

A Multicenter Randomized Phase II Trial Investigating the Effect of Polyglycolic Acid Sheet on the Prevention of Pancreatic Fistula After Gastrectomy with Prophylactic Lymph Node Dissection

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Abstract: Pancreatic fistula after gastrectomy with lymph node dissection is associated with prolonged hospital stay and critical complications such as intra-abdominal bleeding and sepsis. Polyglycolic acid (PGA) sheets are absorbable suture reinforcement materials. A randomized Phase II trial has been planned to evaluate the effect of PGA sheets on preventing postoperative pancreatic fistula. A total of 320 patients will be recruited from thirteen institutions. Patients who are scheduled to undergo distal or total gastrectomy will be randomly allocated into the PGA group or control group, and the dissected area around the pancreas will be covered by the PGA sheet in the PGA group. The primary endpoint will be the maximum value of drain amylase concentration up to 5 days after surgery. The secondary endpoints will be as follows: transition of value of amylases of drain discharge, incidence of pancreatic fistula, incidence of intra-abdominal abscess, white blood cell count, value of C-reactive protein, incidence of postoperative complication, duration of antibiotic agents administration, duration of abdominal drainage, usage of octreotide, duration of hospital stay, incidence of bleeding in abdominal cavity, mortality, and incidence of reoperation.

Keywords: gastric cancer, pancreatic fistula, polyglycolic acid sheet, protocol, randomized clinical trial

Introduction

The standard therapy for gastric cancer is gastrectomy with prophylactic lymph node dissection.¹ Postoperative pancreatic fistula (POPF) is a major complication with a relatively high incidence of 5–22%.^{2–4} In particular, it has been reported that pancreatic fistula occurs more frequently in laparoscopic surgery, which has been widely performed in recent years due to its minimal invasiveness and effectiveness compared to open surgery.⁵ Lymph node dissection around the pancreas requires the removal of tissue containing lymph nodes from the pancreatic parenchyma. Then, pancreatic juice leaks into the free peritoneal cavity due to thermal injury to the pancreas induced by the energy device as well as blunt injury induced by compression and retraction to maintain the surgical field.^{6–8} To reduce subsequent complications caused by pancreatic fistula, packing and localizing pancreatic juice should be applied.

Polyglycolic acid (PGA) sheets (GUNZE MEDICAL LIMITED, NEOVEIL sheet, Osaka, Osaka, Japan) are absorbable suture reinforcement materials that are applied to reinforce suture sites and to prevent air leakage in thoracic surgery by forming a capsule by attaching fibrin and promoting the migration of fibroblasts along the sheet. There have been conflicting reports regarding the preventive effect of PGA sheets covering the pancreaticojejunostomy in pancreatectomy against POPF. Therefore, the preventive effect of this approach has not been proven in pancreatic surgery.^{9,10} It has been

reported that the combined use of PGA sheets and fibrin glue significantly reduced the drain amylase concentration from 1220 U/L to 660 U/L on the first day after gastrectomy; however, this clinical report was a prospective historical control study, and fibrin glue, a biological medical product, was used in combination.¹¹ Prospective randomized trials are required to accurately evaluate the efficacy of PGA sheets in preventing POPF.

This study aims to demonstrate the preventive effect of PGA sheets against POPF after open and laparoscopic gastrectomy with prophylactic lymph node dissection.

Methods

Study Setting

The study will be a multi-institutional, randomized, open-label, Phase II trial. The World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects ethical guidelines will be followed. The study protocol was approved by the Nagoya University Certified Review Board with approval number N0058 and registered in the Japan Registry of Clinical Trials (jRCT) as jRCTs042210090 (<https://jrct.niph.go.jp/>).

Inclusion and Exclusion Criteria

Patients who meet all the following criteria are eligible: scheduled to undergo curative gastrectomy with D1+ or more lymph node dissection, aged 20 years or more at the time of registration, and provided written informed consent. Patients with any of the following criteria will be excluded: history of gastrectomy, history of pancreatectomy, active infection in abdominal cavity, tumor invasion to pancreas, patients who are scheduled to undergo pancreatectomy, patients who are scheduled to undergo splenectomy, emergency surgery, patients who are suspected to have allergy to polyglycolic acid, patients who are scheduled to undergo planned robotic assisted gastrectomy, and ineligible for the study based on the physician's assessment.

Randomization

After screening patients using the inclusion and exclusion criteria, registration and randomization will be performed using the online Electronic Data Capture tool. Patients will be randomly assigned to the PGA group or control group at a 1:1 ratio by the minimization method with the following adjustment factors: open or laparoscopic surgery, distal or total gastrectomy, D1+ or D2 lymph node dissection, and institution.

Treatment Methods

Patients diagnosed with gastric cancer or neuroendocrine tumors (NETs) will undergo distal or total gastrectomy with prophylactic lymph node dissection. The extent of lymph node dissection is defined by Japanese gastric cancer treatment guidelines 2018 (5th edition). In the PGA group, the dissected area around the pancreas (No. 6, 8a, 11p, 11d lymph node area) will be covered by a PGA sheet. The drain amylase concentration will be measured on the first, third and fifth postoperative days. To ensure the quality of surgery, physicians with more than 60 surgical experiences will perform the surgery as operators or teaching assistants in both open surgery and laparoscopic surgery. Moreover, photographs will be taken after peripancreatic dissection, and the quality of the dissection will be evaluated.

Endpoint

The primary endpoint is the maximum value of drain amylase concentration up to 5 days after surgery. The secondary endpoints are as follows: transition of value of amylases of drain discharge, incidence of pancreatic fistula, incidence of intra-abdominal abscess, white blood cell count, value of C-reactive protein, incidence of postoperative complication, duration of antibiotic agents' administration, duration of abdominal drainage, usage of octreotide, duration of hospital stay, incidence of bleeding in abdominal cavity, mortality, and incidence of reoperation. Pancreatic fistula is defined as Grade B or C in ISGPS definition.¹²

Sample Size Setting and Statistical methods

In a previous study that reported the utility of PGA sheets and fibrin glue, the mean and standard error of drain amylase concentration on the first day after gastrectomy were 660 U/L and 172 U/L in the intervention group (n = 34) and 1220 U/L and 430 U/L in the control group, respectively. The standard deviations were 1003 U/L in the intervention group and 3440 U/L in the control group. Using the two-sample *t* test for the means of inequality of variance, 126 cases per group are required for this study to detect a one-sided significance level of 0.2 and a power of 0.8. Considering the potential for dropouts, we set the sample size at 160 cases per group.

For postoperative drain amylase levels in the control and PGA groups, the Shapiro–Wilk test will be used to assess the normality of the data distribution, and Student's *t* test or the Wilcoxon rank test will be used to examine statistical significance.

Participating Institutions

The following institutions will participate: Nagoya University Hospital, Aichi Cancer Center Chuo Hospital, Ichinomiya Municipal Hospital, Okazaki City Hospital, Kainan Hospital, Gifu Prefectural Tajimi Hospital, Konan Kosei Hospital, Tosei General Hospital, Komaki City Hospital, Yokkaichi Municipal Hospital, Chuno Kosei Hospital, Toyohashi Municipal Hospital, and Nagoya Medical Center.

Discussion

Pancreatic juice that leaks due to thermal injury or blunt injury of the pancreatic parenchyma causes serious complications such as intra-abdominal bleeding due to pseudoaneurysm rupture and surrounding tissue damage and multiple organ failure or sepsis caused by intra-abdominal abscess due to infected pancreatic juice. Moreover, subsequent prolonged hospital stay and increased medical expenses are important medical issues. The development of a procedure that can prevent POPF is an important issue to solve these problems. Covering the exposed pancreatic parenchyma after removal of the anterior pancreatic fascia and packing and localizing the leaked pancreatic juice are expected to reduce the postoperative drain amylase concentration and reduce subsequent complications. If this facile procedure reduces the complications due to postoperative pancreatic fistula, it should bring about favorable consequences in terms of patient management, medical safety, and medical economics.

Disclosure

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