This is an English translated copy of the original trial protocol and statistical analysis plan "Korean version", which has been submitted to the IRB/ethics committee. This trial was performed by domestic hospitals only. That is the reason why the English document submitted to the IRB/ethics committee was not required in this trial.

Use of Polyethylene Glycolic Acid to Prevent Pancreatic Leak Following Distal Pancreatectomy: Prospective Multicenter Randomized Study

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Seoul National University Hospital
1. Background

- Distal pancreatectomy is called left-sided pancreatic resection or distal partial pancreatectomy and a term applied to resection of that portion of the pancreas extending to the left of the neck of pancreas that has a relatively thin parenchyma thickness and covers the confluence of the superior mesenteric vein and splenic vein. Distal pancreatectomy is performed for a variety of benign and malignant conditions including chronic pancreatitis (24%), benign pancreatic cystadenoma (22%), and pancreatic adenocarcinoma (18%).

- A general definition of pancreatic fistula is an abnormal communication between the pancreatic ductal epithelium and another epithelial surface containing pancreas-derived, enzyme-rich fluid. However, a postoperative pancreatic fistula (POPF) represents failure of healing/sealing of a pancreatic-enteric anastomosis, or it may represent a parenchymal leak not directly related to an anastomosis such as one originating from the raw pancreatic surface (eg, left or central pancreatectomy, enucleation, and/or trauma).

- The diagnosis of POPF may be suspected on the basis of the many clinical or biochemical findings. A broad definition begins with the following criteria: Output via an operatively placed drain (or a subsequently placed, percutaneous drain) of any measurable volume of drain fluid on or after postoperative day 3, with an amylase content greater than 3 times the upper normal serum value.

- POPF is the leading cause of morbidity after distal pancreatectomy, with a frequency of 13% to 64%. A variety of methods to prevent POPF has been applied including ligation of the main pancreatic duct, stapled closure, pancreatico-intestinal anastomosis, biologic glues, mesh reinforcement, and medication like somatostatin analogue, none of which has proven priority.

2. Objective

Mesh reinforcement is a method wrapping around the remnant pancreatic stump after distal pancreatectomy. Among meshes introduced, polyglycolic acid mesh (PGA, Neoveil, Gunze, Osaka, Japan) is a bioabsorbable recombinant membrane made of a synthetic polymer with a cellulose-like structure. Recently retrospective studies showed that the rate of POPF was 5.6 to
27% with PGA mesh reinforcement and 38.9 to 42% without that (Yamamoto et al; 2009, Ochiai et al; 2010). Therefore, this prospective randomized control study is designed to evaluate the ability of PGA mesh reinforcement to prevent POPF after distal pancreatectomy.

3. Patients

3.1 Inclusion criteria
Patients were included if they (1) were 20 to 85 years of age; (2) had an expected life expectancy of at least 24 months; (3) had potentially curable benign, pre-malignant, or malignant disease of the pancreatic body or tail, as shown by preoperative imaging (computed tomography, magnetic resonance imaging, and/or positron emission tomography); and (4) provided written informed consent.

3.2 Exclusion Criteria
Patients were excluded if they (1) had a chronic pancreatitis-induced atrophic pancreas or calcification of pancreatic parenchyme; (2) were receiving immunosuppressive therapy; (3) had previously undergone chemoradiotherapy; or (4) were known to be substance abusers.

4. Methods

4.1 Randomization and trial design
After confirming patient eligibility, patients are randomized 1:1 to undergo stapled transection of the pancreas followed by wrapping the remnant pancreatic stump with PGA mesh (PGA group), or to undergo stapled transection alone (control group). Randomization is performed using a Web-based system just before surgery. The allocation sequence is computer generated and randomly stratified by the surgeon.

4.2 Surgical procedures and study protocol
The consensus on surgical procedures is determined during a meeting of the participating surgeons before the study is started. Patients in the PGA group undergo transection of the pancreas and application of fibrin glue, followed by tightly wrapping the PGA mesh around the remnant pancreatic stump and stitching it with peripancreatic soft tissue. The type of cartridge is based on the thickness and texture of the pancreas and is selected by each surgeon during
the operation. Suture reinforcement of the transection margin is not performed. Before closure, one closed suction drain is inserted into the bed of the removed portion of the pancreas and maintained for at least 3 days postoperatively to prevent intra-abdominal fluid collection and identify POPF.

4.3 Postoperative management

Perioperatively, none of the patients is allowed use of prophylactic somatostatin analogues to prevent POPF development. Each patient is allowed sips of water on postoperative day (POD) 1 and a soft blended diet on POD 2.

4.4 Primary endpoint: the development of a clinically relevant POPF (grade B or C by the ISGPF grading system)

- Output through an operatively placed drain or a subsequently placed percutaneous drain, of any measurable volume of drain fluid on or after 10 postoperative day 3, with an amylase content greater than three times the upper normal serum value.

- Main parameters for POPF grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical conditions</td>
<td>Well</td>
<td>Often well</td>
<td>Ill appearing/ bad</td>
</tr>
<tr>
<td>Specific treatment</td>
<td>No</td>
<td>Yes/ no</td>
<td>Yes</td>
</tr>
<tr>
<td>US/CT (if obtained)</td>
<td>Negative</td>
<td>Negative/positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Persistent drainage (after 3 weeks)</td>
<td>No</td>
<td>Usually yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reoperation</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Death related to POPF</td>
<td>No</td>
<td>No</td>
<td>Possibly yes</td>
</tr>
<tr>
<td>Signs of infections</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sepsis</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Readmission</td>
<td>No</td>
<td>Yes/ no</td>
<td>Yes/ no</td>
</tr>
</tbody>
</table>

US, Ultrasonography; CT, computed tomographic scan; POPF, postoperative pancreatic fistula. Partial (peripheral) or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or minimal invasive drainage.

4.5 Secondary endpoint: the evaluation of risk factors for POPF

Operation-related risk factors: estimated blood loss, operation time, laparoscopic/open, etc.

5. Sample size
Study sample was calculated by assuming that the clinically relevant POPF rates would be less than 3.8% and 27% in the PGA and control groups, respectively, based on retrospective findings (Ochiai et al; 2010). Enrolling 106 patients would therefore provide 80% power to detect such a difference with an adjusted significance level $\alpha = 0.025$, $\beta = 0.2$, and an expected dropout rate of 23%, as determined by the Medical Research Collaborating Center, Seoul National University Hospital using Power Analysis and Sample Size software (NCSS, LLC. Kaysville, Utah, USA).

6. Assessment

• PGA / control group
• Pathologic indications for distal pancreatectomy
• Date of operation and discharge
• Postoperative hospital stay
• Demographics: age, gender
• Pancreatic duct diameter
• Pancreatic texture
• Thickness of pancreatic resection line
• Used cartridge size
• Operation time
• Estimated blood loss
• Postoperative pancreatic fistula (grade A, B, or C by ISGPF)
• Postoperative complications
• Risk factors for clinically relevant pancreatic fistula

7. Statistical analysis

Results are presented as mean ± standard error of the mean. Patient demographics and clinical characteristics are compared using the chi-square test or Fisher's exact test for categorical variables, and Student's t test and the Mann-Whitney test for continuous variables. In assessing risk factors associated with POPF, only variables statistically significant by univariate analysis are included in the multivariate analysis, which is performed using logistic regression. All statistical analyses are performed using SPSS, version 21.0 (SPSS Inc, Chicago, IL), with P-values < 0.05 considered statistically significant.
8. References


7. Sohei Satoi, Hideyoshi Toyokawa, Hiroaki Yanagimoto, Tomohisa Yamamoto Reinforcement of Pancreticojejunostomy Using Polyglycolic Acid Mesh and Fibrin Glue Sealant Pancreas 2011;40:16-20

