Standard Whipple's Operation versus Pylorus Preserving Pancreaticoduodenectomy: A Randomized Controlled Trial Study

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Objective: *A single-institution randomized controlled trial was conducted to compare the results of standard whipple operation (SW) with those of pylorus-preserving pancreaticoduodenectomy (PPPD).*
Material and Method: *Between January 2000 and December 2004, 27 patients with pancreatic or periampullary adenocarcinoma were enrolled into the study. All patients were randomly allocated to either a SW or a PPPD resection. Patients' characteristics, postoperative mortality and morbidity, and survival up to two years were compared.*
Results: *There were no significant differences in baseline characteristics between the two groups of patients. There were also no significant differences in blood loss and operative time. Delayed gastric emptying (DGE) occurred more frequently in the PPPD group, but other operative complications, hospital mortality, and the length of hospital stay were similar for the two groups. There were no significant survival differences at two years after operation.*
Conclusions: *SW and PPPD were comparable in terms of operation time, blood loss, operative mortality and morbidity, and survival. Although the incidence of DGE was higher in the PPPD group, the hospital stay was similar for both groups. Both surgical procedures were equally effective for the treatment of pancreatic and periampullary carcinoma.*

Keywords: *Whipple operation, Pylorus-preserving, CA pancreas*

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Pancreatic cancer is one of the most fatal malignant diseases. Five-year survival after pancreaticoduodenectomy for pancreatic cancer ranges from 10% to 29%[1-6]. The introduction of pancreaticoduodenectomy is credited to Codivilla, an Italian surgeon, in 1898; and Kausch, a German surgeon from Berlin, in 1912[7]. Later, in 1935, this technique was refined by Whipple et al[8].Several modifications to the procedure have since been reported, including the pylorus-preserving pancreaticoduodenectomy (PPPD) described by Watson in 1944[9].

PPPD was reintroduced by Traverso and Longmire in the late 1970s for the treatment of chronic pancreatitis[10]. Preservation of the pylorus in pancreaticoduodenectomy has been shown in retrospective studies to lead to a long-term improvement in gastrointestinal function, as indicated by more postoperative weight gain, fewer peptic ulcers, and less dumping symptoms. Furthermore, the preservation of the pylorus simplifies the operation, leading to shorter operative times and less intraoperative blood loss[11]. The present randomized controlled trial was conducted to compare PPPD with standard Whipple (SW) procedure in terms of operative time, blood loss, postoperative morbidity and mortality, incidence of delayed gastric emptying time and overall survival.

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Material and Method

The study protocol was approved by the Hospital's research ethics committee. Informed consent was obtained from all participants. Patients were

randomly allocated to treatment with either a SW or a PPPD.

Preoperatively, a CT scan of the upper abdomen and a chest x-ray were obtained for all patients suspected of having pancreatic or periampullary cancer. In most patients, an endoscopic retrograde cholangiopancreatography (ERCP) was also performed.

Patients with suspected pancreatic or periampullary cancer evaluated to have resectable disease were included in the present study. Patients with a previous gastric resection, or those who had distant metastasis or locally unresectable tumors were excluded. Patients who had tumor invasion of the pylorus or stomach were also excluded, as were those who refused to participate in the present study.

Randomization was done via a computer-generated random number list. Concealment of allocation was via sealed opaque envelopes, which were opened only after it was ascertained that either SW or PPPD was feasible in the patient.

Prophylactic antibiotics consisted of 2 gm of cefazolin and 500 mg of metronidazole given intravenously for all patients. Octreotide was given postoperatively for seven days, at a dosage of 100 μg administered subcutaneously three times daily.

The PPPD involved division of the duodenum 2 cm distal to the pylorus with resection of the remaining duodenum, removal of the gallbladder and common bile duct (proximal to the level of the cystic duct junction) and resection of the head, neck, and uncinate process of the pancreas. SW involved a distal gastrectomy varying from 20% to 40% of the whole stomach, an end-to-side invaginated pancreatico jejunostomy, an end-to-side hepaticojejunostomy, and a side-to-side gastroenterostomy or an end-to-side pylorus-jejunostomy.

All patients were managed according to a standard postoperative care plan. All patients received H2-receptor antagonists as prophylaxis against stress ulceration. At the end of the operation, a drain was left in the area of the pancreaticojejunostomy and the hepaticojejunostomy. The drain was removed if the amylase concentration in the drainage fluid was less than 300 U/L (less than twice the serum concentration) and if production was less than 50 mL per day, or after the 10^{th} postoperative day. Pancreatic fistula was defined as drainage of amylase-rich fluid of more than 50 mL per day and persisting after the 10^{th} postoperative day.

The nasogastric tube was removed when its output has decreased to less than 300 mL per 24 hours. Delayed gastric emptying was defined as gastric stasis requiring nasogastric intubation for 10 days or more or the inability to tolerate a regular diet at three months after operation.

On pathological examination, resection margins of the specimen were stained and were considered positive if the cancer was present at the pancreatic neck, uncinate process, common bile duct, duodenum/gastric resection area, mesenteric artery and/or the portal vein.

Patients were followed every three months after surgery for up to 60 months. All patients were followed for at least two years. Follow-up data were obtained via office records from the outpatient clinic, and was completed up to December 2006. Patient characteristics, intraoperative variables, pathologic findings, and postoperative course were recorded. These included blood loss, duration of operation, incidence of delayed gastric emptying, intraoperative and postoperative complications, length of hospital stay, and hospital mortality.

The primary endpoints in the present study were intraoperative blood loss, operative time, and length of hospital stay. The secondary endpoints were the occurrence of delayed gastric emptying and survival at two years. Statistical hypotheses comparing categorical variables or continuous variables between the two groups were tested using Chi-square or Fisher's exact test and Student's t-test or mann whitney U test when appropriate. Statistical significance was defined as two-tailed p-value of 0.05 or less.

Results

Twenty-seven patients with histology-proven pancreatic and periampullary adenocarcinoma were included in the present study. Thirteen patients were randomized to receive SW, and 14 patients were randomized to receive PPPD. The median age of patients in the SW and PPPD groups were 63.3 years (range, 52 to 72 years) and 61.8 years (range, 51 to 74 years), respectively. The proportion of men to women were 62% (8/13) to 38% (5/13) and 71% (10/14) to 29% (4/14) in the SW and PPPD groups, respectively. These two characteristics were not significantly different between the two groups.

The median intraoperative blood loss was 1946 cc (range, 1200 to 2600 cc) in the SW resection group and 1850 cc (range, 1300 to 2400 cc) in the PPPD group. The difference was not statistically significant (p-value = 0.44). The median operative time was 316.4 minutes (range, 287 to 360 minutes) in the SW group and 303.12 minutes (range, 345 to 367 minutes) in the

PPPD group. This difference was also not significant (p-value = 0.17).

Postoperative complications, hospital mortality and survival at one and two years after operation are presented in Table 1. The incidence of delayed gastric emptying was significantly different between the two groups (15% (2/13) in SW group and 64% (9/14) in the PPPD group), although the length of hospital stay was similar for both groups. Other postoperative complications, hospital mortality and survival at two years were also similar for both groups.

Pathological findings are presented in Table 2. Pancreatic adenocarcinoma was found in 10 patients (77%) in the SW group and in eight patients (57%) in the PPPD group. Tumor-positive lymph nodes were found in 11 patients (86%) in the SW group versus 10 patients (71%) in the PPPD group. None of these differences was statistically significant.

Discussion

In the present study, the hypothesis was that PPPD is associated with a shorter operative time, less blood loss, shorter hospital stay, and a more physiological food passage. Two small randomized controlled trials reported a shorter operative time, less blood loss, fewer blood transfusions, and a lower morbidity for PPPD[12,13]. However, a larger multicenter randomized controlled trial did not show significant differences between PPPD and SW in all measured outcome[14].

In the present study, the duration of the operation was similar for the two procedures. The median blood lost also did not differ significantly between the two groups. Compared with reports from some centers, blood loss in the present series was two times higher[15,16]. However, in comparison with other multicenter studies[17,18], there were only small differences.

The overall operative mortality rate in the present study was 22% (6/27). Compared with results from other studies, in which the operative mortality ranged from 5% in Italy[18], 5.3% in Netherlands[14], to 10% in France[19] and 17.2% in the United States[20], the present mortality rate was rather high.

PPPD has been associated with increased incidence of delayed gastric emptying (DGE). Warshaw and Torchiana first reported this phenomenon in their

Table 1. Postoperative complications, hospital mortality and survival

Complications	SW (n = 13)	PPPD (n = 14)	p-value
Pancreatic fistula	4 (30.8%)	5 (35.7%)	0.99
Gastroenterostomy leakage	2 (15.4%)	1 (7.1%)	0.60
Bile leakage	0	2 (14.3%)	0.48
Postoperative bleeding	1 (7.7%)	1 (7.1%)	0.99
Intra-abdominal abscess	2(15.4%)	2 (14.3%)	0.99
Other complications	6 (46.2%)	5 (35.7%)	0.70
Hospital mortality	2 (15.4%)	4 (28.6%)	0.65
Delayed gastric emptying	2 (15.4%)	9 (64.3%)	0.02
Median hospital stay (days)	20 (11-24)	22 (12-28)	0.76
Survival at 1 year	9 (69.2%)	8 (57.1%)	0.70
Survival at 2 years	4 (30.8%)	5 (35.7%)	0.99

SW, standard Whipple; PPPD, pylorus-preserving pancreaticoduodenectomy

Table 2. Pathological findings

Characterictics	SW (n = 13)	PPPD (n = 14)	p-value
Pancreatic adenocarcinoma	10 (76.9%)	8 (57.1%)	0.42
Periampullary adenocarcinoma	3 (23.1%)	6 (42.9%)	0.42
Positive peripancreatic LN	11 (84.6%)	10 (71.4%)	0.65
Mesenteric vessels involvement	2 (15.4%)	2 (14.3%)	0.99

SW, standard Whipple; PPPD, pylorus-preserving pancreaticoduodenectomy; LN, lymphnode

study of eight patients in 1978[21]. According to the literature, the incidence of DGE is estimated to range between 25% and 70%[21-30]. The incidence of DGE in the present study was 15% (2/13) in the SW group, and 64% (9/14) in the PPPD group. This difference was statistically significant ($p = 0.02$).

DGE has been thought to be caused by local ischemia of the antrum, the absence of duodenal hormones, inflammation from pancreaticoenterostomy, edema from duodenojejunostomy, and gastric atony caused by vagotomy. Moreover, reported results of univariate analyses have suggested that factors associated with DGE after PPPD are the length of the preserved proximal portion of the duodenum, volume of gastric juice, duration of gastric tube placement, and administration of cisapride[30]. However, the true mechanism of DGE is still unknown, and its pathophysiology has not been elucidated. Yeo et al[31]. reported in a randomized trial that administration of erythromycin, a motilin agonist, decreased the incidence of DGE by 37%. Since this difference was not statistically significant, erythromycin was not included as standard therapy in the present study. But Sriussadaporn S et al reported a low incidence of early DGE in PPPD (5.4%)[32] that DGE could be prevented by careful and faultless surgical techniques. Comprehensive postoperative care and early parenteral and enteral nutritional support can usually overcome the problem of DGE.

In the present study, a median hospital stay of 20 days for the SW group and 22 days for PPPD group were not significantly different ($p = 0.76$). The one- and two-year survival did not differ significantly between the two groups and were comparable to the results of other randomized controlled trials[13,18].

Conclusion

PPPD and SW operations seemed to be equally effective for the treatment of resectable pancreatic and periampullary adenocarcinoma. There were no significant differences between the two groups in terms of the duration of operation, blood loss, length of hospital stay, hospital mortality, and overall survival at two years. PPPD was associated with a higher incidence of DGE.

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การผ่าตัดแพนครีเอติโคดูโอเดเนกโตมีชนิดมาตรฐานวิปเปิ้ลและชนิดเก็บหูรูด: การศึกษาเปรียบเทียบโดยการทดลองแบบสุ่ม

ฉัตรชัย ศรีนามวงศ์, ประกอบ ลือชาเกียรติศักดิ์, วสันต์ ประสิทธิ์วิไล

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบโดยการทดลองแบบสุ่ม ในสถาบันเดียว ถึงผลลัพธ์ของการผ่าตัด แพนครีเอติโคดูโอเดเนกโตมีชนิดมาตรฐานวิปเปิ้ลกับชนิดเก็บหูรูด*

วัสดุและวิธีการ: *เป็นการศึกษาผู้ป่วย จำนวน 27 ราย ที่เป็นมะเร็งบริเวณตับอ่อนและบริเวณแอมพูล่าออฟวาเตอร์ ระหว่างเดือนมกราคม พ.ศ.2543 ถึง เดือนธันวาคม พ.ศ.2547 ผู้ป่วยทุกรายได้รับการผ่าตัดแพนครีเอติโค ดูโอเดเนกโตมีชนิดมาตรฐานวิปเปิ้ล หรือ ชนิดเก็บหูรูดโดยการสุ่ม ได้ศึกษาเปรียบเทียบลักษณะเฉพาะของผู้ป่วยภาวะแทรกซ้อนหลังผ่าตัด อัตราตายและการรอดชีวิตหลังผ่าตัดในระยะเวลา 2 ปี*

ผลการศึกษา: *พบว่าไม่มีความแตกต่างในลักษณะเฉพาะของผู้ป่วย การเสียเลือด และระยะเวลาในการผ่าตัดของผู้ป่วยทั้งสองกลุ่ม ภาวะกระเพาะอาหารกลับมาทำงานได้ช้า จะพบมากในการผ่าตัดชนิดเก็บหูรูด แต่ภาวะแทรกซ้อนอื่น ๆ จำนวนวันนอนในโรงพยาบาลของทั้งสองกลุ่มไม่แตกต่างกัน อัตราการรอดชีวิตของทั้งสองกลุ่มเมื่อติดตามในระยะเวลานาน 2 ปี พบว่าไม่มีความแตกต่างกัน*

สรุป: *การผ่าตัดแพนครีเอติโคดูโอเดเนกโตมีชนิดมาตรฐาน วิปเปิ้ล และชนิดเก็บหูรูดไม่มีความแตกต่างกันในแง่ของเวลาในการผ่าตัด จำนวนเลือดที่เสีย ภาวะแทรกซ้อนของการผ่าตัด และอัตราตาย ถึงแม้ว่าภาวะกระเพาะอาหารกลับมาทำงานช้า จะพบมากในการผ่าตัดชนิดเก็บหูรูด แต่จำนวนวันนอนในโรงพยาบาลไม่แตกต่างกัน การผ่าตัดทั้งสองชนิดนี้ มีประสิทธิผลในการรักษามะเร็งตับอ่อน และบริเวณแอมพูล่าออฟวาเตอร์ ได้เท่าเทียมกัน*