Case Study: Pancreas cancer with Whipple's operation

Blaauw R, (PhD Nutrition), Associate Professor, Stellenbosch University
Correspondence to: Renée Blaauw, e-mail: rb@sun.ac.za
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The following case study was discussed at the SASPEN Workshop held during the Nutrition Congress 2014. It is a reflection of the general opinion of the audience, followed by a rationale of the latest literature on the topic. Herewith follows a summarised discussion of the case.

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Introduction

A pancreaticoduodenectomy (PD), also known as Whipple's operation, is used for the surgical management of pancreatic head malignancies. It is characterised by removal of the pancreas head, duodenum, distal common bile duct, gallbladder and gastric antrum.[1-3] Variations from the standard procedure are sometimes made which are necessitated by the tumour location and size. The most common variation is the preservation of the pylorus and gastric antrum, known as the pylorus-preserving pancreaticoduodenectomy (PPPD).[1,2]

Gastrointestinal continuity is re-established by various anastomoses to the remaining jejunum. Most commonly the remaining part of the stomach is anastomosed to the jejunum (gastrojejunostomy). The rest of the pancreas is anastomosed to the jejunum (pancreaticojejunostomy) and the bile duct to the jejunum (hepaticojejunostomy).[1,2]

The nutritional management of patients post surgery is dependent on the preoperative nutritional status, disease involvement and surgical procedure, i.e. resected areas and anastomoses made.

Case study

A 75-year old male was admitted to hospital on 30 July 2014 with a three-week history of jaundice, pruritus, pale stools and dark urine. He had a history of alcohol abuse, a stable angina and was on medication for hypertension.

The differential diagnoses of hepatitis or gallstones or cancer of the pancreas and gallbladder was made.

His anthropometric values on admission were:

- *Weight:* 53 kg.
- *Height:* 170 cm.
- *Usual body weight:* 65 kg (i.e. 18% weight loss in less than six months).

His biochemical values on day 1 were as follows:

- A low serum albumin (25 g/l).
- Raised total bilirubin (206 µmol/l).
- Raised conjugated bilirubin (173 µmol/l).
- Raised gamma-glutamyl transferase (1 356 u/l)
- Raised alkaline phosphatase (1 127 u/l).

During hospitalisation (preoperatively), he was placed on a full ward diet. On average, he consumed 60% of his food, and sometimes complained of vomiting after meals. He also presented with blood glucose values ranging from 6-16.8 mmol/l.

After a computed tomography (CT) of the abdomen, the diagnosis of pancreas head carcinoma with obstructive jaundice was made. Aorta calcifications were also noted.

The patient was scheduled for surgery on 17 August and kept *nil per mouth* from the previous evening. Owing to another medical emergency, he could not go to theatre as planned, and only underwent a PD (standard Whipple's operation) on 18 August 2014. Extensive unresectable spreading of the tumour was noted.

Postoperatively, he was admitted to the intensive care unit for monitoring. He was placed on free nasogastric (NG) drainage and received sips of water. On 19 August 2014, he was prescribed a diabetic fluid diet, but owing to abdominal distention and episodes of vomiting, this was not given. An insulin sliding scale was started, and he received between 12 and 20 units of short-acting insulin daily to control his blood glucose values.

Oral intake was initiated daily, but he was unable to consume more than one third of his fluid diet due to intermittent nausea and vomiting. By 23 August 2014, he was successfully tolerating his diet. It was decided to advance him to a full diabetic diet.

Question 1: Could you please comment on the nutritional status of the patient on admission, and on any contributing factors?

On admission, the patient had a body mass index of 18.3 kg/m^2, indicating undernutrition. Significant weight loss of 18% in less than six months also supports this diagnosis. Contributing factors to the patient's poor nutritional status could have been the presence of pancreas carcinoma, the poor dietary intake (as evidenced by the weight loss,) and a reported history of alcohol abuse.

Rationale

Preoperative nutritional status assessment can assist with early identification of patients with special nutritional needs. It is regarded as an important contributor to postoperative morbidity and mortality.[2,4-6] Certain components warrants special attention. Preoperative serum albumin values are highly regarded as a predictive prognostic variable postoperatively.[2,4,6] A preoperative serum albumin of < 21 g/l is associated with 29% postoperative mortality and 30-day mortality of 65%.[7] Jaundice due to tumour obstruction can indicate the extent of the damage.[2] As always, anorexia and loss of appetite can contribute to weight loss, the extent and duration of which needs to be determined.[2] Cancer cachexia is diagnosed if the weight loss is ≥ 10% in six months.[2,4] The combination of anorexia and weight loss ≥ 10% is considered a poor prognostic sign.[4]

Pancreatic cancer is associated with malnutrition and cachexia.[2,4] Potential contributing mechanisms of cachexia include sustained proinflammatory cytokine response, catabolic effects of sepsis owing to increased energy expenditure, a poor dietary intake and early satiety, as well as gastrointestinal tract side-effects, e.g. vomiting, malabsorption and abdominal pain.[2,4]

Upon diagnosis, the majority of patients are already metastatic and the five-year survival rate are less than 5% in the case of extensive metastasis.[1,8] Larger tumours also contribute to poor survival.

Surgery or chemotherapy, or a combination thereof, are the most common treatment options for pancreas cancer.[1,3] The former can only be performed in cases of tumours that have not metastasised. Postoperative morbidity can be reduced by decreasing surgical stress, ensuring adequate pain control and early mobilisation, as well as the early introduction of nutrition.[5] Alcohol abuse is also linked to twofold increased morbidity postoperatively. Similarly, daily cigarette smoking (> 2 cigarettes per day for one year) is known to increase postoperative complications. Hence, one month's abstinence preoperatively is strongly recommended in alcohol abusers and smokers.[5] Prolonged operating time, increased preoperative bilirubin, decreased preoperative albumin, advancing age and an advanced stage of cancer, are factors that are linked to increased postoperative mortality.[1,4]

Question 2: Do you agree with the preoperative fasting guidelines followed in this case?

No. The patient was kept *nil per os* for longer than 12 hours for the initial scheduled surgery, which had to be extended by another day. This is in contrast to the literature recommendations.

Rationale

Traditionally, overnight fasting is implemented before any surgical procedure. This is performed to decrease gastric content and the risk of pulmonary aspiration.[5,9] However, evidence for the latter effect is slim.[9]

The latest recommendations state that the consumption of solids up to six hours, and clear fluids up two hours, before anaesthesia, does not increase gastric residual volume and is recommended before elective surgery. The intake of clear, carbohydrate-rich drinks results in enhanced glucose control postoperatively. Also, the patient is less anxious and presents with less hunger and thirst, and experiences accelerated recovery and a decreased risk of wound dehiscence.[5,9-11]

Preoperative carbohydrate-containing drinks should not be given to patients with diabetes mellitus until further information is obtained. However, the guidelines for solids still apply.[5,9]

Question 3: Postoperatively, the patient suffered from delayed gastric emptying. Could you speculate on the contributing factors, classify the delayed gastric emptying staging and indicate your treatment strategy?

The patient suffered from grade 1 delayed gastric emptying (DGE). The presence of uncontrolled blood glucose (diabetes mellitus), the consequences of Whipple's operation (antral resection) and decreased motilin release (upper small bowel resection) were contributing factors to the DGE in this case.

Management include optimal glucose control, promotility drugs and medication to control the acid environment. An oral intake plus supplements should be tried as a first option to achieve optimal intake. Alternatively, enteral nutrition via the nasojejunal route using a semi-elemental or polymeric product should be investigated. The latter is only possible if a feeding tube is inserted during the operation.

Rationale

DGE is regarded as the most common complication post-Whipple's operation. It affects from 10-60% of patients,[1,2,3,5] and is the largest contributing factor to postoperative morbidity.[1] Prominent symptoms include nausea, vomiting, bloating, early satiety and abdominal pain.[3]

As a result of DGE, oral intake is delayed. This affects the overall quality of life and lengthens hospital stay.[1,2,8] It is recommended that promotility agents are prescribed to these patients.[1,2]

The most common causes for the development of DGE include diabetes mellitus; decreased motilin release, owing to small bowel resection; intra-abdominal complications and infections; the use of octreotide, i.e. somatostatin analogue; and surgical techniques, i.e. injury to the vagus nerve or pylorus muscle.[1,2,8]

Motilin is secreted by the duodenum and jejunum, and requires an alkaline medium for effective release. The main functions of motilin include controlling gastrointestinal motility by stimulating the gastric contractions and enhancing gastric emptying.[1,2] It is also involved in the release of somatostatin, gall bladder contraction and

Table I: The grading of delayed gastric emptying[1,2]

	Grade A	Grade B	Grade C
Nasogastric tube required	4-7 days or reinserted > postoperative day 3	8-14 days or reinserted > postoperative day 7	> 14 days or re-inserted > postoperative day 14
Unable to tolerate solid oral intake by postoperative day	7	14	21
Vomiting or gastric distention	No/yes	Yes	Yes
Use of nutrition support	No	Required for first 3 weeks postoperatively	Required for more than 3 weeks

the stimulation of endogenous release of the endocrine pancreas. Erythromycin and related antibiotics act as non-peptide motilin agonists, and are therefore sometimes used for their ability to stimulate gastrointestinal motility.[1] Somatostatin slows down digestion, the muscle contractions of the gastrointestinal tract, blood flow to the intestines, and hence gastric emptying. Thus, the use of octreotide, a somatostatin analogue, could contribute to the development of DGE.[1]

According to a recent systematic review, the risk factors most consistently and significantly associated with DGE were postoperative complications [odds ratio (OR) of 4.71], pancreatic fistula (OR of 2.66) and preoperative diabetes (49% increased risk).[8]

The grading of DGE, as recommended by the International Study Group for Pancreatic Surgery, can be seen in Table I. The diagnosis and grading take into account the duration of NG tube placements, as well as the need for tube reinsertion, the duration of insufficient oral intake and presence of gastrointestinal side-effects. It is important to always eliminate the presence of any obstruction or stenosis. [2]

Treatment options include:

- *Prokinetic agents:* Examples are erythromycin (a motilin receptor agonist)[1,2] and metoclopramide[2] (stimulates smooth muscle and increases gastric emptying). The antrum still needs to be present for optimal function with metoclopramide.
- *Proton-pump inhibitors:* Proton-pump inhibitors (PPIs) decrease gastric secretions and result in a more alkaline environment.[1]
- Insulin therapy for optimal glucose control.[1]

Question 4: Please could you comment on the need for an insulin sliding scale to control blood glucose variations?

The extent of pancreatic damage due to cancer of the pancreas before surgery, linked to the partial pancreas resection, could result in diabetes mellitus owing to loss of endocrine function.

Rationale

Between 20% and 50% such patients develop diabetes mellitus after pancreatic resection. Blood glucose levels are raised immediately postoperatively due to stress and the use of certain medications.[2,3] This should resolve in many cases.[1,2] However, up to 80% of individuals with pancreatic cancer have diabetes mellitus preceding the diagnosis. This is probably caused by long-term destruction of the pancreatic island tissue by the tumour.[2]

Treatment includes insulin therapy, preferably via constant infusion to manage blood glucose levels. Owing to reduced glucagon levels post surgery, patients are also prone to episodes of hypoglycaemia, and this should be managed by regular blood glucose monitoring.[4,5]

Question 5: Would you expect this patient to suffer from malabsorption postoperatively? If "yes", how would you manage it?

Yes. The extent of the pancreatic damage due to the cancer of the pancreas before surgery, linked to the partial pancreas resection, could also result in malabsorption due to loss of exocrine function.

Management includes a low-fat intake (the amount is determined by the patient's tolerance), small frequent meals, oral nutrition supplements to ensure optimal intake, and pancreatic enzymes replacement, i.e the amount determined by fat malabsorption.

Rationale

The majority (68-92%) of patients with cancer of the pancreas suffer from exocrine pancreatic insufficiency (EPI).[1,2] This may continue postoperatively.[1] A decreased secretion of bicarbonate by the ailing pancreas results in an acidic environment which denatures the available digestive enzymes. This contributes to insufficient exocrine function.[1]

The consequences of EPI include diarrhoea, steatorrhoea (> 90% resected or long-standing pancreatitis), micronutrient deficiencies and weight loss.[2,6] Cancer of the pancreas is also associated with the highest levels of malnutrition. [2]

A 72-hour faecal fat test (100 g fat intake) needs to be performed for a diagnosis of EPI to be made. A positive test is reported if > 7% of the total amount of fat consumed is present in the stool.[1]

Treatment options include reduced dietary fat intake, individualised according to tolerance, and the use of pancreatic enzymes.[1-3] Although most pancreatic enzymes are enteric coated (except for Viokase®), it is still recommended that PPIs are also administered to neutralise the environment because an acid environment can inactivate the pancreatic enzymes.[1,2]

Pancreatic enzymes can be administered via a jejunal feeding tube provided the capsule is opened and the content is mixed with water and bicarbonate. After leaving the mixture for 15-20 minutes, it can be flushed down the tube or mixed with the formula.[1] The recommended dosage is 2 000-4 000 units of lipase/gram fat or 25 000-40 000 units per meal to a maximum of 10 000 units/kg/day.[1]

Question 6: Could you please comment on the nutritional management of this patient?

Oral intake should always be used initially, as was implemented in this case. This can be accompanied by oral nutritional supplements if the intake is insufficient. If the combination approach still does not meet the patient's needs, enteral tube feeding (nasojenunal) should be initiated.

Rationale

The main goal of nutritional management in a patient with cancer of the pancreas is to alleviate the effects of cancer cachexia.[4] An individualised approach should be followed so that any specific complications that may arise post surgery can be taken into consideration.

The use of the enteral versus parenteral route has been debated extensively. As always, the principle of "if the gut works, use it" should be the first approach.

Early postoperative enteral feeding should be aimed for, as appropriate.[4] The advantages and disadvantages of early enteral feeding are summarised in Table II. The placement of a feeding tube distal to the anastomoses areas (nasojejunal or jejunostomy tube) is ideal.[4] Cyclic feeding seems to be the recommended administration method because it results in less postoperative gastric stasis.[4]

Table II: The consequences of early enteral feeding[4,12,13]

Advantages	Disadvantages
Enhances the immune function	Diarrhoea
Decreases infection rates	Abdominal cramping
Maintains gut integrity	Excess gas production
Promotes wound healing	Delayed gastric emptying
Results in less complications	Dislocation or blockage of the tube
Is associated with decreased costs	Intra-abdominal leakage
Is a quicker transition to oral intake (versus parenteral nutrition)	Small bowel necrosis

The consequence of DGE owing to early enteral feeding was refuted in a recent systematic review which found no significant effect in the development of DGE between patients receiving early enteral feeding and those who did not (OR of 1.05).[8]

The use of immunonutrition for 5-7 days perioperatively,[1,4,5] and seven days postoperatively,[4] should be considered because it may reduce the prevalence of infectious complications in patients undergoing major open abdominal surgery.

Oral intake in the form of clear fluids can be initiated as soon as possible in such cases where the NG tube has been removed.[1] However, debate exists about the implementation of a clear fluid diet versus allowing the patient to choose which foods he or she prefers. Provided that patients are informed about the potential of impaired gut function in the early postoperative period and advised on management thereof, the latter option results in improved patient satisfaction and an earlier attainment of nutritional needs.[1,5] Oral nutrition supplements, in combination with oral food intake, are an attractive alternative to the use of enteral nutrition.[4] Ensuring that the nutritional goals are met and individualising the prescription of a given patient should remain the main priority.

The routine use of parenteral nutrition (PN) as a sole source of nutrition is not recommended, and this option should only be applied when the oral and enteral routes have been unsuccessful.[4] The combination of early enteral nutrition with PN is thought to be superior to PN alone, as found in a recent study which showed decreased infectious complications, a shorter hospital stay, improved nutritional status and improved glucose control in the group receiving the combination therapy.[12]

A recent systematic review assessed the outcomes of the different feeding strategies post PD. No major differences in outcome were found between the oral, enteral and parenteral feeding routes. Since the oral route was not inferior to, and in some cases resulted in better outcomes, than the enteral or parenteral route, oral feeding should be considered as the preferred route after PD.[14]

Summarising the section on nutritional management

According to the Enhanced Recovery after Surgery Society practice guidelines for PD, the routine use of preoperative artificial nutrition is not warranted, but significantly malnourished patients should be optimised with oral supplements or enteral nutrition preoperatively. Postoperatively, patients should be permitted a normal diet after surgery without restrictions. They should be cautioned to begin carefully and to increase intake according to tolerance over 3-4 days. Enteral tube feeding should be given only according to specific indications, and parenteral nutrition should not be employed routinely.[5]

Discussion

DGE, a pancreatic fistula, diabetes mellitus or glucose intolerance, malabsorption and vitamin and mineral deficiencies are the most common complications encountered post Whipple's operation.[1-3]

The patient discussed in this case study suffered from three of these complications. For the sake of completeness, the other two complications will be discussed briefly.

Pancreatic fistula

Pancreatic fistulas develop in 12-38% of patients postoperatively.[1,2] Well-known risk factors for this complication include being of an age > 65 years, being male, a BMI > 23 kg/m^2, a short main pancreatic duct (< 3 mm), the presence of other co-morbidities, raised preoperative C-reactive protein values, malnutrition and delayed enteral feeding postoperatively.[1]

The diagnosis of a fistula, as defined by the International Study Group for Pancreatic Fistulas (ISGFP) is made in the presence of an output via a drain of any fluid on or after postoperative day 3, and when the amylase content of the fluid is greater than three times the upper normal serum value.[1,2] The ISGFP has defined a grading classification for pancreatic fistulas (Table III).

Table III: The grading of pancreatic fistulas[1]

	Grade A	Grade B	Grade C
Sign of infection	No	Yes	Yes
Sepsis	No	No	Yes
Evidenced by a CT scan or ultrasound	No	Possibly	Yes
Reoperation required	No	No	Possibly
Nutritional intervention	None specific	Possibly NPO with EN/PN	Definitely NPO with EN/PN

CT: computed tomography, NPO: *nil per os,* EN: enteral nutrition, PN: parenteral nutrition

The treatment includes octreotide, a somatostatin analogue, which inhibits pancreatic secretions,[1,2] enteral access distal to the pancreas or PN in the case of a high-output fistula. The use of somatostatin analogues are not recommended as the primary treatment option by the European Society for Clinical Nutrition and Metabolism[5] since they do not produce consistent benefits on outcome. A general description of the management of fistulas was provided in a recent case study discussion.[15]

Vitamin and mineral deficiencies

The duodenum and proximal jejunum are important sites for the absorption of iron, folate, fatty acid, protein and trace elements. Surgical resections which result these parts of the small bowel being bypassed could result in impaired absorption of iron, calcium, zinc, copper, selenium and fat-soluble vitamins.[1-3] In addition, the occurrence of small intestine bacterial overgrowth, as a result of gastric stasis and the decreased release of gastric acid, is found in up to 40% of patients with pancreas insufficiency. Deficiency of vitamin B_{12} and folate is common during the presence of small intestine bacterial overgrowth.[1,3]

Conclusion

Significant factors are associated with the high rate of mortality in patients with pancreatic cancer. These include the advanced stage of the disease by the time of diagnosis, the inherent aggressive biology of pancreatic adenocarcinoma and a poor nutritional status. The surgical procedure dictates the postoperative complications and management to a large extent. An individualised approach in treating complications and in selecting the most appropriate route of nutrition support is advocated.

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