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Total pancreatectomy and salvage completion pancreatectomy-early and late outcomes without Islet cell auto-transplantation

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Abstract

Background: Total pancreatectomy was abandoned for decades because of high peri and post-operative morbidity and mortality. However, with better peri-operative outcome and post-operative management of exocrine and endocrine insufficiency, the hesitancy to perform total pancreatectomy has been disappearing.

Objectives: This study aims to study exocrinal and endocrinal effects of total pancreatectomy without Islet cell auto-transplantation and compare quality of life index among total pancreatectomy with Whipple patients.

Methodology: This is a prospectively conducted matched-pairs study. Group A underwent total or completion pancreatectomy after non-salvageable complications of Whipple operation. A matched-pairs analysis of quality of life index of these patients by using SF-36 questionnaire were compared with Group B who underwent Whipple operation during the same period of time, according to age, gender and pre-operative diagnosis.

Results: In four years (from February 2016 to February 2020), 160 patients underwent Whipple operation. The mean age of the patients was 59.9 +/-14.3 years. A total of nine patients underwent total pancreatectomy, among which two had per-operative decision of total pancreatectomy and seven had completion pancreatectomy. Median post-operative hospital stay was 11 days with two mortalities. Median follow-up of 12 months and quality of life index of total pancreatectomy patients were comparable to Whipple patients, although a few single quality of life items were reduced.

Conclusion: Exocrinal pancreatic supplements and long acting insulin have augmented control of diabetes despite of not using Islet cell auto-transplantation. Quality of life index of total pancreatectomy patients were comparable to that of Whipple patients. Hence, this study signifies the importance of completion pancreatectomy following non-salvageable complications after Whipple operation in order to save life.

Key words: Completion pancreatectomy; Islet cell auto transplant; Total pancreatectomy; Whipple operation.

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INTRODUCTION

Total pancreatectomy (TP) used to be considered as a procedure of obligations because of its high post-operative complications in the last few decades.[1-3] However, many recent studies have shown its feasibility with good post-operative outcomes when needed for different purposes as indications for elective total pancreatectomy has broadened from being part of radical surgery for R0 resection in pancreatic cancer[4,5] to multifocal IPMN,[6,7] beside completion pancreatectomy for post Whipple complications like anastomotic leakage or bleeding with uncontrolled sepsis.[8,10]

As the number of TP has increased, lots of researches have focused on Islet cell auto-transplantation during index surgery[11-14] and look for its post-operative exocrine, endocrinal insufficiency and its effect on patient's physiology and psychology in terms of quality of life (QoL).[15-20]

However, in a developing country like Nepal where Islet cell transplant is not available, we have tried to evaluate the peri-operative results and long-term course of patients with total pancreatectomy in terms of exocrine and endocrinal insufficiency after total pancreatectomy and its effect on QoL by matching with patients who have undergone Whipple operation for pancreatic malignancy during same period depending on age, gender and pre-operative diagnosis.

METHODOLOGY

The study was conducted at the Department of General Surgery, Kathmandu Medical College Teaching Hospital, Nepal between February 2016 and February 2020 by prospectively entering data (in an electronic database) of patients undergoing a Whipple operation and total pancreatectomy performed by a single surgical team.

Operative Details

After Cattell Braasch maneuver, artery first approach was used in most Whipple operation with demonstration of superior mesenteric artery (SMA) origin and inferior pancreaticoduodenal artery.[21-23] Duct to mucosa pancreaticojejunostomy was done with 5.0 polydioxone suture according to Heidelberg technique.[24] Use of nasogastric tube was avoided and early feeding with mobilization was done according to ERAS protocol.[25]

Indication for Total Pancreatectomy

Pathological cause:

- Huge tumor involving whole of pancreatic parenchyma.
- Multifocal IPMN.

Technical cause:

- Soft pancreas with small duct less than 2 mm with precarious pancreaticojejunostomy or failure of modification of pancreatic stump anastomosis.

Completion Pancreatectomy:

It was indicated in patients with anastomotic leakage with sepsis or bleeding not manageable conservatively and/or with intervention radiology. It was done either with or without spleen preservation.

Patient were monitored and followed up in 1 month, 3 months, 6 months and a year after discharge from the hospital. Patients were followed up in the outpatient clinic and interviewed using a standardized questionnaire. Post-total pancreatectomy exocrinal function was assessed objectively with fecal elastase level and subjectively with bowel movement history whereas endocrinal function was assessed with total units of insulin required in 24 hours.

Quality of Life Assessments

The Medical Outcomes Study (MOS) 36-item Short Form (SF-36) health survey was used as a measure of subjective feeling with quality of life (QoL).[26, 27] The SF-36 gives a health status profile along eight dimensions corresponding to the following scale scores: physical functioning, role limitations attributed to physical health problems, bodily pain, general health, social functioning, vitality, role limitations attributed to emotional health problems, and mental health. The scale scores range between 0 and 100 with higher values signifying more positive health attributes. These eight-scale scores are the basis of the Physical Component Summary (PCS) and the Mental Component Summary Scale (MCS) scores. This scoring for total pancreatectomy was then compared with a match paired control that had undergone Whipple operation during the same period of time according to age, gender and pre-operative clinical diagnosis.

Statistical Analysis

Statistical Package for the Social Sciences version 16 was used for statistical analysis.[28] QoL parameters from the SF-36 questionnaire were used and age and follow-up time are presented as mean with standard deviation and as median. Comparisons of groups of patients were performed using Fisher exact test. Continuous parameters were compared between groups of patients using the nonparametric Mann-Whitney *U* test and considered statistically significant if $p< 0.05$.

RESULTS

In a four-year period (February 2016 to February 2020), a total of 160 patients underwent Whipple operation. Indications for a Whipple operation were pancreatic and peri-ampullary adenocarcinoma (n=113), other neoplastic pancreatic tumors (intraductal papillary mucinous neoplasms, neuroendocrine tumors, solid pseudo-papillary tumors; n=34), and chronic pancreatitis (n=13). There were 73 males and 87 females with a mean age of 59.9 +/- 14.3 years.

A total of nine pancreatectomies were performed among which two patients underwent total pancreatectomy along with antrectomy without vagotomy during per-operative decision. Among them, one patient had a huge solid pseudo-papillary tumor with a small pancreatic remnant without pancreatic duct visualization and the other patient had distal cholangiocarcinoma and very soft pancreas with pancreaticojejunostomy attempted twice but had failed.

Seven patients underwent completion pancreatectomy because of severe post-operative complications (Clavien-Dindo classification[29] Grade IIIb/ IVb) after elective pancreatic resection, among which pancreatic remnant necrosis, severe pancreatic leakage because of small duct PJ with sepsis, bleeding from pancreaticojejuno (PJ) anastomosis uncontrolled by interventional radiological approach occurred in four, two and one patient respectively.

Among the nine patients who underwent total pancreatectomy, two patients died. The first patient had undergone completion pancreatectomy on 5th post-operative day following Whipple operation and died because of septic shock due to pancreatic remnant necrosis; the other 74 years female developed diffuse peritonitis on the 12th post-operative day following Whipple surgery and was found to have diffuse thrombosis of celiac trunk with complete gangrene of pancreas remnant and part of stomach. However, the liver was spared because of accessory right hepatic artery from SMA (Mitchel type III).

In all Whipple patients, conventional gastrojejunostomy without pylorus preservation was performed except in two patients who underwent total pancreatectomy as intra-operative decision. Vagal sparing antrectomy along with total pancreatectomy was done with the view that gastric transit time might be shortened due to wide gastrojejunostomy and decrease the source of acid secretion so that post-operative exocrine pancreatic supplement can be adequate after supplementation. Among them three patients had spleen preserving total pancreatectomy (Table 1).

Mean age in total pancreatectomy was 49.42+/-17.08 years whereas mean age in Whipple operation was 50+/-17.13 years (Table 2). Total hospital morbidity after Whipple operation was 27.5%, among which surgical morbidity needing surgical intervention (in terms of drain mobilization or insertion of pigtail drainage under ultrasound guidance or surgical site infection) was 15% whereas medical morbidity was 12.5%. Total hospital mortality among total Whipple operation was 1.25%. According to Clavien-Dindo classification, it could be classified as Grade I - 12.5%, Grade II – 4.8%, Grade IIIa – 5.8 %, Grade IIIb - 3.75%, Grade IVa - 0%, Grade IVb - 0.65% and Grade V - 1.25%.

Patients were assessed for subjective quality of life (QoL) by using the SF-36 questionnaire after one year of total pancreatectomy or completion pancreatectomy and were pair matched with patients who underwent Whipple operation according to age, gender and pre-operative diagnosis during the same period of time. There was not much difference among both in terms of physical functioning and emotional well-being except in patients with total pancreatectomy or completion pancreatectomy who felt more role limitation due to physical and emotional problems compared to patients who underwent Whipple operation (p-0.03 and 0.000 respectively) (Table 3).

Table 1: Indications for total pancreatectomy and salvage completion pancreatectomy.

Indication for salvage completion pancreatectomy	Total patients (N=9)
Severe pancreatic leakage with uncontrolled sepsis	
• Pancreatic remnant necrosis	4 (one with spleen preservation)
• Severe pancreatitis	2
Bleeding from pancreaticojejunostomy anastomosis uncontrolled by interventional radiological approach	1
Indication for total pancreatectomy (per operative decision):	
• Huge solid pseudo-papillary tumor with small pancreatic remnant without pancreatic duct visualization	1 (with spleen preservation)
• Soft pancreas with twice pancreaticojejunostomy attempted but failed with short remnant stump	1 (with spleen preservation)
Indication for salvage completion pancreatectomy	Total patients (N=9)

Table 2: Pair matched between total pancreatectomy and Whipple operation according to age, gender and pre-operative diagnosis.

	Total pancreatectomy	Whipple operation	p–value (significant if p< 0.05)
Age (years)	49.42+/-17.08	50.0+/-17.1	0.982
BMI	23.21+/-1.62	24.57+/- 0.97	0.140
Hospital stay(days)	13.7+/-3.9	5.42+/-0.53	0.005
Hb1Ac	6.28+/-0.55	5.6+/-0.84	0.287
Insulin requirement (units/24 hours)	16.42+/-3.45	None	0.030
Fecal Elastase –F1	100-200 µg per gram of stool	More than 200 µg per gram of stool	0.001

Table 3: Pair matched between total pancreatectomy and Whipple operation according to age, gender and pre-operative diagnosis in terms of Quality of Life index using SF-36 questionnaire.

SF-36 Questionnaire	Total pancreatectomy	Whipple operation	p–value (significant if p< 0.05)
Physical functioning	69.28+/-9.75	88.57+/-4.7	0.249
Role limitation due to physical health	42.85+/-53.45	89.28+/-28.34	0.03
Role limitation due to emotional problem	42.85+/-53.45	100	0.000
Energy / fatigue	47.85+/-2.6	51.42+/-5.5	0.73
Emotional well-being	38.28+/-6.8	64.57+/-8.1	0.453
Social functioning	48.21+/-13.36	87.50+/-7.2	0.142
Pain	44.28+/-12.64	84.28+/-10.37	0.650
General health	37.85+/-8.5	58.57+/-6.26	0.346

DISCUSSION

This study has emphasized the significance of total pancreatectomy if indicated or salvage completion pancreatectomy when non-salvageable complication occurs after Whipple operation in order to save life. Our study shows a mortality rate of 1.25% (n=2) after Whipple operation with intervention of completion pancreatectomy. Moreover, survival benefit of 4.37% (n=7) was found in those patients who underwent completion or total pancreatectomy. Besides, our study has shown that quality of life (QoL) index did not differ much among both in terms of physical functioning and emotional well-being but had some role limitation.

In the past, after total pancreatectomy many feared of exocrine insufficiency leading to symptoms like weight loss, diarrhea and malabsorption leading to significant decrease in quality of life.[30-32] Steatorrhoea has been associated with loss of fat-soluble vitamins, especially vitamin D, leading to osteoporosis as well as deranged liver functions.[33-35] Endocrinal insufficiency has been more difficult to manage as insulin dependent diabetes causes blood glucose to be unstable and is often difficult to control.[36,37] Hence, total pancreatectomy was abandoned and considered as a non-viable option.[38,39] However, there has been paradigm shift in the management of controlling diabetes mellitus and improvements in modern pancreatic enzyme preparations have helped to control endocrine and exocrine pancreatic insufficiency to tackle post-operative consequences.[40-42]

In two of our patients who underwent total pancreatectomy as an intra-operative decision, vagal sparing antrectomy along with total pancreatectomy was done, with the view that it might shorten gastric transit time due to wide gastrojejunostomy and decrease the source of acid secretion so that post-operative exocrine pancreatic supplement can be adequate after supplementation. However, the rationale of it needs to be proved by a large powered study.

Studies from multiple large cohorts have shown that there have been improved survival outcomes along with significant improvement in quality of life with the use of exocrine supplements following pancreatic cancer surgery.[43-47] In our study, despite use of exocrinal

pancreatic supplements at 12000 USP units of lipase four times a day, fecal elastase-F1 seemed to be in the intermediate level (100-200 µg/g of stool), which helped us to guide the increase in dosage of pancreatic supplement to adequate level along with other fat soluble vitamin supplements.

Islet cell auto-transplantation has been advised after total pancreatectomy as it helps to decrease the 24-hour insulin demands and might also potentially achieve insulin independence.[48-50] However, NSQIP data in 2014 has shown that total pancreatectomy with islet cell auto-transplantation has been associated with high morbidity rate, with longer hospital stay and three fold in transfusion rate than those who have undergone total pancreatectomy alone.[51] Moreover, in a developing country like Nepal where lack of resources has been the main constraint, many centers cannot afford it and with improvement of long acting insulin, endocrinal insufficiency can be well managed. In our study, endocrinal insufficiency seems to be well tolerated with mean Hb1Ac of 6.28+/-0.55 without islet cell transplantation and average insulin requirement seems to be within 10-20 units per day.

The most feared complications were brittle diabetes, lifelong dependency on insulin and exocrine supplements which made patients prone to psychological distress influencing their quality of life.[52-54] In our study, patients were followed up till 1 year and were assessed with the use of RAND SF-36 which did not show much difference among both, in terms of physical functioning and emotional well-being except in patients with total pancreatectomy or completion pancreatectomy who felt more role limitation due to physical and emotional problems. This could probably be due to repeated insulin dependence for blood glucose control and exocrinal supplement of pancreatic enzymes.

LIMITATIONS OF THE STUDY:

1. Small sample size of patients with total pancreatectomy.
2. Short term follow up was targeted in this study. However, long term follow up is necessary to look for long term effect of total pancreatectomy, overall disease free survival rate and overall survival rate.

CONCLUSIONS

This study signifies the importance of completion pancreatectomy following non-salvageable complications after Whipple operation in order to save life. Post-operative exocrine and endocrine supplements are adequate for existing BMI of Nepalese populations without Islet cell transplantation.

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