# TRIAL PROTOCOL

**Effects of negative pressure wound therapy technology combined with intermittent instillation in the treatment of neck anastomotic leakage after esophageal cancer surgery**

Short title: **NPWTi in neck anastomotic leakage treatment**

Acronym: **NPWTi Treatment-Trial**

Version: 1.1

Date: 2021-10-22

CLINICAL TRIALS IDENTIFIER: ChiCTR2100052240

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**Abstract: Title:** Effects of negative pressure wound therapy technology combined with intermittent instillation in the treatment of neck anastomotic leakage after esophageal cancer surgery. **Trial acronym:** NPWTi Treatment-Trial (negative pressure wound therapy combined with intermittent instillation in the treatment of neck anastomotic leakage ) **Background:** Experimental studies and previous clinical trials suggest negative pressure wound therapy technology is an effective and economic way for promoting wound healing but data still lacks in the treatment of neck anastomotic leakage after esophageal cancer surgery and the optimal negative pressure resource of the treatment is not known. **Intervention:** Patients within in trail period were randomly allocated to the conventional nursing group (20 patients), the hospital central NPWTi instillation group (23 patients), and the portable NPWTi instillationgroup (21 patients). The central NPWTi instillationgroup was treated with hospital central negative pressure combined with intermittent instillation, and the portable NPWi instillationgroup was treated with portable negative pressure system combined with intermittent instillation. Indicators of fistula healing, healing days, treatment costs, comfort, and nursing satisfaction were examined in each group. **Design:** Single- centre, randomised trial to compare the effect with normal care in totally 64 patients undergoing AL after esophageal cancer surgery. **Inclusion criteria:** have been diagnosed with neck AL (for which symptoms include fever, chest pain, and chest tightness after surgery); (II) have clinical manifestations, such as saliva-like fluid flowing out of the neck, which may be accompanied by a foul smell, palpation, and a feeling of a mixture of gas and liquid around the neck incision; and (III) have undergone a transesophageal barium swallow angiography that confirmed the occurrence of AL. Written informed consent was obtained from all patients. **Exclusion criteria:** have been diagnosed with neck AL (for which symptoms include fever, chest pain, and chest tightness after surgery); (II) have clinical manifestations, such as saliva-like fluid flowing out of the neck, which may be accompanied by a foul smell, palpation, and a feeling of a mixture of gas and liquid around the neck incision; and (III) have undergone a transesophageal barium swallow angiography that confirmed the occurrence of AL. Written informed consent was obtained from all patients. **Primary outcome:** Wound

healing rate (The number of days it took to start negative pressure treatment to reach the cleansing of the wound was recorded) and Anastomotic fistula healing time(The number of days it took to start the negative pressure treatment to heal was recorded). **Secondary outcomes:** Anastomotic granulation tissue coverage on days 1, 3, 5, and 7 after the intervention. Negative pressure treatment costs and Feeling of comfort with VAS pain score assessed . Nursing quality satisfaction indicted the level of satisfaction with their overall treatment

**List of abbreviations**

| | |
|---|---|
| NPWT | Negative pressure wound therapy |
| NPWTi | Negative pressure wound therapy combined with instillation |
| AL | Anastomotic leakage |

**Trial flow chart**

**Group 1 the conventional nursing group**

**###Routine care**

Patients underwent the following routine care: (I) Fasting and no water. (II) Gastrointestinal decompression (to aspirate acidic gastric juice, reduce gastroesophageal reflux, avoid gastric acid irritation to the anastomosis, and reduce the tension of the anastomosis). (III) Nutritional support (enteral nutrition was administered via a naso-intestinal tube to ensure an intake of 1,800–2,400 kcal each time. Parenteral nutrition was provided as necessary to promote the healing of the fistula as soon as possible). (IV) Anti-infection treatment(broad-spectrum and high-efficiency antibiotics were used in the early stage, and sensitive antibiotics were then selected based on the results of a susceptibility test).

**Group 2 the hospital central NPWTi instillation group**

### **Hospital central negative pressure combined with intermittent instillation (the hospital central NPWT instillation group)**

The treatment comprised 5 steps. In Step 1, a double sleeve (a scalp needle hose) was inserted into the sputum suction tube. In Step 2, the wound was washed with saline and dried with dry square yarn. The front side holes of the double sets holes were coated with lipid hydrocolloid dressing, then tightened with surgical sutures and placed at least 1 cm inside into the fistula. In Step 3, a 1-piece stoma pouch was sealed with an aperture 0.3 cm larger than the fistula. A thin colloid was attached and a “cross” opening was cut to the transparent pouch. The double sleeve was then worn through the chassis by the transparent pouch mouth and fixed with a colloidal seal (see Figure 1). In Step 4, the central negative pressure underwent continuous attraction, and the negative pressure was maintained at 125–150 mmHg for over 22 hours a day. The dressing was replaced and the wound was observed every 2–3 days. Next, normal saline (30 mL of 0.9% normal saline each time) was used to wash the wound 4 times a day, and negative pressure after washing wa maintained.

Finally, the treatment costs and wound healing rates were evaluated according to the course of treatment (the course of treatment took 7 days).

**Group 3 ###Portable Negative pressure system combined with intermittent instillation group (the portable NPWT instillation group)**

Steps 1–3 were the same as those in the central NPWT instillation group (see above). However, in Step 4, a negative pressure meter was connected outside the suction tube using negative pressure drainage (Urgo Company, extriCARE2400). The negative pressure was maintained at 125–150 mmHg for over 20 hours a day. (It was suspended for 2 minutes every 5 minutes). Step 5 was the same as that used in the hospital central NPWT instillation group (see above).

**Assessment criteria**

**###Anastomotic granulation tissue coverage**

The wound tissue and surrounding skin were observed before treatment and at each dressing change. Redness and swelling, the volume, character and smell of secretions, changes in wound size and depth, and changes in new skin and granulation tissue were observed. Pictures were taken of the wound and granulation tissue areas on the surface of the neck fistula, which were also measured(7-8). The coverage of anastomotic fistula granulation tissue on days 1, 3, 5, and 7 after the intervention was recorded. The calculation formula was as follows: granulation tissue coverage ratio = granulation tissue area/wound area ×100.00.

**###Wound healing rate**

The following formula was used: (wound area before treatment—wound area after treatment)/wound area before treatment ×100%(21). The standard for wound cleaning was that the redness and swelling of wound tissue and surrounding skin subsided; the purulent discharge was well drained; the necrotic tissue and foreign bodies were basically cleared; the

granulation tissue was fresh, had a fine granular texture, and bled easily when touched. The number of days it took to start negative pressure treatment to reach the cleansing of the wound was recorded.

### Anastomotic fistula healing time

A gastrointestinal angiography was conducted to confirm that the anastomosis was completely healed. The following indicated that the anastomotic fistula had healed: the patient had meals normally had a smooth meal, and there was no swelling or infection on the neck skin. The number of days it took to start the negative pressure treatment to heal was recorded.

### Negative pressure treatment costs

Various consumables were required for NPWT, such as a suction tube, ostomy bag, irrigation fluid, and a negative pressure instrument. All the costs associated with negative pressure treatment were recorded.

### Feeling of comfort [22]

The visual analogue scale (VAS pain score) was used to evaluate patients' overall comfort with the treatment after the treatment. Each patient was shown a straight line (100 mm in length) on which one end of the line was marked "0" (which represented "no comfort at all"), and the other end was marked "100" (which represented "maximum comfort"). Each patient marked the intensity of their own comfort feeling on the straight line, and the length from 0 to the marked point represented their comfort level.

### Nursing quality satisfaction

The patient was asked to indicate their level of satisfaction with their overall treatment using a scale with the following 3 options: very satisfied, satisfied, or dissatisfied.

## Steering group

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2. **Bao-Jia Luo**, MD, Wound Therapy, Sun Yat-Sen University Cancer Center
3. **Hui-Qin Zhang**, BD, Wound Therapy, Sun Yat-Sen University Cancer Center
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5. **Xiang-Zi He**, BD, Traditional Chinese Medicine and VIP Region, Sun Yat-Sen University Cancer Center
6. **Fang Shen**, BD, Gastric Surgery Department, Sun Yat-Sen University Cancer Center
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8. **Yong-Shan Wen,** BD, Wound Therapy, Sun Yat-Sen University Cancer Center
9. **Jin-Bo Li,** BD, Thoracic Surgery and Nursing , Sun Yat-Sen University Cancer Center

## Intervention management group

Principal investigator, senior investigator and chief trialist.

**Trial Sites**

| Country: | Hospital: | Site investigator: |
|---|---|---|
| China | Sun Yat-Sen University Cancer Centre | Hui-Qin Zhang |
| | Sun Yat-Sen University Cancer Centre | Bao-Jia Luo |
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| | Sun Yat-Sen University Cancer Centre | Mei-Chun Zheng, |
| | Sun Yat-Sen University Cancer Centre | Yong-Shan Wen[1], |
| | Sun Yat-Sen University Cancer Centre | Jin-Bo Li |

**Main monitoring bureau:** Nursing Department, Sun Yat-Sen University Cancer Centre
Ming-zhu Xin

**Ethical approvals**

The study was approved by the Ethics Committee of the Sun Yat-Sen University Cancer Center (approval number GYX2019-011).

## 1. Introduction/background

Esophageal cancer is a common malignant tumor of the digestive tract in China my country [1]. Currently, surgical resection is still the most effective radical treatment for esophageal cancer, especially early and mid-stage esophageal cancer. [2].However, gastroesophageal anastomosis inevitably needs to be performed to reconstruct the digestive tract after removing the diseased esophagus. Among the complications following anastomosis, anastomotic leakage (AL) is not only the most common and serious complication after esophageal cancer surgery, but is also the main cause of surgical death[1] (3-5). Notably, the incidence of neck AL is 4–30%, and the mortality rate is up to 50%(6). AL seriously affects

patients' short-term quality of life and delays or suspends subsequent treatments, thereby reducing patients' long-term survival rates (7-8).

The current clinical treatment of AL mainly comprises non-surgical symptomatic treatment, such as fasting and water prohibition, gastrointestinal decompression, adequate drainage, the insertion of a naso-intestinal tube, or making a jejunum-ostomy fistula for nutritional support, and anti-infection treatment. The traditional treatment method for AL is routine dressing changes. As the amount of exudate, saliva, and secretions is large, the number of dressing changes required per day is large; however, this is very cumbersome and places a great burdens on clinics. Patients also feel abnormal pain when the dressing is being changed, which increases their psychological burden and produces fear, which may in turn lead to a decrease in treatment compliance. Sticky secretions or residues often lead to poor drainage of the fistula, which may extend the infection to the thoracic cavity or mediastinum, causing the infection to persist and even become life threatening. The incidence of anastomotic stenosis remains about 10% even if the AL is completely healed(9). The key to treating neck anastomotic fistula is to maintain effective drainage. Thus, the question of how to continuously discharge sticky secretions and strong irritating digestive fluid to avoid siltation, promote the relative cleanliness of the anastomosis, and accelerate growth is the primary issue in the treatment of anastomotic fistula after esophageal cancer.

Negative pressure wound therapy (NPWT) is a new treatment that has emerged in recent years to promote wound healing. It combines traditional negative pressure attraction technology with closed dressings to remove the leachate and infection source of the wound.(10) Continuous negative pressure prevents the spread of infection and protects the wound environment(10). It also produces a moist healing environment and stimulates the expression of a variety of healing-promoting genes and repair signals by promoting blood flow perfusion and granulation tissue to promote the synthesis and release of a variety of

growth factors and enzymes around the wound surface, leading to epithelial regeneration(11). Additionally, NPWT effectively reduces edema around the wound tissue and enhance material exchange between the wound and around the wound to accelerate wound healing(12-13). NPWT is effective in treating pressure ulcers, lower extremity ulcers, poor postoperative healing, diabetic foot, and other wounds(14-15). However, very little research has been conducted on the application of NPWT in the treatment of fistula after head and neck tumors(16-17). Previous studies have shown that the combination of NPWT and intermittent instillation (NPWTi) has certain advantages in the treatment of anastomotic fistula(18). The instillation fluid dilutes secretions and flushes out the dissolved necrotic tissues and bacteria to avoid blockages caused by excessive viscosity, and then combines with the negative pressure to suck out exudates and bacteria to control infection and promote healing(19). The overall healing time and speed of granulation crawling and epithelial localization of NPWTi were found to be better than those of simple NPWT(20-21).

The main source of negative pressure is central negative pressure and negative pressure treatment instruments(20). Notably, central negative pressure has high suction intensity, a low price, and is easy to obtain(15). However, central negative pressure limits the patient's activities to a certain extent, and the pressure fluctuation is easily affected by the utilization rate of the whole hospital. Negative pressure treatment instruments are portable, lightweight, and unaffected by patient activity during use; however, they are expensive and patients' acceptance of them is low. The 2 different negative pressure sources have their own advantages and disadvantages. At present, no research appears to have been conducted on which method provides better therapeutic effects and economic benefits. Thus, NPWTi was innovatively applied to the nursing of anastomotic fistula after esophageal cancer, and the treatment effects of NPWTi were compared between the different source of negative

pressure and further to analyzed to determine its economic benefits and clarify its application prospects in the treatment of cervical anastomotic fistula after esophageal cancer surgery.

### 1.1 Informed consent

This trial will be conducted according to national and international standards of good clinical practice. This protocol and any amendments will be submitted to the ethics committee for review and formal approval to conduct the trial. Written information and the consent form will be subjected to review and approval by the ethics committee.

### 1.2 Trial conduct

This trial will be conducted in compliance with the protocol approved by the competent authorities, and according to good clinical practice standards. No deviation from the protocol will be implemented without the prior review and approval of the ethical committees except where it may be necessary to eliminate an immediate hazard to the trial participants. In such a case, the deviation will be reported to the regulatory authorities without delay.

## 2. Trial objectives and purpose

Primary objective: The results of this study provide a basis and a guidance to choose the optimal treatment for clinical cases.

## 3. Trial design

### 3.1 Trial design

Single- centre, randomised trial to compare the effect with normal care in totally 64 patients undergoing AL after esophageal cancer surgery.

### 3.2 Randomisation

Trial sites will have access to internet based randomisation to allow for immediate allocation and to ensure adequate allocation concealment and adequate generation of allocation sequence. Each patient will be assigned a unique trial and randomisation number. Randomisation will be generated into dynamic blocks and stratified for trial site.

### 3.3 Trial intervention

The intervention is the negative pressure wound therapy technology combined with intermittent instillation. The different recourse of the negative pressure, hospital central negative pressure or from the portable negative device depended on the randomised groups.

### 3.4 Blinding

Patients and their legal representatives will only be informed that they have received negative pressure therapy with intermittent instillation. Outcome assessors will be blinded to the allocated intervention. The steering committee and the management committee will be blinded to the type of intervention during the entire trial period.

### 3.5 Trial procedure

**Group 1 the conventional nursing group**

**###Routine care**

Patients underwent the following routine care: (I) Fasting and no water. (II) Gastrointestinal decompression (to aspirate acidic gastric juice, reduce gastroesophageal reflux, avoid gastric acid irritation to the anastomosis, and reduce the tension of the anastomosis). (III) Nutritional support (enteral nutrition was administered via a naso-intestinal tube to ensure an intake of 1,800–2,400 kcal each time. Parenteral nutrition was provided as necessary to promote the healing of the fistula as soon as possible). (IV) Anti-infection treatment(broad-spectrum and high-efficiency antibiotics were used in the early stage, and sensitive antibiotics were then selected based on the results of a susceptibility test).

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### 3.6 Discontinuation of individual participants

Withdrawal from intervention: A patient will be withdrawn from the NPWTi therapy if *the intervention is suspected to cause* the patient uncontrolled bleeding, life threatening arrhythmia or refractory cardiogenic shock, at the discretion of the attending physician. The reason for withdrawal will be collected and reported.

### 3.7 Intervention accountability

The trial site investigator is responsible for:

1) Screening and listing eligible patients

2) Performing stratified randomisation

3) Achieving negative pressure and the installation control according to the allocated intervention

4) Collection and reporting of data according to trial protocol and case record forms.

6) Achieving informed consent in writing from patients that regain consciousness.

7) Performing and reporting follow-up according to trial plan.

### 3.8 Data collection

Data will be entered into an electronic web-based case record form from patient notes by site personnel under the supervision of the trial site investigator.From the electronic forms the trial database will be established after data export, in a relevant data-format, to the data manager at Sun Yat-Sen University Cancer Center.

The sponsor supplies a standard description of all laboratory units of measurement, which have influence on the data. To the extent that a trial site uses different unit of measurement, it must submit a correction list to the data centre and the sponsor and, if necessary, have its data capture module modified accordingly**.**

Data not obtainable will be registered as missing and measures to obtain data should not delay intervention (i.e. central line not in place at the time of data collection).

## 4. Selection and withdrawal of participants

### 4.1 Inclusion criteria

1. have been diagnosed with neck AL (for which symptoms include fever, chest pain, and chest tightness after surgery);
2.Display physical signs of AL, such as saliva-like fluid flowing out of the neck, which may be accompanied by a foul smell, palpation, and a feeling of a mixture of gas and liquid around the neck incision;
3. have undergone a transesophageal barium swallow angiography that confirmed the occurrence of AL.
4. Written informed consent was obtained from all patients.

### 4.2 Exclusion criteria

1. had thoracic fistula, mediastinal fistula, sepsis, multiple organ failure, a bleeding tendency, bleeding disorders, a mental disorder, or cognitive dysfunction after surgery;
2. had been discharged, died, or quit voluntarily after treatment for less than 7 days;
3. displayed poor compliance during the study period, or failed to comply or attempt to comply with the prescribed protocol;
4. and/or had an adverse reaction or their condition worsened during the study, which led to their withdrawal from the study.

### 4.3 Participant withdrawal

A participant is free to withdraw his/her informed consent from the trial at any time after regaining consciousness. A patient will be withdrawn from the trial if this patient withdraws consent. The reason for withdrawal will be collected and reported. The patient will be asked to specify which aspects of the trial he/she is withdrawing consent and participation from: attending the follow-up visits, diagnostic testing, inclusion of their data (including survival data) in a database, registry, or publication. The patient making the withdrawal will be asked for permission to use data obtained prior to withdrawal and to obtain data for the primary outcome measure. If this is achieved the patient will be included in the final analyses. If the patient declines, all data from that patient will be destroyed.

## 5. Assessment of outcome measures

### 5.1 Primary outcome

- All-cause mortality at maximal follow up which will be at least 180 days

### 5.2 Secondary outcomes

- Composite outcome of all-cause mortality and poor neurological function (CPC 3 and 4) at hospital discharge and at 180 days.

- All-cause mortality at hospital discharge and at 180 days.
- CPC at hospital discharge and at 180 days
- Neurological function and Quality of life at 180 days (see below).
- Best neurological outcome during trial period according to the CPC-scale.
- Neuron specific enolase at 24, 48 and 72 hours
- Safety measures: Bleeding, pneumonia, sepsis, electrolyte disorders, hyperglycaemia, hypoglycaemia, cardiac arrhythmia and the need for renal replacement therapy.

**6. Conflicts of interest**

All membership of the trail has been restricted to individuals free of conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature.

**7. Statistical monitoring guidelines**

The outcome parameters are defined in the trial protocol.

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Article information: https://dx.doi.org/10.21037/jgo-21-605