

# Merits of Enhanced Recovery after Surgery Protocol following Whipple Pancreaticoduodenectomy: A Pilot Study

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## ABSTRACT

**Introduction:** While Enhanced Recovery After Surgery (ERAS) has been widely implemented in upper and lower gastrointestinal operations, its application after Whipple pancreaticoduodenectomy remains at an experimental level and has not been accepted as a standard of care in most centers including ours.

**Aim:** To assess the merits and safety of ERAS after Whipple pancreaticoduodenectomy.

**Materials and Methods:** This was a pilot study (prospective cohort study design) conducted at Christian Medical College Vellore, Tamil Nadu, India. Total 30 consecutive patients who underwent Whipple procedure between September 2016 and May 2017 were managed using the ERAS protocol in the postoperative period. The operations were performed by one of the three senior surgeons and a standard method of reconstruction was followed. All patients underwent a feeding jejunostomy as part of the operation. The primary end point was duration of hospital stay and secondary end points were number of days required for urinary catheter removal, ambulation, cessation of intravenous fluids, discontinuation of infusional analgesia, removal of nasogastric tube, normal oral intake and drain removal. The rates of complications including Postoperative Pancreatic

Fistula (POPF), Delayed Gastric Emptying (DGE), intra abdominal collection, post pancreatectomy haemorrhage and death were also calculated and compared with previous year data to assess the safety of ERAS protocol.

**Results:** Mean age of patients was 53.9 years. There were 26 males and four females in this study. Total 21 out of the 30 patients had ampullary adenocarcinoma. More than 80% of the patients achieved milestones like urinary catheter removal, ambulation, cessation of i.v. fluids and infusional analgesia. Total 14 out of 30 (46.6%) patients tolerated normal diet by day 6 and 17 patients were managed without utilising the feeding jejunostomy. Drains were removed only in seven patients as per protocol. The mean hospital stay was 20.1 in comparison to the mean stay of the previous year which was 22.8 days. However, 15 patients were fit for discharge by day 15 based on discharge criteria, but were not discharged as the patients wanted to stay longer. There was no increase in morbidity or mortality in comparison to the previous year.

**Conclusion:** The implementation of ERAS protocol appears to have no negative impact in the postoperative recovery in the patients with a potential for shortening hospital stay without added postoperative morbidity.

**Keywords:** Critical pathway surgery, Delayed gastric emptying, Fast track surgery, Postoperative pancreatic fistula

## INTRODUCTION

Whipple pancreaticoduodenectomy is the operative procedure for malignancy in and around the ampullary region which includes ampullary adenocarcinoma, distal cholangiocarcinoma, duodenal adenocarcinoma and carcinoma head of pancreas. Though it is a complex operation, the mortality related to the operation has been reduced to less than 5% over the years [1]. However, the morbidity rates continue to remain high at 30-50% [2]. The most common morbidities are Delayed Gastric Emptying (DGE) and Postoperative Pancreatic Fistula (POPF), both of which cause significant delay in postoperative recovery and thereby prolonging the hospital stay [3]. However, in the absence of significant postoperative morbidity, early rehabilitation is one of the most important ways of shortening hospital stay [4]

Enhanced Recovery After Surgery (ERAS), Fast-Track or critical pathway are multimodal perioperative care pathways intended to achieve early retrieval after surgical procedures by maintaining preoperative organ function and reducing the profound stress response following surgery [5]. The main objective of such fast track programmes is to reduce morbidity and enhance recovery by reducing surgical stress by optimal control of pain, early oral diet and early mobilisation thereby shortening the length of hospital

stay [6]. Such fast-track programs have proven to be very successful following colorectal and upper gastrointestinal operations [7,8]. Pancreaticoduodenectomy is associated with high morbidity rate of 30-50% [2,9]. Owing to the relatively high morbidity rates associated with pancreaticoduodenectomy, the recommendations of the ERAS society have been evolving in an attempt to make it the standard of care [10].

The aim of this study was to assess the feasibility of the standard ERAS protocol in the postoperative recovery of patients undergoing pancreaticoduodenectomy and to assess duration of hospital stay, which was the primary outcome.

## MATERIALS AND METHODS

This was a pilot study (prospective cohort study design) conducted at Christian Medical College Vellore, Tamil Nadu, India, between September 2016 and May 2017, wherein, 30 consecutive patients who underwent Whipple pancreaticoduodenectomy for malignancies in and around the ampulla were managed using the ERAS protocol in the postoperative period. The study was approved by Institutional Ethical Committee. Informed consent was obtained from the participants.

**Inclusion and Exclusion criteria:** All patients above 18 years of age, were included in the study. Patients in whom Whipple procedure

was abandoned due to distant metastases and who underwent palliative bypass procedures were excluded from the study.

## Study Procedure

The operation was carried out by three senior surgeons with over 15 years of experience in Hepatopancreatobiliary surgery, with no difference in outcomes between them. Right subcostal with midline vertical incision was used. Classical pancreaticoduodenectomy was carried out by the uncinate first approach. End to side duct to mucosa pancreaticojejunostomy was done using 5-0 prolene sutures by the modified Blumgart method and stents were not placed. End to side hepaticojejunostomy was done with 4-0 or 5-0 polydioxosilicate sutures. Antecolic posterior gastrojejunostomy was done in the same limb in a single layer with 3-0 prolene continuous sutures. Feeding jejunostomy was routinely done. Two abdominal drains, one each adjacent to the pancreaticojejunostomy and hepaticojejunostomy were placed at the end of the operation. Feeding jejunostomy was routinely done in all patients by Stamm's technique, using 18 Fr Foley's catheter. Nasogastric tube was retained in the postoperative period till the patient started taking oral liquids, as this was the routine practice in our centre. Urinary catheter, epidural catheter and central venous catheter were placed at the beginning of the operation and were removed at various points as mentioned in the ERAS protocol.

A stepwise protocol was followed in the postoperative period [Table/Fig-1] was designed and all patients who consented to be part of the study and underwent whipple procedure, were managed based on this protocol.

Postoperative day	Target to be achieved
0	Nil by mouth, epidural infusion, intravenous fluids
1	Ambulate to chair, sips of oral liquids, Heparin thromboprophylaxis, intravenous fluids
2	Removal of nasogastric tube, oral liquids at 50 mL per hour, to begin walking, supplementary intravenous fluids
3	Removal of urinary catheter, oral liquids at 80 mL per hour, supplementary intravenous fluids
4	Removal of epidural catheter, cessation of intravenous fluids, oral liquids at 100 mL/hour
5	Soft solid diet, Drain removal if drain amylase level is less than 300 IU/mL and if volume less than 300 mL
6	Normal diet
7	Discharge from hospital

[Table/Fig-1]: Enhanced Recovery After Surgery (ERAS) protocol.

The data collection sheet also had information on patient demographics including age, sex, indication for Whipple procedure, the presence or absence of preoperative biliary drainage and neoadjuvant chemotherapy. Gallery fistula risk score was calculated to classify pancreas as negligible risk, low risk, moderate risk and high risk [11].

**Parameters assessed:** The primary end point was to calculate the mean hospital stay. The number of days taken to achieve each of the milestones based on the ERAS protocol was recorded during the postoperative period. The secondary end points were number of days required for urinary catheter removal, ambulation, cessation of intravenous fluids, discontinuation of infusional analgesia, removal of nasogastric tube, normal oral intake and drain removal. The percentage of patients who achieved the milestones based on ERAS protocol was calculated. The rates of complications including POPF, DGE, post pancreatectomy haemorrhage and death were also calculated and compared with previous year data (June 2015 to June 2016) to assess the safety of ERAS protocol.

Nasogastric tube was reinserted if there was significant postoperative vomiting. Feeding jejunostomy was started only if oral intake was less than 1 litre on day 3 and soft solids by day 5. The mean hospital stay was also calculated. The rate of the most common complications

following Whipple procedure were also calculated to ensure safety of this protocol, based on comparison with rates from our centre and those accepted by the International Study Group of Pancreatic diseases Society (ISGPS) [12-14].

## STATISTICAL ANALYSIS

The results were expressed in terms of frequency and percentages.

## RESULTS

The patient demographics and preoperative characteristics were tabulated [Table/Fig-2]. The mean age of the patients undergoing Whipple pancreatoduodenectomy in this pilot study was 53.9 (standard deviation of 10.28). The age of the patients ranged from 32-72 years. There were 26 males and four females in this study. Total 21 out of the 30 patients had ampullary adenocarcinoma. Gallery fistula risk score was calculated based on consistency of pancreas, primary diagnosis, pancreatic duct diameter and intraoperative blood loss. A total of 23 patients had low risk pancreas, (5/23 developed a POPF) and five patients had moderate risk pancreas (3/5 developed POPF). The other two patients had negligible risk (no fistula in this group) and none had high risk pancreas. Total 17 out of the 30 patients had preoperative biliary drainage with endoscopic stent. Only four patients underwent stenting at our centre as we had very specific indications for preoperative biliary drainage which included cholangitis or persistent hypoalbuminemia. Level of bilirubin was not considered for biliary stenting. The other thirteen patients were referred to our centre after biliary stenting. Six out of the eight patients with pancreatic fistula had biliary stent.

Patient characteristics	Number of patients (N=30)
Mean age (years)	53.9
Males	26
<b>Diagnosis</b>	
Ampullary carcinoma	21
Carcinoma head of pancreas	5
Distal cholangiocarcinoma	3
Duodenal adenocarcinoma	1
Preoperative biliary drainage	17
Neoadjuvant chemotherapy	0
<b>Gallery fistula risk score</b>	
Negligible	2
Low	23
Moderate	5
High	0

[Table/Fig-2]: Patient demographics and preoperative characteristics.

The number and percentage of patients who achieved milestones as per the ERAS protocol was calculated [Table/Fig-3]. Around 90% of patients were able to achieve early ambulation, removal of urinary catheter and cessation of intravenous fluids. Though nasogastric tube was removed on day 2 in 93% of patients, it had to be reinserted in 60% of them most commonly due to DGE. Total 47% of patients tolerated normal diet by day 5 and 43% of patients did not require utilisation of feeding jejunostomy.

Clinically relevant pancreatic fistula (Grade B/C) was present in 8 (7+1) patients out of the 30 (26.6%). The DGE was noted in 9 patients (30%). Three patients required re-exploration, one each for grade C POPF and gastrojejunostomy leak. The third patient who required re-exploration for hepatic artery blow-out was the one mortality recorded in our study. In this patient, the rate at which he achieved the targets of ERAS protocol were documented, included in analysis and he was discharged on day 20. However, he was readmitted on day 22 with severe hypotension and underwent emergency laparotomy. He was found to have hepatic artery blow

Target	Yes	No	Reason for failure
Ambulation	27	3	<ul style="list-style-type: none"> <li>Pulmonary embolism-1</li> <li>Consolidation-1</li> <li>Persistent hypotension-1</li> </ul>
Nasogastric tube removal	28	2	<ul style="list-style-type: none"> <li>Pulmonary embolism-1</li> <li>Consolidation-1</li> </ul>
No nasogastric tube reinsertion	18	12	<ul style="list-style-type: none"> <li>Reexploration-2</li> <li>Upper gastrointestinal bleed-2</li> <li>Delayed gastric emptying-8</li> </ul>
Normal diet by day 5	14	16	<ul style="list-style-type: none"> <li>Nasogastric tube reinsertion-12</li> <li>Delayed gastric emptying-3</li> <li>Clostridium difficile diarrhoea-1</li> </ul>
Removal of urinary catheter	27	3	<ul style="list-style-type: none"> <li>Pulmonary embolism</li> <li>Consolidation</li> <li>Persistent hypotension</li> </ul>
Cessation of intravenous fluids	25	5	<ul style="list-style-type: none"> <li>Re-exploration-3</li> <li>Lung consolidation-1</li> <li>Upper gastrointestinal bleeding-1</li> </ul>
Drain removal	7	23	<ul style="list-style-type: none"> <li>Biochemical leak-2</li> <li>Grade B pancreatic fistula-7</li> <li>Re-exploration-3</li> <li>Chyle leak-2</li> <li>Post pancreatectomy haemorrhage-1</li> <li>High volume drain output-8</li> </ul>
Avoiding feeding jejunostomy	17	13	<ul style="list-style-type: none"> <li>Grade A delayed gastric emptying-2</li> <li>Grade B delayed gastric emptying-6</li> <li>Grade C delayed gastric emptying-1</li> <li>Re-exploration-2</li> <li>Post pancreatectomy haemorrhage-2</li> </ul>

**[Table/Fig-3]:** Compliance to targets on Enhanced Recovery After Surgery (ERAS) protocol.

out which was managed by ligation of common hepatic artery for uncontrolled haemorrhage. He subsequently developed cholangitis with uncontrolled sepsis from to which he succumbed.

The mean hospital stay was 20.1 days (standard deviation of 9.15). The most important reason (complications) for extended hospital stay was DGE and POPF with wound dehiscence or additional percutaneous drain placement. Three patients had a hospital stay of more than 30 days (two patients who underwent re-exploration and one who had post pancreatectomy haemorrhage). Out of the other 27 patients two were readmitted within 30 days, one for abdominal pain and the other patient was the mortality in our series.

## DISCUSSION

Whipple pancreaticoduodenectomy still remains an operation with high morbidity of 30-50% and mortality rate of 2-3% even in high volume centres [1,2]. ERAS was not practiced following Whipple pancreaticoduodenectomy at our centre prior to this pilot study. The primary end point was length of hospital stay which was 20.1 days in this study. It was shorter than the mean hospital during the previous year (June 2015 to June 2016) which was 22.8 days. This was comparable to the length of hospital stay recorded in the randomised control trial from Japan [15] and was much more than the length of stay reported from the west which was 16.5 days [16]. The reason for longer stay in our centre was because it not only included postoperative recovery but also rehabilitation during the same admission, owing to the lack of step-down/domiciliary care centres in peripheral small towns where most of our patients came from. The secondary end points were compliance to the targets as per ERAS protocol. The compliance was around 90% endpoints including early ambulation, cessation of intravenous fluids, removal of urinary catheter and removal of nasogastric tube. However, nasogastric tube had to be reinserted in 60% of the patients owing to postoperative nausea and vomiting or DGE. In terms of nutritional recovery, normal diet was tolerated on day 5 by 47% of the patients and feeding jejunostomy was avoided in 43% of patients. Though the protocol mentioned volume less than 300 mL as a criterion for drain removal, the clinical value of this is questionable as none of these patients had any evidence of any POPF or anastomotic leak during the postoperative recovery. After

this study however, the drain volume was no longer considered a criterion for drain removal in our centre.

The outcomes of this study was compared to the data from the previous year at our centre and to the data published by Cameron J and He J on 2000 consecutive pancreaticoduodenectomies [Table/Fig-4] [17]. The most common complication during the study period was DGE. Total 12 out of 30 patients had DGE, amounting to 40%. This was comparable to our previous year data where the rate of DGE was 33.3%. This rate was higher than that reported in the series of 2000 consecutive pancreaticoduodenectomies by Cameron J and He J where the rate was 21% [17]. The next most common complication was POPF which was seen in 8 patients amounting to 26.6%. This was higher than the previous year because the definition of POPF was modified in 2016, with retention of drains longer than three weeks being classified as grade B irrespective of drain amylase level [13,18]. The rate of pancreatic fistula during the study period was also higher than that reported in the series by Cameron J and He J where it was 15% [17]. The most likely reason for both POPF and DGE being higher in our centre was probably the indication for whipple pancreaticoduodenectomy being different. Total 47% of the patients in the series by Cameron J and He J underwent Whipple procedure for carcinoma head of pancreas, whereas at our centre the most common indication was ampullary adenocarcinoma making up 70% [17]. It has been proven by the Callery fistula risk score that carcinoma head of pancreas and the firm/hard consistency of pancreas that is associated with carcinoma head of pancreas contribute to negligible/low risk for pancreatic fistula. However, ampullary adenocarcinoma and the consequent soft pancreas both contribute to moderate/high risk for pancreatic fistula [19]. The next most frequent complication was post pancreatectomy hemorrhage which was seen in 6% of patients as compared to 4.16% in our previous year and 2% in the series by Cameron J and He J [17]. The mortality rate in our series was 3% compared to 4.1 % in our previous year, which is comparable to data most high volume centres [1,17].

Outcome	Current study (September 2016- May 2017) N/30 (%)	Previous study (July 2015- July 2016) N/24 (%)	Cameron J and He J [17], 2000 consecutive pancreaticoduodenectomies %
Mean hospital stay (days)	20.1	22.8	10
Delayed gastric emptying	12 (40%)	8 (33.3%)	21
Clinically relevant post operative pancreatic fistula	8 (26.6%)	3 (12.5%)	15
Postpancreatectomy haemorrhage	2 (6%)	1 (4.16%)	2
Gastrojejunostomy or hepatocoelejejunostomy leak	1 (3%)	0 (0%)	6
Re-exploration	3 (10%)	2 (8%)	3.5
Death	1 (3%)	1 (4.1%)	1.6

**[Table/Fig-4]:** Comparison of outcomes in pre ERAS and post ERAS Whipple operations [17].

## Limitation(s)

The limitation of this study was the small number of patients and the lack of randomisation, statistical analysis. Given the comparable and encouraging results from this pilot study, ERAS protocol has been adopted as the standard of postoperative care in our unit. However, a randomised control trial with calculation of cost-effectiveness and quality of life indices will add to the merits of this protocol.

## CONCLUSION(S)

The safety of ERAS protocol in patients undergoing Whipple pancreaticoduodenectomy was confirmed as the morbidity and

mortality rates were comparable to the data from previous year. The higher rates of DGE and POPF compared to western data were attributed to the most common indication for Whipple being ampullary adenocarcinoma as opposed to carcinoma head of pancreas in the west. These rates were comparable to our previous year data. Among the compliance to ERAS targets, drain removal and tolerance of normal diet were very low, which was again explicable based on the higher rates of POPF and DGE in our population.

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