

Trans-drain Occlusion for Postoperative Pancreatic Fistula- A Double Blind Randomized Clinical Trial

A multicenter, investigator initiated, prospective, superiority, parallel-group, randomized, double-blinded trial comparing the efficacy of **trans-drain occlusion** to standard of care for postoperative pancreatic fistula

ISRCTN registration will be performed after ERC approval
ClinicalTrials.gov: registration will be performed after ERC approval

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List of Abbreviations

CFR	Code of Federal Regulations
ICH	International Conference on Harmonisation
CRF	Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IRB	Institutional Review Board

1 Background

Although mortality after pancreatectomy has decreased to approximately 2% at high-volume centers, the operative morbidity after these procedures has remained between 30% and 50%.¹⁻³ The most common major complication after pancreatic resection is postoperative pancreatic fistula (POPF), which may result in intra-abdominal abscess, sepsis, hemorrhage, or delayed adjuvant chemotherapy.¹⁻³ POPF is defined as a drain output of any measurable volume of fluid on and after postoperative day 3 with an amylase content > 3 times the upper limit of normal serum level.⁴ A recent multicenter, multinational report of > 4000 pancreaticoduodenectomies indicated an overall clinically relevant POPF (CR-POPF, with persistent fistula drainage more than 3 weeks) rate of 11%.⁹ A prospective randomized trial of 450 distal pancreatectomies also reported an overall POPF rate of 36% at 30 days after operation.¹⁰ The incidence of POPF remains stable despite various preventive measures,^{8,9} underscoring the need for methods to accelerate POPF closure.

Gradual withdrawal (2 cm every several days) of surgically placed drains in patients who are clinically stable and tolerate a diet is generally adopted to hasten closure of POPF.⁸ In brief, drain withdrawal is initiated after postoperative days 5 to 7 and continued at outpatient visits until output is less than 10 mL per day, and then the drain is removed. For high-output fistulas (> 150–200 mL of amylase-rich fluid per day), patients are initially managed with fasting and enteral or parenteral nutrition. If fistula output decreases substantially with these measures and the patient remains clinically well, drain withdrawal is initiated and oral intake is slowly restarted. If fistula output fails to decrease with these measures, drains are initially left in place to control the fistula. If the patient remains well despite high fistula output, drains are slowly withdrawn in an attempt to decrease the output

and close the fistula. If patient develops fever, abdominal pain, or an inability to tolerate oral intake, drains are not withdrawn and an abdominal computed tomographic (CT) scan is arranged. If any drainable fluid collection is identified, the patient is treated with broad-spectrum antibiotics and undergoes interventional radiology–guided drainage, which is kept in place and flushed daily. When the output decrease to less than 10 mL per day, the drains are removed.

However, the current standard practice of gradual drain withdrawal is time consuming. Although clinically stable can be discharged with the drain, the drainage tube often remains in place for a prolonged period, with patient discomfort and increased medical cost. In our pilot study, 32.5% (37/114) of POPF patients required drainage for longer than 21 days. Besides, there is also considerable risk of recurrent fluid collection along the drain tube tract after drain removal.¹¹ Measures that can accelerate drain removal and reduce the risk of recurrence may reduce POPF-related morbidity and reduce hospital costs and length of stay.

1.1 Investigational Treatment

Our experience has shown that trans-drain occlusion of the drain tract achieves fistula closure, enabling immediate removal of the drain. Trans-catheter occlusion requires the fluid collection to become walled-off, which usually takes 3 weeks. As the walled-off fluid collection can drain either via the percutaneous drain or via the pancreatic duct into the jejunum, occluding the point of entry of the drain tube into the fluid collection by gelfoam stops further fluid flowing through the drain tube. After occlusion, the secreted pancreatic juice can only drain through the pancreatic cut into the jejunum, and therefore the drain can

be removed right after embolization without recurrence of fluid collection along the tract of the drain.

1.2 Preclinical Data

In a pilot study, 20 patients underwent trans-catheter occlusion for POPFs that persisted for more than 3 weeks after placement of drainage tubes. No subjective symptoms or abnormalities in blood tests were noted in 17 patients after the procedure. Three patients had abdominal pain without signs of infection, and the pain spontaneously subsided after conservative treatment. POPF healed immediately after occlusion in all of the 20 patients without recurrence during follow-up.

1.3 Risk/Benefits

In the aforementioned pilot study, occlusion achieved rapid closure of POPF in all the patients. Pain developed in 3 of 14 patients (21.4%) after occlusion that resolved uneventfully after conservative treatment. No other adverse effects were noted. These preliminary results suggest that trans-catheter occlusion is effective in achieving rapid POPF closure with minimal risk.

1.4 Trial Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible.

1.5 Population

Patients 18 years of age or older who undergo pancreatic resection and subsequently develop POPF (i.e. drain output of any measurable volume of fluid on and after postoperative day 3 with amylase content > 3 times ULN) that persists for longer than 3 weeks are target population of the trial.

During surgery, 7mm-calibered drains are placed before closing the wound; the type, number of drain tubes placed and the location of placement are at the discretion of the operating surgeon. The number and amylase concentration of the drainage fluid is measured on the 3rd, 5th, and 7th postoperative day, and when drainage color changes. POPF is defined as a drain output of any measurable volume of fluid on and after postoperative day 3 with an amylase content > 3 times the upper limit of normal serum level.⁹ After the diagnosis of POPFs, the route of nutrition is (oral, enteral, or parenteral) is at the discretion of the doctor caring the patients. Patients are assessed daily for fistula output and fistula- or treatment-related complications. If fever occurs, broad-spectrum antibiotics are administered and abdominal CT is performed. Additional interventional radiology-guided catheter drainage is performed for any drainable fluid collections identified by CT. If output of a drain tube is below 10 ml during 48 hours, the drain tube is removed. If a drain tube (rarely more than 1) still cannot be removed on day 21 from the onset of POPF, the patient is diagnosed to have a POPF that persists for 3 weeks and further evaluated for eligibility and enrollment.

1.6 Literature

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2 Trial Objectives

To assess the effectiveness and safety of trans-drain occlusion for postoperative pancreatic fistula (POPF) that fails to close after 3 weeks of drainage.

3 Trial Design

This is a multicenter, investigator initiated, prospective, superiority, parallel-group, randomized, double-blinded trial to compare trans-drain occlusion followed by gradual withdrawal of drain and gradual withdrawal of drain alone.

3.1 Primary Study Endpoints/Secondary Endpoints

Efficacy end points:

- The primary efficacy end point is the days from the randomly allocated treatment to fistula closure. The date of fistula closure is defined as the date on which the drain is removed after an output of ≤ 10 mL during 48 hours, without recurrence of POPF within the next 3 months.
- Secondary efficacy end points:
 - 30-day fistula closure rate: the proportion of patients in whom the drain can be removed by 30 days after occurrence of POPF, without recurrence of POPF within the next 3 months.
 - Rate of persistent or recurrent POPF after initial drain removal: the proportion of patients with fluid collection^a on follow-up CT, which is to be performed at 3 months after removal of drain or when recurrence of POPF is suspected clinically.
 - Length of hospital stay and hospital costs after the assigned treatment.
 - Rate of fistula-related complications: the proportion of patients who develop fever/infection^b, ileus^c, postpancreatectomy hemorrhage (PPH)^d from undergoing the assigned treatment to end of follow-up.

Safety end points:

- Fever/infection* or pain** that develops within 48 hours after the allocated treatment, or any adverse events judged to be related to the treatment.

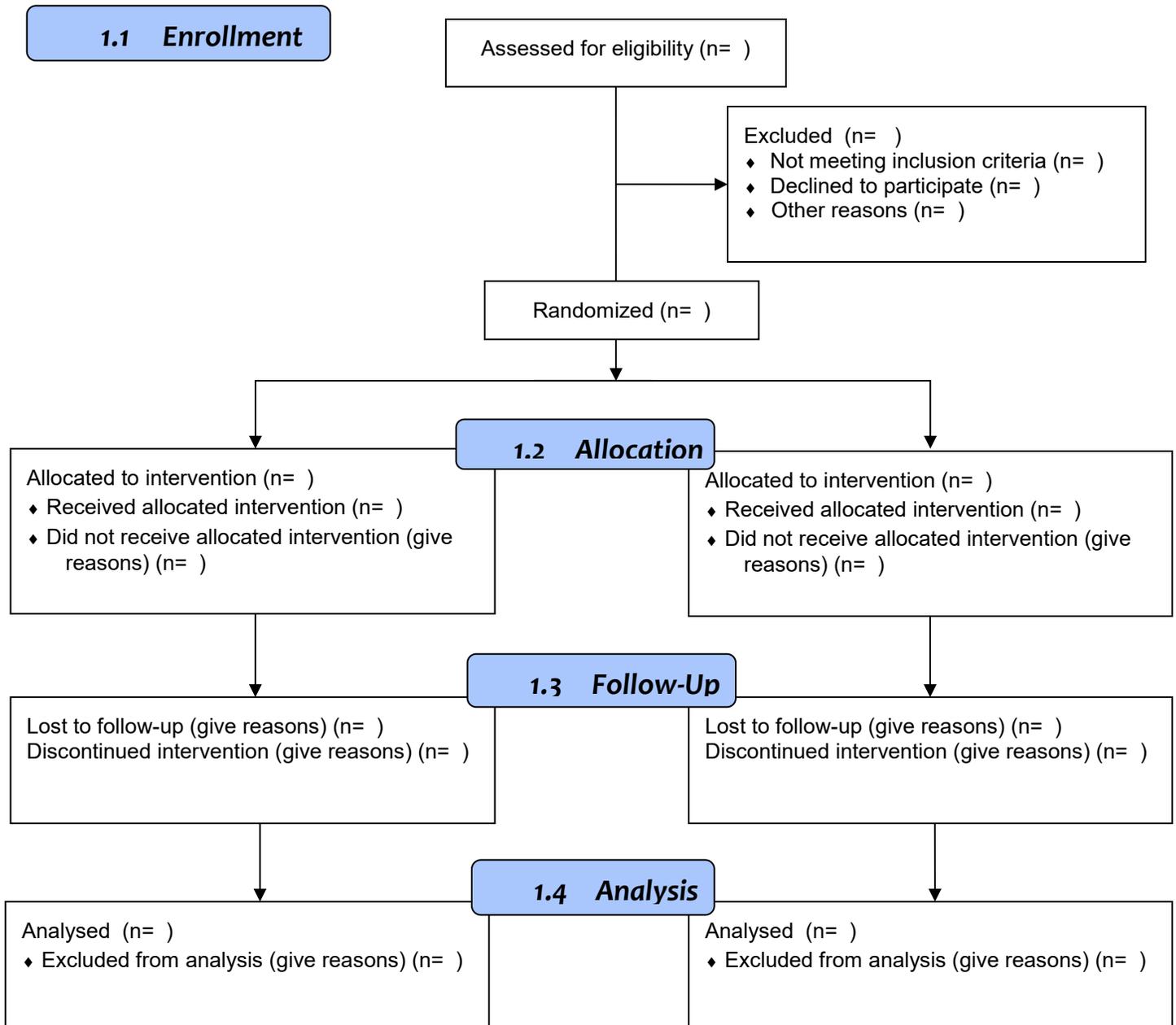
*Fever/infection: body temperature $\geq 38.5^{\circ}\text{C}$, leukocytosis (WBC count $>12,000$ /uL) or leukopenia (WBC count $<4,000$ /uL)

**Pain: new-onset or worsening of pre-existing pain (≥ 1 point increase in VAS).

3.2 Study Design/Type

This trial is a prospective, superiority, parallel-group, randomized, double-blinded trial.

CONSORT 2010 Flow Diagram



3.3 Randomization

Patients fulfilling the inclusion and exclusion criteria will be randomly assigned in a 2:1 ratio to receive embolization or standard care. Block randomization is performed, stratified according to center. For each participating center, a randomization list is produced randomly with block size of 3. The Research Electronic Data Capture (REDCap) software program is used to generate randomization numbers.

3.4 Maintenance

The randomization procedure will be conducted and maintained by Clinical Trial Statistical Center, National Taiwan University Hospital.

3.5 Trial Treatment

In patients randomized to receive standard care, only fistulography is performed to assess the condition of the fistula; occlusion is not performed. However, after fistulography, the drainage tube will be pulled outward for 2 cm in length and then fixed at skin again. Thereafter if patient remains asymptomatic, the drainage tube will be gradually withdrawn by 2 cm in length each day. The drainage tube will be removed when 48 hours drainage amount is less than 10 cc.

In patients randomized to undergo occlusion, the patient receives fistulography to assess the condition of the fistula, and then occlusion is performed using the following methods:

- In patients with a 7mm-calibered CW(closed wound) drain (perforated flat drain or round channel drain):

1. Use a Kelly or Mosquito forceps to clamp the tube of CWV drain.

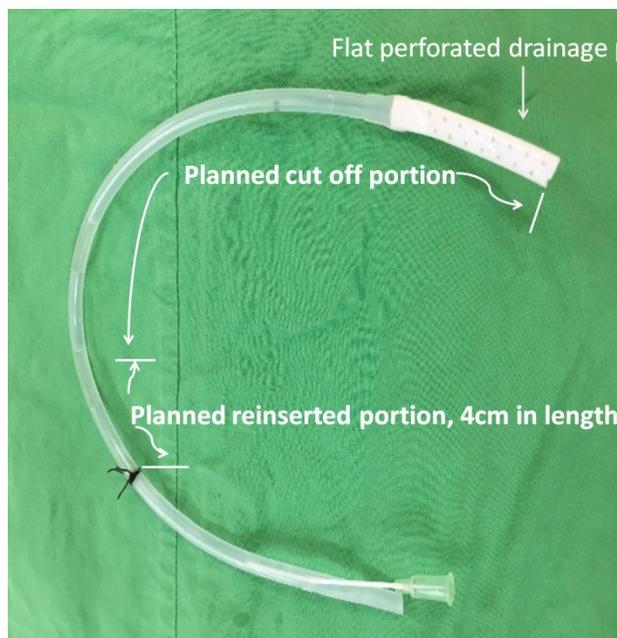
2. Then an 18G puncture needle is inserted into the tube and remove the inner needle.

The small amount of diluted contrast medium can be slowly injected into the CWV tube. The tube and the route can be more clearly identified (fistulography).

3. A 0.035-inch guidewire can be inserted via the 18G puncture needle.



4. Remove the CW drain under the fluoroscopy. There may be some resistance initially when removing the CW drain. The proximal part of the removed CW drain is cut at 4 cm proximal to the previous skin fixation site (as shown in the following figure) and preserved in sterility for reinsertion.



5. A 40cm, 5Fr KMP catheter (Cook company) is inserted via the guidewire, and then the guidewire is removed.

6. Rinse the catheter hub and KMP catheter with 3ml 5% glucose water (Dextrose). Then the glue (33%, 1:2, 0.5ml of NBCA + 1ml Lipiodol) is slowly injected into the KMP catheter. Withdraw the catheter and continuously inject the glue until 5cm-long catheter remained inside the tract. The guidewire is inserted back through the catheter.

7. The planned reinserted portion of the original drain tube is inserted back into the drain tract via the guidewire. The guidewire is removed and the drain tube is fixed to the skin at previous fixation site.

8. Thereafter if patient remains asymptomatic, the drainage tube will be gradually withdrawn by 2 cm in length each day. The drainage tube will be removed when 48 hours drainage amount is less than 10 cc.





- In patients with a pigtail drainage of the post-operative fluid collection:
 1. The small amount of diluted contrast medium can be slowly injected into the pigtail to localize the tube location.
 2. A 0.035-inch guidewire is inserted via the pigtail hub.
 3. Remove the pigtail under the fluoroscopy. The proximal part of the removed CW drain is cut at 4 cm proximal to the previous skin fixation site (as shown in the following figure) and preserved in sterility for reinsertion.
 4. A 40cm 5Fr KMP catheter (Cook company) is inserted via the guidewire, and then the guidewire is removed.

5. Rinse the catheter hub and KMP catheter with 3ml 5% glucose water (Dextrose). Then the glue (33%, 1:2, 0.5ml of NBCA + 1ml Lipiodol) is slowly injected into the KMP catheter. Withdraw the catheter and continuously inject the glue. The guidewire is inserted back through the catheter and the planned reinserted portion of the original pigtail drainage tube is inserted back into the drain tract via the guidewire. The guidewire is removed and the pigtail drain tube is fixed to the skin at previous fixation site

6. Thereafter if patient remains asymptomatic, the drainage tube will be gradually withdrawn by 2 cm in length each day. The drainage tube will be removed when 48 hours drainage amount is less than 10 cc.

3.6 Duration

If drain(s) cannot be removed after 21 days from the occurrence of POPF, the patient is enrolled and randomized if he or she fulfils the eligibility criteria, and then receives the assigned treatment. After undergoing the assigned treatment, patients are assessed daily for drain output and any complications. Drains are removed when the drainage amount is below 10 ml during 48 hours, and patients are discharged if they tolerate oral intake well and remain afebrile for 2 days after removal of all drains. After discharge, in-office visits were scheduled at week 1, 2, 4, 8, and 12. A follow-up CT is performed when there is clinical suspicion of POPF recurrence, or at 3 months after removal of the drain, whichever comes first. Therefore, the expected duration of subject participation is between 3 to 4 months.

3.7 Discontinuation

An individual patient's participation is discontinued if the patient decides to withdraw from the study, or the attending surgeon/physician-in-charge advises withdrawal from the trial based on medical reasons. According to intention-to-treat, the data of patients who withdraw from the study after being randomized are included for analysis.

4 Selection and Withdrawal of Subjects

4.1 Inclusion Criteria

Patients who undergo pancreatoduodenectomy (with or without pylorus preservation) and develop POPF that persists for 3 weeks after its occurrence.

4.2 Exclusion Criteria

- Patients are excluded if they are younger than 20 years of age, have active infection that is not adequately controlled [defined as body temperature $\geq 38.5^{\circ}\text{C}$ and/or leukocytosis (WBC count $>12,000$ /uL) or leukopenia (WBC count $<4,000$ /uL)], have current or history of severe heart, lung, kidney, or liver failure, have a Karnofsky Performance Score of <60 , are pregnant or lactating, or have received somatostatin or its analogue during the index admission, or decline to participate.

4.3 Subject Withdrawal

Patients can withdraw from the study after participating in the study. If a patient withdraws before being randomized, the patient is considered as being excluded because of decline to consent. If a patient withdraws after being randomized but before receiving the randomly assigned treatment, the assigned treatment is not given but the patient is included in the analysis according to the randomly assigned group (ITT). The type of treatment is

chosen according to the attending physician and his/her discussion with the patient. After withdrawal, patients are followed according to the follow-up scheme of this trial. The type and timing of the data to be collected for withdrawn subjects are the same as those who remain in the trial. No replacement for withdrawal is attempted.

4.4 Treatment of Subjects

Except the randomly assigned study/placebo intervention, patients are treated according to general surgical and clinical practice at the discretion of the attending physician.

4.5 Medication

Somatostatin or its analogue is not allowed throughout the trial period (during the index admission and follow-up period).

4.6 Monitoring for treatment effect

After receiving the assigned treatment, patients are assessed daily for fistula output and fistula- or treatment-related complications until the drain is removed. After drain removal, patients are assessed according to usual postsurgical inpatient care.

5 Assessment of Efficacy

5.1 Efficacy Parameters

- The primary efficacy end point is the days from the randomly allocated treatment to fistula closure. The date of fistula closure is defined as the date on which the drain is removed after an output of ≤ 10 mL during 48 hours, without recurrence of POPF within

the next 3 months.

- Secondary efficacy end points:
 - 30-day fistula closure rate: the proportion of patients in whom the drain can be removed by at day 30 after occurrence of POPF, without recurrence of POPF within the 3 months after removal of drain.
 - The rate of persistent or recurrent POPF after initial drain removal: fluid collection^a on follow-up CT, performed when recurrence of POPF is suspected clinically or at 3 months after removal of drain).
 - Length of hospital stay and hospital costs after the assigned treatment.
 - The rate of fistula-related complications: fever/infection^b, ileus^c, postpancreatectomy hemorrhage (PPH)^d after receiving the assigned treatment.

(a) Fluid collection: fluid accumulation on abdominal computed tomography with a diameter ≥ 4 cm.

(b) Fever/infection: body temperature $\geq 38.5^{\circ}\text{C}$, leukocytosis (WBC count $>12,000$ /uL) or leukopenia (WBC count $<4,000$ /uL). Fever/infection that is attributed to causes other than POPF is not considered as a fistula-related complication.

(c) Ileus: intolerance of oral or enteral feeding with distention of bowel on abdominal X-ray.

(d) Postpancreatectomy hemorrhage (PPH): all postoperative episodes of intraabdominal (blood in drainage fluid or hematoma on CT with dropped hemoglobin level) or gastrointestinal hemorrhage (blood in nasogastric tube, hematemesis, bloody or tarry stool), according to the International Study Group of Pancreatic Surgery (ISGPS) definition.³

5.2 Method and Timing

- Days from the assigned treatment to fistula closure: daily fistula output is assessed and recorded after fistulography with or without occlusion. Drains are removed when the drain output is ≤ 10 mL during 48 hours.
- 30-day fistula closure rate: the day on which POPF is diagnosed is day 1. The outcome is assessed at 3 months after initial removal of the drain. If recurrence is noted within 3 months after initial removal of the drain, the fistula is considered not healed by 30 days regardless of whether the drain could be removed by day 30 after the onset of POPF.
- The proportion of patients with persistent or recurrent POPF: a contrast-enhanced abdominal CT (non-enhanced CT is acceptable if contrast injection is contraindicated) is performed 3 months after removal of drains, or when there is suspicion of POPF recurrence, as suggested by the appearance of fever, ileus, or abdominal pain. Any intraabdominal fluid collection larger than 4 cm in its largest dimension is considered as evidence of POPF recurrence.
- Length of hospital stay and hospital costs after the assigned treatment: assessed at the date of discharge.
- The proportion of patients with fistula-related complications (fever/infection, ileus, bleeding/ postpancreatectomy hemorrhage (PPH) that develop after receiving the assigned treatment till 3 months after removal of drains. Patients are assessed daily for these complications during admission, and at week 1, 2, 4, 8, 12 after discharge at scheduled in-office visits.

6 Assessment of Safety

6.1 Safety Parameters

Safety end points:

- Fever or pain that develops within 48 hours after the allocated treatment, or any adverse events judged to be related to the treatment.
 - Fever/infection: body temperature $\geq 38.5^{\circ}\text{C}$, leukocytosis (WBC count $>12,000$ /uL) or leukopenia (WBC count $<4,000$ /uL)
 - Pain: new-onset or worsening of pre-existing pain (≥ 1 point increase in VAS).

6.2 Method and Timing

Patients are assessed for vital signs and pain scores every 8 hour after the assigned treatment as per admission routine. Leukocyte count is checked at 48 hours after the assigned treatment, or earlier if fever occurs. Whether the patients develop safety end points are assessed at 48 hours after the treatment and recorded.

6.3 Adverse Event Reporting

Any adverse event (AE) that occurs in randomized patients during the entire trial period should be carefully documented in the electronic case report form (eCRF) regardless of classification, seriousness, intensity, outcome, or causality.

Details of serious adverse events will be communicated by the local investigator to the local institutional review board (IRB).

The investigator should specify and report in the eCRF the nature of the sign or symptom, the date of onset, the date of resolution (duration), the intensity, the causality, interventions performed (if any), the relationship to trial treatment, and the outcome.

In the case of knowledge of an SAE, the investigator must immediately (within one working day of being notified of the event):

- Fill out at a minimum the following items of the internet-based SAE report: date of the AE, term of the AE, patient identification, name of reporter, treatment, result/outcome, assessment of both the seriousness and the relationship to the investigational treatment
- As soon as further information regarding the event is available (e.g. discharge note), the investigator should complete in the documentation in the eCRF and sign it electronically.
- Copies of the discharge note, of all the reports regarding examinations carried out and/or diagnostic findings should be sent to the lead investigator.

Periodic safety reports will be prepared by the lead investigator and forwarded to the IRBs of the participating sites.

6.4 Definitions

Adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs including abnormal laboratory findings in patients, whether related to the investigation treatment or not.

- Procedure-related AEs: any event that is judged as causally related to the treatment procedure.
 - ◆ Serious adverse events (SAEs): an adverse event that leads to death, a life-threatening illness or injury, a permanent impairment of a body structure or a body function, in-patient (except the index admission) or prolonged hospitalization, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body

function.

NOTE:

- Planned hospitalization for a pre-existing condition without serious deterioration in health is not considered an SAE.
- Life-threatening in the definition of an SAE or adverse reaction refers to an event in which the patient is at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

6.5 Adverse Event Follow-up

Follow-up of any SAE that is fatal or life-threatening should be provided within one additional calendar week.

7 Statistical Plan

7.1 Statistical Methods

Descriptive statistics will be computed for all variables and presented. Continuous variables will be summarized by the number of patients, mean and standard deviation. Categorical variables will be summarized by frequency counts and percentages for each category.

The primary efficacy end point will be compared between the two trial groups using a Log-rank test on an intention-to-treat basis. Cox proportional hazards model is used to analyze the rate of POPF closure with adjustment for covariates. Secondary efficacy end points and safety end points are analyzed using Chi-square tests, Fisher's exact tests, two sample T-tests, Mann-Whitney U tests, and multivariable linear and logistic regression models, where appropriate. In all analyses, statistical uncertainty will be quantified by means of 95% confidence intervals.

7.2 Sample Size Estimation

With 2:1 randomization, it is estimated that 51 patients, 34 for the occlusion group and 17 for the standard care group, are needed to have 80% power to detect a hazard ratio for removal of drain of 2.5, on the basis of a log-rank test with a two-sided significance level of 5%. Assuming a 10% dropout rate, the planned number of patients to be enrolled is 57, 38 for the occlusion group and 19 for the standard care group. All randomized subjects are analyzed according to intention-to-treat.

7.3 Significance

The level of significance is 5%.

7.4 Termination Criteria

The trial is terminated when the number of subjects enrolled reach the planned number of enrollment.

7.5 Accountability Procedure

Medical records and case report forms are reviewed to resolve missing or implausible data.

7.6 Deviation Reporting

Any deviation from the original statistical plan and the justification for such deviation are described in the protocol as an amendment and in the final report.

8 Direct Access to Source Data/Documentation

All investigators will permit monitoring, audits, review of ethical committees and regulatory authorities direct access to source data and documents.

9 Quality Control and Quality Assurance

The principle investigator will have responsibility for training trial site investigators, research nurses, and other research assistances before the initiation of the trial. After initiation, the trial site investigators and research nurses will be responsible for entering all relevant data into the electronic case report forms (CRFs). The CRFs will be constructed to ensure data quality with reliable values. This data quality procedure will make sure that the trial data is processed accurately.

10 Ethical Considerations

This study will be conducted according to Good Clinical Practice. This protocol and any amendments will be submitted to the National Taiwan University Hospital Institutional Review Board (IRB) for formal approval to conduct the study. All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11 Data Handling and Record Keeping

All data will be kept according to the regulations (e.g. Personal Data Protection Law, Human biological database management regulations) in Taiwan. Individual patient data will be entered into the electronic database built by Research Electronic Data Capture

(REDCap) and be kept strictly within the research team in National Taiwan University Hospital. The data will be analyzed anonymously. The study data will be maintained for 15 years if requested by the relevant authorities.