allocation

number assigned in the case report form (CRF), and these numbers will be used as participant identifiers in the clinical trial database.

- Only the investigators can identify participants by linking their test data to the identification information stored. Original medical records will be kept strictly confidential.
- Data protection and privacy regulations must be followed when collecting, transmitting, processing, and storing participant data, and participants should be informed accordingly. Before starting the clinical trial, participants should be informed of the data usage and handling procedures, and written consent should be obtained.
- According to relevant regulations and guidelines, all essential documents for conducting the clinical trial, as well as all supporting documents verifying the data collected from each participant, must be appropriately and accurately maintained and stored. The investigator should keep these two types of documents for three years from the end date of the clinical trial, after which the documents can be destroyed following written approval from the principal investigator.

11) Post-Clinical Trial Care and Treatment Standards for Participants

- Standard treatment methods for breast cancer include mastectomy, radiotherapy, chemotherapy, hormone therapy, and targeted therapy. The attending physician will determine the treatment method based on the participant's clinical and pathological characteristics. Both the experimental and control groups will receive the same treatment.
- If ipsilateral lymphedema occurs at the surgical site, treatment will include physical therapy in collaboration with the department of rehabilitation medicine, along with using stockings and other aids.

12) Study plan

	Time line, months after research start						
	3	6	12	18	24	30	36
Protocol preparation							
Enrollment, operation, CRF collection							
Analysis							
Manuscript writing							

11. Measures for Ensuring the Safety and Protection of Research Participants

1) Basic Measures to Ensure Research Ethics

The study will follow the principles of the most recent version of the Declaration of Helsinki, as revised at the 64th World Medical Association (WMA) General Assembly in Fortaleza, Brazil, in 2013. In

accordance with local regulations, the clinical trial protocol and related documents will be submitted to the Institutional Review Board (IRB) before starting the clinical trial, and the trial will only commence after receiving approval. All personnel involved in the research, including the principal investigator, will comply with Good Clinical Practice (GCP).

2) Consent Process for Research Participants

Before conducting the study, the research staff will explain the purpose and method of the study to the participants (those hospitalized for breast cancer surgery) and seek their consent. Participants will be given enough time to consider their decision and will be clearly informed that refusal will not result in any undue influence or coercion. The study will be explained in a language that the participants understand, and all details included in the study protocol will be provided.

3) Compensation for Research Participants

There is no monetary compensation for participating in this study. Additionally, participants will bear the cost of surgical equipment, as it corresponds to standard surgical fees. This study involves standard treatment methods that are part of routine care. Medically, the study is not expected to result in additional risks beyond those in standard clinical care, and participants are not expected to suffer any significant physical or mental harm or unusual injury from the study. Routine safeguards will be applied to participants, and before the study begins, they will be fully informed about its purpose and methods. If anticipated or unanticipated adverse events occur due to the additional procedures and interventions from clinical trial participation, the participants will receive the best possible treatment and, if there is a reasonable causal relationship between the clinical trial and the injury, they will be compensated.

4) Privacy Protection Plan for Research Participants

① The data collected will not include personally identifiable information. All relevant data, including clinical information, will be stored only on the computers of the principal investigator and staff, protected by encryption to minimize potential exposure of personal information.

② Genetic information or pedigrees that can identify individuals and families will not be collected.

③ Backup data in Excel files will be stored on the hard disk of the research computer in the Breast Surgery Department. A backup file will be stored on the external hard disk for breast surgery research to prevent data damage. The principal investigator will encrypt the external hard drive and take care to prevent data leakage.

④ Outpatient visit records and test information after discharge will be entered into the data under the responsibility of the research staff. The information will be kept confidential to prevent exposure of participants' data.

⑤ The principal investigator, co-investigators, and research staff will be able to view the files and

work on the research but will not be allowed to use them for personal purposes without the approval of the management committee, nor can they share them with others without permission.

⑥ Research-related records will be kept for three years from the end of the study, according to Article 15 of the Bioethics Act Enforcement Rules. After the retention period, personal data in the documents must be destroyed according to Article 16 of the Personal Information Protection Act. However, to accumulate records for follow-up studies, it is planned to keep them for more than three years. Documents past the retention period will be permanently deleted using an irreversible method, and signed and printed materials will be shredded.

⑦ Participants will be informed that the clinical information collected for this study may be provided to third parties or registered in public databases. If it is registered in public databases, it will be anonymized.

12. References

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