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Enhanced Recovery after Surgery (ERAS) Implementation after Pancreaticoduodenectomy: Interim Result

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Abstract: Objective: Pancreaticoduodenectomy is a technically challenging surgery requiring longer period of recovery post operatively. This study aims to examine the implementation of an enhanced recovery after surgery (ERAS) protocol following pancreaticoduodenectomy. Methods: All patient undergone pancreaticoduodenectomy were managed following ERAS protocol. Outcomes measured include postoperative morbidity, mortality, length of stay and readmission rate within 30 days. Protocol targets were: removal of NG tube (PoD1), resumptions of oral fluids (PoD2), mobilization, removal of IV fluids, removal of H-J drain and urinary catheter and discharges from high dependency unit (PoD3), tolerating soft diet (PoD4), removal of P-J drain (PoD5), tolerating normal diet and full mobilization (PoD6) and hospital discharge (PoD7). Results: Data were collected for 15 patients. Rates of mortality, morbidity and readmission were 7%, 53% and 20% respectively. The median length of stay was 10 days. The proportions of patients achieving key targets were; 40% for NGT removal; 67% for resumption of oral fluids; 60% for urinary catheter removal; 53% for HDU discharge; 53% for tolerating diet; 67% for meeting mobility targets and 33% and 67% for H-J and P-J drain removal respectively. PoD 7, eight patients by PoD 11, discharged four patients and 2 complicated patients were discharged within day 17. Conclusion: ERAS protocol implementation in pancreaticoduodenectomy (PD) is feasible and safe. Achieving key target protocol was challenging. A further modification of the ERAS protocol may be needed to ensure more compliance.

Key words: ERAS · Pancreaticoduodenectomy · Pancreatic cancer · Fast track

INTRODUCTION

Enhanced recovery after surgery (ERAS) programmes is a multimodal strategy aim to improve and accelerate functional capacity and rehabilitation after surgery without compromising patients' safety [1]. The implementation of ERAS targeting to patients undergoing major gastrointestinal (GI) surgery such as in colorectal and liver surgeries are expected to be safe and feasible, with morbidity reduction has been shown [2-5]. There are growing evidences that implementation of ERAS program are feasible in complex GI surgery such as pancreaticoduodenectomy [6-9].

Post-operative morbidity remains the main setback in patients' recovery [6, 10-14]. There are however, other independent factors that may impede post-operative recovery. Reduction of the post-operative surgical stress, optimisation of pain control, early resumption of oral diet and early mobilisation, are principal factors incorporated in an ERAS protocol to hasten recovery, thereby reducing the length of stay and cost. Several experiences with ERAS protocols designed using evidence based principles of care in respective centre had been successful in various major GI surgeries and proved to be cost effective.

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In Malaysia, pancreatic cancer is the thirteenth highest incidence of malignancy in male and the fifteenth in female [15]. Pancreaticoduodenectomy (PD) remains the only treatment option for periampullary malignancy and offers the only chance of long term survival [11-13]. With current practices of post-operative management following PD reliant on the surgeon's experience, there is a need for a prospective ERAS protocol design and implementation, to be validated across different institutions and healthcare system.

The objectives of the this study is to evaluate the effectiveness of ERAS protocol implementation for patients after PD and evaluate the outcomes based of these parameters; postoperative morbidity, mortality, length of stay and readmission rates.

MATERIAL AND METHODS

Patients were selected from UKMMC hepatobiliary clinics and referrals with concordance to the inclusion/ exclusion criteria from January 2013 to December 2014. 15 patients were included and followed prospectively using standard data proforma and recorded on daily basis. Collected data includes patient's demographics, co-morbidities, indication for PD, preoperative bilirubin level, type of surgical procedure, duration of surgery, estimated blood loss and postoperative complications following PD. The protocol for ERAS has been developed following the Guidelines for Perioperative Care for Pancreaticoduodenectomy: Enhanced Recovery after Surgery (ERAS) Society Recommendations, published literatures and feasibility of our surgeon and resources. Inclusion criteria includes any patients between 16 to 80 years old with periampullary tumour requiring pancreaticoduodenectomy. This study is approved by the local ethics committee of UKM medical center.

Outcome Measurement: Data collection of patient's demographics, co-morbidities, indication for PD, preoperative bilirubin level, type of surgical procedure, duration of surgery, estimated intraoperative blood loss and postoperative complications following PD (Including morbidity and mortality within 30 days, readmission within 30 days), hospital length of stay post operatively before being allowed for discharge.

Table 1: Protocol for the Enhanced Recovery After Surgery (ERAS) programme following PD

PoD	Targets for postoperative management	
0	*Postoperative analgesia*	Epidural or PCA
	Mobilisation	Up to sit
1	*Postoperative analgesia*	Epidural or PCA
	Mobilisation	Up to sit for 1 hour
2	*Postoperative analgesia*	Oral analgesia following NGT removal
	Nasogastric tube	Remove if drainage volume <500ml (Refer to nasogastric tube removal criteria)
	Mobilisation	Up to sit 2 hour
	Fluid balance	Allow free clear fluids; reduce i.v. fluids to 1L/day if oral intake >500ml
	Intra-abdominal drains	Shorten drain bag to improve mobility
3	*Postoperative analgesia*	Stop epidural or PCA
	Mobilisation	Up to sit for 2 hour and short walk around bed
	Fluid balance	Stop i.v. fluids if oral intake >1L
	Urinary catheter	Remove urinary catheter
	HDU discharge	Consider discharge from HDU (Refer HDU discharge criteria)
	Intra-abdominal drains	Fluid amylase levels of drains sent to laboratory; remove drain if amylase level <5000 U/L and drain output <100 ml (Refer to intra-abdominal drain removal criteria)
4	*Nutrition*	Allow soft diet
	Mobilisation	Walking for 20 minutes
5	*Intra-abdominal drains*	Fluid amylase levels of drains sent to laboratory; remove drain if amylase level <300 U/L and drain output <100 ml (Refer to intra-abdominal drain removal criteria)
6	*Nutrition*	Allow solid food intake
	Mobilisation	Walking for 30 minutes
7	*Hospital discharge*	Consider discharge if hospital discharge criteria are met (Refer hospital discharge criteria)

PoD, postoperative day; PCA, patient-controlled analgesia; HDU, High dependency unit

Table 2: Outline of postoperative management targets in the protocol for the ERAS programme

Management	Criteria
NGT removal	if 24 hours postoperative NGT drain is <500ml, NGT can safely be removed and clear oral fluids initiated
	EXCLUSION: if significant preoperative gatric outlet obstruction was present, seek consultant surgeon opinion prior to removal of NGT
	if persistent vomiting is present thereafter, consider replacement if NGT
	DGE = NGT remains in place for >3 days or has been reinserted for persistent vomiting after PoD 3 or inability to tolerate solid diet by PoD7
HDU discharge	*Respiratory*
	Requiring <40% oxygen
	Respiratory rate <20 and >10 breaths per minute
	SpO2 >95%
	Good cough reflex and cooperation with physiotherapy
	Cardiovascular
	Not requiring ECG or CVP measurement (although CVP line may be in place)
	Not requiring an arterial line, inotropes
	Able to mobilize out of bed without need for inotropes
	Renal
	Stable renal function
	Urea and creatinine level not increasing
	Neurological
	Patient alert and obeying command
	Analgesia
	Pain is well controlled on current analgesic method
	Blood tests
	Stable or improving
	General
	able to mobilize out of bed
Intra-abdominal drain removal	Monitor daily drain output volumes
	PoD2: drains cut and bagged to facilitate mobilisation
	PoD3 or PoD5: assessment of drain nature and amylase content
	Drains removed if:
	drain volume <100 ml
	fluid is clear in colour
	fluid amylase is <5000 IU/L (PoD 3) or <300 IU/L (PoD5)
	If drain removal criteria not met, further drain management will be at discretion of the consultant
Hospital discharge	Patient must achieve all the following:
	Adequate pain control on oral analgesia
	Ability to eat and drink with no requirement for i.v. fluids in previous 24-hours
	Independent mobility (can mobilize independently to toilet)
	Ability to perform ADL without help from nursing staff
	Return of blood test to normal range
	Willingness to go home

NGT, nasogastric tube; HDU, high dependency unit; DGE, delayed gastric emptying; PoD, postoperative day; SpO2, saturation of peripheral oxygen; ECG, electrocardiogram; CVP, central venous pressure

Pancreatic fistula, intraabdominal abscess, intraabdominal haemorrhage, delayed gastric emptying and surgical site infection with delayed in discharge are considered as major post operative complications. The definitions of these complications are as per below:

Major Complications:

Pancreatic Fistula: a drain output of any measurable volume on or after PoD 3 with amylase content of more than 3 times serum Amylase level (ISGPF-International Study Group of Pancreatic Fistula Guidelines) [16].

Intraabdominal Abscess: a collection of fluid >5cm in diameter on CT or US (ISGPF - International Study Group of Pancreatic Fistula Guidelines) [16].

Intraabdominal Hemorrhage: Based on classification and guidelines of Post Pancreatectomy Haemorrhage by ISGPS (International Study Group of Pancreatic Surgery) [17].

Minor Complications:

Delayed Gastric Emptying: indicated by NGT that remained in situ or was reinserted after PoD3 or inability to tolerate oral intake by PoD7 (Definition by ISGPS- International Study Group of Pancreatic Surgery) [18]

Surgical site infection [19]

As a standard of care in the postoperative period, all patients who had underwent PD were prescribed with thromboprophylaxis in terms of subcutaneous low molecular weight heparin (LMWH) (Fondaparinux 2.5mg daily or enoxaparin 2000U daily), somatostatin analogue (Octreotide 100-200 µg, three times daily), anti-emetics (Maxolon 10mg, three times daily).

RESULT

Demographics:

Implementation of the ERAS Protocol: All patients were commenced on either patient controlled analgesia (PCA) or Epidural (n=15). In this series, most of the analgesia were discontinued on PoD3 (60%) while the remaining patients were discontinued on PoD4.

Six patients had their NGT removed PoD2 and the remaining patients on PoD4. Only 1 had his NGT removed on PoD12. Those patients who failed to remove NGT as per protocol either do not meet the criteria for removal or requires another surgical intervention. There were no reinsertions of NGT in any patients.

Only 3 of 15 had their urinary catheter removed on PoD3 while the rest were removed on PoD4. 1 of the 15 patients had his urinary catheter removed on PoD12 due to the need for close monitoring of fluids for his pancreatic fistula.

Intravenous fluids were stopped on PoD4 in 4 patients. All intravenous fluids were removed on PoD5 once patients tolerate foods. 10 of 15 patients had already started to mobilize on PoD1 with the remaining patient on PoD4. All patient were readily ambulating upon discharge.

Table 3: Age, Sex and Comorbidities of Subjects

Variable	Subjects (n=15)
Malay, n (%)	13 (87%)
Diabetes, n (%)	9 (60%)
Hypertension, n (%)	10 (67%)
Coronary artery disease, n (%)	2 (13%)
Mean age, y	64.0
Male sex, n (%)	7 (46.7%)

Table 4: Key target protocol

ERAS postoperative targets	Subjects achieving key target protocol
NG tube removal PoD 2	6 of 15 (40%)
NG tube removal PoD 3	5 of 15 (33%)
Resumptions of Oral fluid PoD 2	10 of 15 (67%)
Tolerating of solid diet PoD 4	8 of 15 (53%)
PCA/ Epidural stopped PoD 3	9 of 15 (60%)
PCA/Epidural stopped PoD 4	6 of 15 (40%)
Removal of urinary catheter PoD 3	3 of 15 (20%)
Removal of urinary catheter > PoD 5	5 of 15 (33%)
IV drip stopped PoD 4	4 of 15 (7%)
IV drip stopped > PoD 5	11 of 15 (73%)
Daily mobilization PoD 1	10 of 15 (67%)
Daily mobilization > PoD 4	5 of 15 (33%)
Removal of H-J drain PoD 3	5 of 15 (33%)
Removal of H-J drain > PoD 4	10 of 15 (67%)
Removal of P-J drain PoD 5	10 of 15 (67%)
Removal of P-J drain > PoD 6	13 of 15 (87%)
Hospital discharge PoD 7	4 of 15 (27%)
Hospital discharge PoD 11	8 of 15 (53%)
Readmission within 30 days	3 of 15 (7%)

Table 5: Complications after pancreaticoduodenectomy

Complication n= 15	
Major	
Pancreatic fistula	2 (13%)
Intraabdominal abscess	1 (7%)
Minor	
Delayed gastric emptying	2 (13%)
Surgical site infection	3 (20%)

We advocate the removal of drains based on the location and Amylase level on PoD3 for hepaticojejunostomy (H-J) and PoD5 for pancreaticojejunostomy (PoD5). Only 5 patients manage to remove the H-J drain on PoD3 and 10 had P-J drain removed on PoD5. Drains were removed completely in all patients on PoD8. Only one patient had drain removed on PoD18 due to the presence of P-J leakage.

Postoperative Outcomes: The overall morbidity was 53% (8 patients) with mortality of 7% (1 patient). There were 3 readmissions (20%) occurring within 30 days in this study. There were 3 readmissions within the 30 days period. One patient was readmitted on day 12

postoperative with a diagnosis of severe hospital acquired pneumonia. Despite aggressive antibiotics and chest physiotherapy, she succumbed to death on day 31. The other patient was admitted on day 21 postoperative with non-specific abdominal pain most likely due to adhesions. The last patient was a man admitted on postoperative day 10. She had an imaging done revealed to have intrabdominal collection. She was treated well with percutaneous drainage. The mortality in this series is a lady who presented with bleeding pancreatic head carcinoma with single liver metastasis. Pancreatoduodenectomy was performed in view of bleeding tumour. She had a good initial recovery and manages to follow the ERAS protocol till hospital discharge PoD7. Unfortunately, she had persistent fever at home. A chest radiograph revealed severe lobar pneumonia. She developed respiratory failure requiring ventilation. However, she succumbed to death in intensive care unit on day 31.

We had 8 morbidities in our series. Two patients developed pancreatic fistula. The first patient was a 35 year-old man presented with mucinous cyst neoplasm of the head of pancreas. Pancreaticoduodenectomy was performed and he developed leak on PoD5. He underwent relaparomy for peritonitis following the leakage. He recovered well after that episode and sent home on PoD11. The second patient was a 60 year-old man who underwent pancreatoduodenectomy for periampullary carcinoma. He had an uneventful surgery with good initial recovery. However, he developed leak on PoD5 by evidence of raised amylase. He was successfully managed conservatively and drain was removed on PoD14. He was discharge home on PoD17. Two patients developed delayed gastric emptying requiring prolonged NGT. However both NGT were removed after one day and discharge on PoD8 and PoD12 respectively. Surgical site infection occurs in 3 patients with no disruption in implementation of ERAS protocol. Based on the ERAS protocol, 4 patients were discharged within the targeted protocol at day 7 and 8 patients were discharged within day 11. Two patients who developed complications were discharged within day 17 after surgery. The median length of stay in uncomplicated ERAS patients were 10 days while the length of stay in patients with postoperative complications was recorded as 11 days.

DISCUSSION

Pancreaticoduodenectomy is a complex and challenging abdominal surgery. It is associated with high risk for postoperative morbidity and mortality. With ERAS protocol, a faster recovery and shorter hospital stay may be feasible and safe without an increase in postoperative morbidity and mortality.

Previous studies on ERAS implementation in pancreaticoduodenectomy are scarce. Up to our knowledge, there is only one prospective study and 2 retrospective studies applying this ERAS protocol for pancreaticoduodenectomy [21]. Although these study shows ERAS is feasible and safe but the results were varied in terms of the protocol aim and achievements.

The results of this interim data support the feasibility and safety of ERAS implementation in postoperative pancreaticoduodenectomy patient. The overall mortality and readmission rates were low and acceptable. Though the morbidity rate were nearly 50% but there were no major disruption in those patients in implementing ERAS protocol. All ERAS patients with or without complications have similar length of stay in the ward. The significant delayed length of stay is only in 2 patients with pancreatic fistula.

Target key protocol were analysed and examined to determine the feasibility and achievement. Analgesia plays an initial role for postoperative recovery. An optimum pain control will help in faster recovery and ambulation and possible early discharge. All patient were prescribed with epidural or patient controlled analgesia (PCAM). Epidural was used in view of a meta-analysis showing a superior and significant improvement in postoperative pain control compared with parenteral opioids in open abdominal surgery [22]. However, not all our patient could be successfully put on epidural. Some of our patients were unable to tolerate the epidural side effects therefore PCAM was given instead. A Cochrane review also demonstrated that continues epidural analgesia is superior to PCA in relieving pain < 72h after open abdominal surgery. Hence an aim of analgesia substitutes was made on PoD3. However, only 9 of 15 patients had their epidural stopped on PoD3. The other 6 needs an additional day of epidural before completely stopped on PoD4. There was no difference in the type of analgesia prescribed with relation to the decision of stopping it. However, the difference of pain tolerance may be attributed to the patient tolerance,

type and size of wound or the difference of PCA and epidural efficacy. A study may be needed to address this issue.

NGT is inserted in view of the need for gastric decompression after pancreaticoduodenectomy. NGT is associated with fever, atelectasis and pneumonia [23]. One comparative study also showed that removal of NGT as early as PoD1 and PoD2 decreased the rate of postoperative nausea and vomiting [24]. However, none of this paper has investigated the need for NGT in pancreatic surgery hence the different opinion among clinical physicians. We use NGT in early postoperative with an aim to remove it on PoD2. More than half of the patients met the target of removing NGT on PoD2 and PoD3. The delay of NGT removal recorded is due to delay gastric emptying (2 patients), relaparotomy (1 patient) and presence of pancreatic fistula (2 patient).

One of the main challenges in achieving the key target would be the removal of drains. We advocate 2 drains inserted at the hepatico-jejunostomy and pancreatico-jejunostomy sites. The aim is to reduce the morbidity with any anastomosis leakage. It also helps in identifying possible of pancreatic fistula. Amylase would be sent on both PoD3 and PoD5 respectively to determine the decision of drain removal. A raised amylase will suggest a possible leak or pancreatic fistula (>5000 units/L). Previous randomized control trial has revealed a significantly reduced rate of pancreatic fistula, abdominal and pulmonary complication with early removal of drain [25]. In our series, only 5 of 15 patients met the criteria of removal on PoD3 while 10 of 15 patients drainage were removed on PoD15 respectively. There were no hepato-jejunostomy leak occurrence; however, 2 patients developed pancreatic fistulas with one require relaparotomy and another was manage conservatively.

Another key target were resumption of oral intake. An early oral intake post pancreaticoduodenectomy occasionally poses a dilema for upper GI and HPB surgeons. This is in view of the complexity of a pancreatic surgery and possibility of delay gastric empyting episodes. Healing is supposedly promoted by restricting amount of anastomosis sites stimulation. However, there were no data to suggest a surgeon's controlled stepwise increment of fluids to solid is superior than early enteral feeding. Early enteral restores the physiological movement of the bowel and aids with early recovery. Most of our patients in this series had their oral intake resume on PoD2 and all patients tolerated oral fluids and solids on PoD4. Intravenous fluids requirement were manage in concordance of oral intake. Most of the patients had their intravenous fluids stopped on PoD4 once the oral intake is sufficient.

The need for fluid balance and monitoring plays a factor in deciding removal of urinary catheter. The necessity of close fluid monitoring after major abdominal surgery poses some difficulty in early removal. Most trials evaluated urinary drainage for 4-7 days. A recent randomized controlled trial found removal of urinary drainage as early as PoD1 to be superior in terms of infection rates and reduced reinsertion rates when compared with removal on day 3 - 5 [26]. 10 of 15 patients in our study had their urinary drainage removed on PoD3 and PoD4. These results were comparable with other studies [27]. The delays in remaining patient were mostly due to the morbidity requiring close fluid management.

The aim of hospital discharge on PoD7 is not easily achieved in most patients. In this series, only 4 of 15 patients were successfully discharge per protocol target. 5 of 15 patients were discharge on PoD8 and PoD9. The other patients were discharge before PoD17. Though the target is not completely successful but the delay period is short and managable. Interestingly, this result is similar with previous 2 studies, which reported an earliest median discharge of 7 days and PoD10 respectively [27]. Among the reasons cited were due to morbidity, logistic and social related. Based on our series, a discharge on PoD7 and PoD8 is feasible especially in uncomplicated patients.

Historical data suggest a reduced in length of stay after the implementation of ERAS. A retrospective study in the New York University suggests a median length of stay of 15 days in pancreaticoduodenectomy patients without complication while a mean of 25 days with complications. [28] However, Nichola *et al* showed a better median length of stay of 9 days without postoperative complications. Our series median length of stay is notably comparable if not shorter than previous studies with a median of 11 days and 10 days in patients with and without postoperative complications respectively [27].

Our series morbidities were comparable with previous studies. The morbidities were inclusive of two pancreatic fistula, two delayed gastric emptying, one intraabdominal abscess and three surgical site infections. Nevertheless, only two of these patients were unable to follow the ERAS protocol completely due to relaparatomy and fistula management.

In conclusion, the result from this study confirms the feasibility and safety of ERAS implementation in pancreaticoduodenectomy patients. Most targets were achieved while some were more challenging. A more practical key target would be beneficial for future ERAS protocol. A further modification of the protocol may help to improve the recovery, length of stay and reduce the mortality and morbidity.

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